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THÈSE

présentée par :

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Towards the synthesis of novel heterocyclic agrophores bearing emergent fluorinated substituents

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À mon père,

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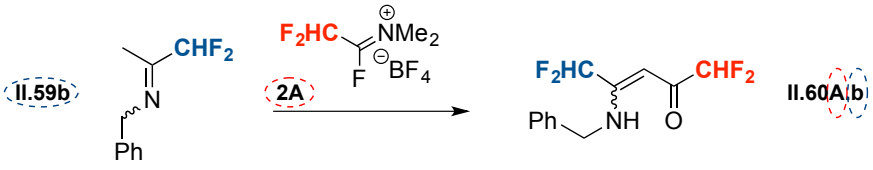
Abbreviations

Ac_2O: acetic anhydride
Al_2O_3: aluminium oxide
anh.: anhydrous
BCS: Bayer Crop Science
BF_3•Et_2O: boron trifluoride diethyl etherate
BOC: *tert*-butoxy carbonyl
$(BOC)_2O$: pivalic anhydride
ca.: circa
CD_3CN: acetonitrile-d_3 or trideuteroacetonitrile
CNRS: centre national de la recherche scientifique
DCM: dichloromethane
DFMMP: ethyl 3- (difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate
DHP: 3,4-dihydro-2*H*-pyran
DIPEA: *N*-ethyl-*N*-isopropylpropan-2-amine
DMAP: *N*,*N*-dimethylpyridin-4-amine
DMF: *N*,*N*-dimethylformamide
DMFDMA: *N*,*N*-Dimethylformamide dimethyl acetal
DMI: demethylation inhibitors
DMPU : 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
EFS: emergent fluorinated substituent
Et_2O: diethyl ether
Et_3N: triethylamine
EtOH: ethanol
EWG: electron-withdrawing group
FAR: fluoroalkyl amino reagent
H_2SO_4: sulphuric acid
HCl: hydrochloric acid
HF: hydrofluoric acid
HFIP: Hexafluoropropan-2-ol
HMBC: heteronuclear multiple bond correlation
HMPA: hexamethylphosphoramide
HNO_3: nitric acid
K_2CO_3: potassium carbonate
KHMDS: potassium bis(trimethylsilyl)amide
LDA: lithium diisopropylamide
MeCN: acetonitrile
MeI: methyl iodide
MoA: mode of action
MS 4Å: molecular sieves (4Å)
MW: microwave irradiation
$NaBH_4$: sodium borohydride
NaH: sodium hydride
NaOCl: sodium hypochlorite
NMR: nuclear magnetic resonance
PFP: perfluoropropene
PhF: fluorobenzene
PTFE: polytetrafluoroethylene
Q_0I: inhibitors of quinol *outer* binding site of the cytochrome bc_1 complex
Rf: fluoroalkyl
rt: room temperature
SDHI: succinate dehydrogenase inhibitors
SiO_2: silica
$SOCl_2$: thionyl chloride
TBDMSCl: *tert*-butyldimethylsilyl chloride
*t*BuLi: *tert*-butyllithium
TFEDMA: 1,1,2,2-tetrafluoro-*N*,*N*-dimethylethan-1-amine
THF: tetrahydrofuran
THP: 2-tetrahydropyranyl
TsOH: *p*-Toluenesulfonic acid (PTSA)
Δ: heating

Explanatory note

During the reading of this manuscript, the use of combined capital and small letters will help the comprehension of the results described. A notice of how to read the information is given below:



Résumé de thèse

Synthèse de Nouveaux Agrophores comportant des Groupes Fluorés Emergents

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Chapitre I

Propriétés du Fluor et Intérêts en Agrochimie

La chimie organofluorée est devenue un domaine important associé à la recherche pharmaceutique et agrochimique, avec de nombreuses applications. Les compagnies agrochimiques majeures ont placé de larges efforts dans le développement de nouveaux composés aromatiques et hétérocycliques contenant des groupements fluorés, mais le développement de composés introduits sur le marché contenant des groupes fluorés émergents a récemment donné un nouveau souffle à ce domaine de recherche. Aujourd'hui plus de la moitié des composés agrochimiques commercialisés contiennent du fluor, et une fraction non-négligeable contient ces groupes fluorés émergents. Un frein au développement de nouvelles structures biologiquement actives reste le manque de stratégies efficaces de synthèse de composés contenant ces groupes.

Les propriétés particulières du fluor font de cet élément un outil pour le développement de composés biologiquement actifs. Le fluor est un élément chimique de symbole F (nombre atomique Z = 9) et le 13ème élément le plus abondant sur Terre. Cet élément existe à l'état élémentaire sous forme de difluor F_2, un gaz hautement toxique et corrosif. Au XIXe siècle, de nombreux scientifiques ont tenté d'isoler ce composé. Un grand nombre fut blessé ou tué par l'acide fluorhydrique durant les premières expériences, avant que Henry Moissan (un chimiste et pharmacien français) ne réussisse sa première isolation en 1886, lui permettant d'obtenir le prix Nobel de Chimie en 1906. De façon surprenante, cet élément est quasi-exclusivement exclu des procédés métaboliques impliqués dans les organismes vivants. Ceci s'explique par ses propriétés extrêmes, incompatibles avec la chimie du vivant :

- son extrême énergie d'ionisation (402.15 kcal/mol) empêche toute réaction d'oxydo-réduction impliquant cet atome,
- sa haute énergie d'hydratation (117 kcal/mol) diminue fortement sa nucléophilie dans des systèmes biologiques aqueux,
- la génération de radicaux fluor est extrêmement difficile, et leur réactivité est incompatible avec les procédés biologiques,
- la force de la liaison C-F est incompatible avec les formations et ruptures de liaisons nécessaires dans la chimie di vivant.

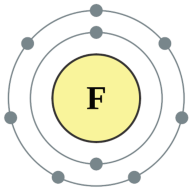
L'introduction de fluor dans des molécules organiques date de la fin du XIXème siècle, mais est restée rare jusqu'aux années 1920 à cause de limitations techniques à manipuler cet élément réactif et corrosif. Après la découverte du Téflon® dans les années 30, les premières fluorations aromatiques furent développées. La découverte d'anesthésiques, d'anti-inflammatoires ou d'anti-cancéreux fluorés a entraîné un développement de la chimie du fluor. Le développement technique et l'utilisation de réactifs de fluoration sûrs rendirent possible le succès de nouveaux composés aromatiques fluorés en chimie médicinale depuis plusieurs décennies.

Dans un contexte de population mondiale et de besoin en ressource alimentaire croissantes, l'utilisation de produits agrochimiques améliorant les rendements et la qualité des cultures fait aujourd'hui face à de nouvelles contraintes. L'efficacité des composés, leur impact environnemental et leur innocuité font l'objet de vifs débats, et les compagnies agrochimiques sont forcées de trouver de nouvelles molécules pour remplir ces objectifs en faisant face à des nouveaux challenges, comme le développement de résistance aux traitements par certaines espèces vivantes destructives, végétales ou animales. Le nombre de composés fluorés introduits sur le marché a connu une croissance forte durant les 30 dernières années, démontrant son importance dans le domaine.
Statistiquement, une majorité de fongicides contienne environ 2 atomes de fluor, alors que les insecticides/acaricides en contiennent 5 ou plus, et les herbicides trois ou plus. La tendance montre une

croissance attendue des composés agrochimiques fluorés dans les décennies à venir. Parmi les composés agrochimiques, 32% contiennent un atome de fluor, et 43% contiennent un groupe CF_3. Cette tendance correspond à un état de l'art avancé dans l'introduction de ces groupes. Cependant, l'introduction de groupes fluorés émergents a déjà démontré un vrai potentiel dans le développement de composés agrochimiques

A. Fluor en Chimie Organique

1. Propriétés Atomiques

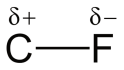


L'élément fluor est le plus léger des halogènes, de configuration électronique $1s^2 2s^2 2p^5$. Il possède un petit rayon atomique (64 pm) dû à une forte attraction nucléaire des 9 protons constituants son noyau sur les électrons de la couche externe, et à un faible effet de masquage des couches intermédiaires. En conséquence, cet élément possède la plus forte électronégativité de tous les éléments (χ = 3,98, échelle de Pauling), et une affinité électronique élevée (333 kJ/mol), pour pouvoir remplir sa couche électronique de valence. A l'opposé, l'énergie d'ionisation du fluor est extrêmement élevée (402.15 kcal/mol, la 3^e plus élevée de tous les éléments chimiques), ce qui rend l'oxydation du fluor très difficile. Du fait de sa compacité, le Fluor est très peu polarisable, avec pour conséquence de faibles interactions intermoléculaires ; de ce fait, les énergies de surface de composés perfluorocarbonées sont faibles. La capture d'un électron par un atome de Fluor est facilitée par l'effet électroattractif fort du noyau dans un atome compact, de ce fait le fluorure F^- est le plus petit et le plus dur des anions. C'est aussi la base la plus forte et dure au sein des halogénures. Sa nucléophilie est cependant influencée par le type de solvant. Dans les solvants polaires protiques, F- est hautement solvaté et est un mauvais nucléophile, mais est au contraire un bon nucléophile dans les solvants polaires aprotiques.

L'atome de fluor possède un seul isotope naturel stable (^{19}F avec 10 neutrons); son rapport gyromagnétique étant élevé, il constitue un noyau de choix pour l'analyse RMN avec son spin de ½. La production de radioisotope ^{18}F est utilisée dans la tomographie à émission de positons (TEP) en imagerie médicale. Cet élément instable est produit dans un cyclotron en bombardant de l'eau lourde avec des protons de haute énergie (~18 MeV). Son temps de demi-vie de 110min est adapté à une utilisation en milieu médical, à l'inverse d'autres radioémetteurs. Cette technique d'imagerie permet l'observation de processus biologiques, ou de biodistribution de médicaments.

2. Introduction de Fluor & Conséquences

La liaison C-F est la liaison la plus forte observée entre un élément et l'atome de carbone (114.7 kJ/mol) et est courte (1.35-1.40 Å). La forte électronégativité du fluor rend la liaison C-F polarisée, et la formation de charges partielles attractives (C_{δ^+}---F_{δ^-}) renforce la liaison.



La présence de 3 paires d'électrons non-liantes sur l'atome de fluor entraîne des effets électroniques particuliers sur les molécules organiques (Figure 1):

- un effet « push » : effets mésomères (+M) ou inductifs donneur ($+I_\pi$) stabilisant les carbocations en *alpha*,
- Un effet « pull » : déstabilisation des carbocations en beta, hyperconjugaison négative (parfois débattue).

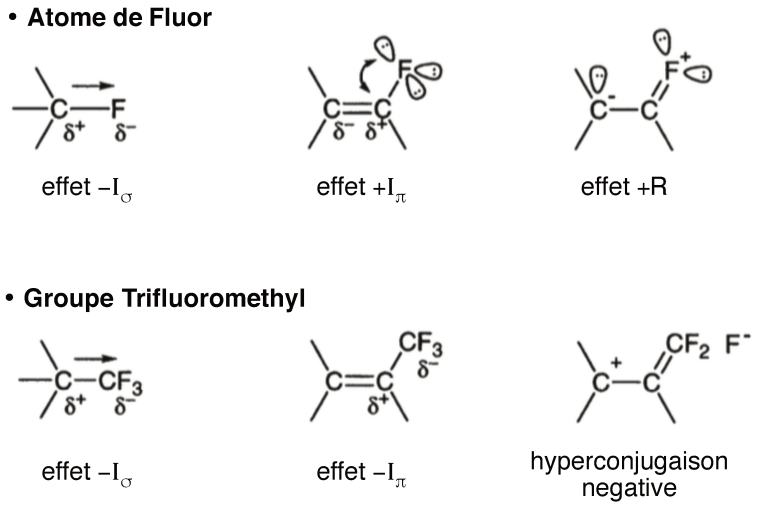


Figure 1: Effet électronique des substituants fluoro- et trifluoromethyl

L'introduction de fluor dans un composé organique a plusieurs effets ; la répartition électronique ainsi que le moment dipolaire sont fortement modifiés dû à la forte électronégativité du fluor. Par ailleurs, la fluoration de composés organiques affecte grandement leur lipophilie, un paramètre important dans le développement de composés biologiquement actifs.

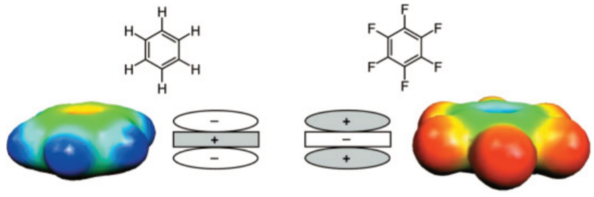


Figure 2: Effet du fluor sur la répartition électronique

La modification du moment dipolaire associée à des variations stériques peut induire des changements conformationnels dans une molécule fluorée. L'exemple du trifluoromethoxybenzene possédant un angle dièdre jusqu'à 90°, quand le methoxybenzene est plan, est une bonne illustration de ce phénomène (Figure 3).

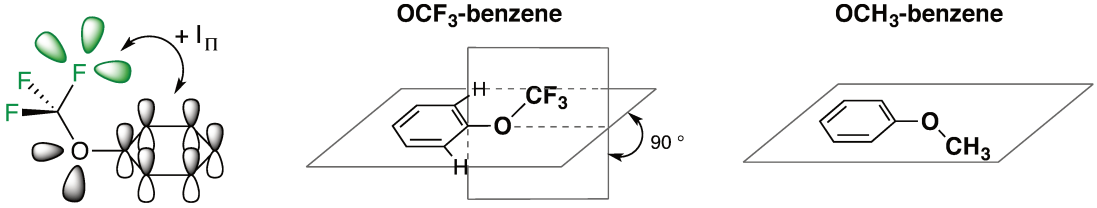


Figure 3: Changement conformationnels relatifs à la présence de groupements fluorés (ici OCF_3)

Dans le développement de nouvelles molécules bioactives, l'introduction de fluor durant les phases d'optimisation de « Lead » est utilisée pour modifier certains paramètres physico-chimiques :

- les pKa de fonctions acido-basiques voisines
- la solubilité (influencée par les changements de polarité et de pKa)
- la lipophilie (ou log P)
- la biodisponibilité (influencée par la lipophilie)
- l'affinité pour un récepteur (influencée par des changement conformationnels et/ou électroniques)
- la formation de liaison hydrogène faibles (influence l'affinité pour un récepteur)
- la stabilité métabolique (en réduisant la susceptibilité à l'oxydation métabolique)

La introduction d'un groupe fluoré en remplacement d'un groupe métaboliquement fragile est une technique communément utilisée pour limiter la dégradation du principe actif et améliorer sa biodisponibilité.

B. Composés Fluorés en Agrochimie

En agrochimie, de nombreux composés aromatiques et hétérocycliques contenant des groups fluorés ont été introduits sur le marché depuis de nombreuses années. Ces composés possèdent un champ d'application large, et traitent une grande variété de cibles *via* des modes d'actions multiples. Certains exemples sont décrits ci-dessous (Figure 4):

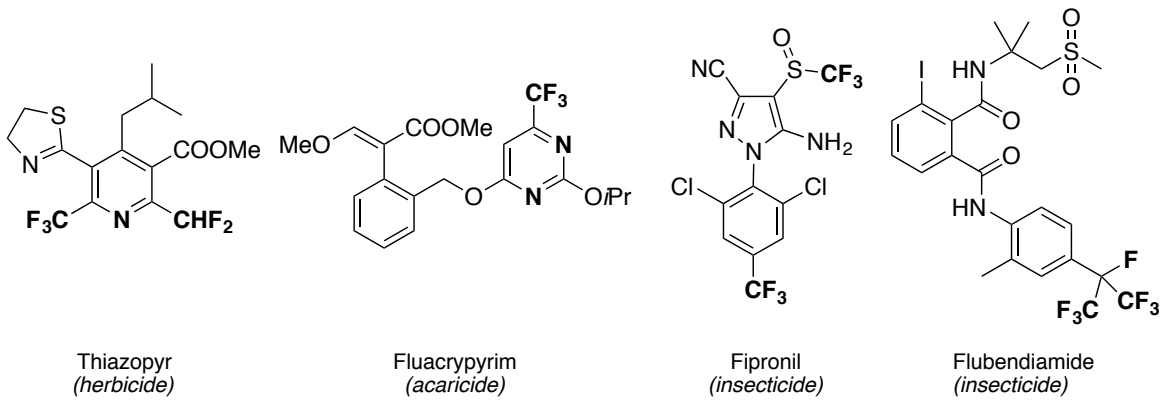


Figure 4: Composés agrochimiques fluorés récemment introduits sur le marché

Chaque classe de composés agrochimiques (herbicides, fongicides, insecticides) possède des composés aux structures chimiques complexes, et sans réelle proximité les unes avec les autres. Ajouté à cela le phénomène de résistance aux traitements développé par certains organismes ou insectes, il y a aujourd'hui un besoin de découvrir de nouvelles structures chimiques pour réussir à restaurer un contrôle sur certaines nuisances de cultures, ou de développer des traitements pour les cibles encore non contrôlées.

Les hétérocycles azotés (pyrazoles, triazoles, pyridines, etc.) tiennent une part importante dans les molécules développées en agrochimie. Les hétérocycles à 5 ou 6 chainons sont hautement représentés dans les composés commercialisés, notamment les pyrazoles, pyridines et pyrimidines.

C. Intérêt des Hétérocycles contenant des Groupe Fluorés Emergents

1. Importance et Effets des Groupes Fluorés Emergents

Depuis quelques années, le développement de nouvelles méthodes de synthèse a permis l'introduction de nouveaux groupes fluorés, tels que le groupe difluorométhyl, etc. Ces nouveaux substituants démontrent progressivement de nouvelles possibilités, et une petite proportion des composés récemment commercialisés contient déjà ces groupes émergents (Figure 5).

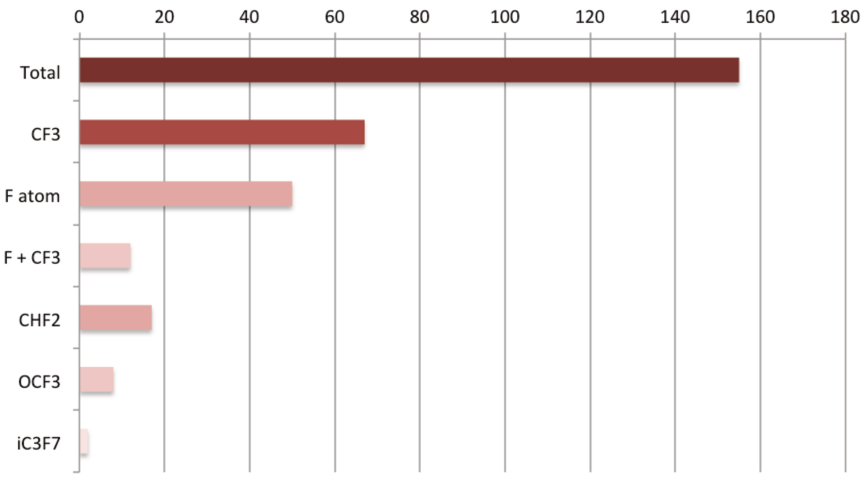


Figure 5: Apparition de nouveaux groups fluorés dans les composes récemment commercialisés

Ces nouveaux groupes fluorés ont démontré un fort potentiel dans le développement de nouveaux agrophores, notamment le groupe difluorométhyl. Certaines molécules vendues sur le marché sont décrites ci-dessous (Figure 6):

La combinaison de groupes fluorés émergents avec des structures hétérocycliques azotées possède un fort potentiel pour le développement de nouvelles molécules bioactives. L'introduction de ces groupes fluorés émergents pourrait donner lieu à de nouvelles possibilités de modification et d'optimisation des propriétés physico-chimiques de molécules actives, ou de la découverte de nouvelles molécules inaccessible jusqu'à maintenant.

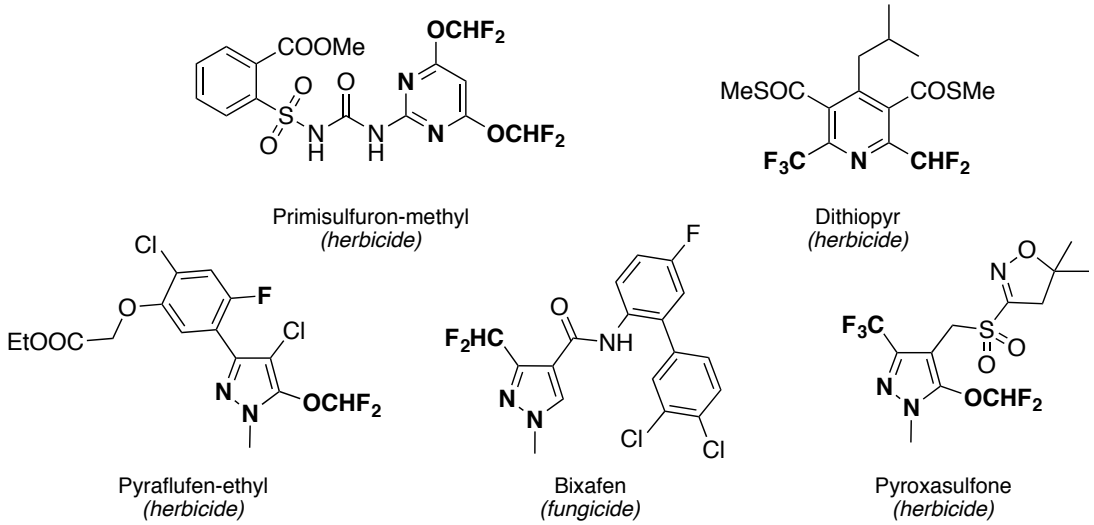


Figure 6: Exemples d'hétérocycles azotés comportant des groupes fluorés émergents récemment commercialisés

Un groupe fluoré émergent a été étudié en priorité, après avoir été récemment employé dans le développement de nouveaux fongicides de dernière génération, ou fongicides SDHI. Un exemple est décrit en Figure 6 (Bixafen, Bayer CropScience).

Le motif CHF_2 est le groupe fluoré émergent le plus représenté dans les composés agrochimiques fluorés récemment commercialisés (Figure 5), du fait de ses propriétés spécifiques. Il possède un caractère électroattracteur similaire au CF_3 avec une capacité de donneur liaisons hydrogène supplémentaire. Son introduction peur permettre à des composés d'avoir une meilleure lipophilie et donc de traverser plus efficacement les membranes cellulaires. C'est un isostère des fonctions alcool ou thiol, avec une polarité similaire.

2. Méthodes de Difluorométhylation

L'introduction du groupement -CHF_2 se fait selon différentes stratégies :

- *via* Déoxofluoration de composés carbonylés
- *via* Difluorométhylation directe (avec transfert du group CHF_2)
- *via* Difluorométhylation indirecte (avec transfert d'un dérivé difluorométhylé et transformation ultérieure en CHF_2)

L'utilisation de réactifs de déoxofluoration est connue mais présente certains désavantages, comme la préparation parfois complexe des composés de départ, ou l'utilisation de réactifs toxiques et chers. Concernant la difluorométhylation directe, de nombreuses équipes de recherche développent des méthodes innovantes pour le transfert de groupe CHF_2 sur des composés aromatiques, mais son introduction dans des hétérocycles azotés reste plus difficile. L'utilisation de réactifs spécifiques et souvent chers est souvent requise. Enfin, la difluorométhylation indirecte a également été largement étudiée, et permet le transfert de groupements –CF_2COOEt, -CF_2SO2Ph, etc. Leur transformation ultérieure n'est pas toujours aisée, et les exemples appliqués à des hétérocycles azotés sont rares.

D. Objectifs de la thèse

Dans ce projet de thèse, nous avons décidé de poursuivre les efforts précédemment réalisés au sein de notre groupe dans le développement de méthodes de synthèse de composés innovants contenant des groupes fluorés émergents, notamment les groupe CHF_2 et OCF_3.

L'objectif était de développer un accès facile, peu cher et efficace à des hétérocycles azotés comportant un ou plusieurs groupes fluorés émergents, à l'aide d'un type de réactifs appelés Fluoroalkyl Amines (ou FARs). En effet, ce type de composés reste difficile à préparer par des méthodes simples et efficaces.

L'étude de la réactivité d'un FAR appelé TFEDMA (ou réactif de Petrov) fut définie comme objectif initial. L'accès à des pyrazoles substitués par des groupes fluorés émergents était également un objectif central. La préparation de building-blocks de type hétérocycles azotés à 6 chainons contenant des groupes fluorés émergents était hautement souhaitée, notamment des cycles de type pyrimidines et pyridines, très répandues dans la recherche pharmaceutique et agrochimique.

Chapitre II

Les FARs comme Nouveaux Outils pour la Synthèse de Pyrazoles et Analogues Comportant des Groupes Fluorés Emergents

Au début du projet de thèse, l'étude des Réactifs de type Fluoroalkyl Amines (ou FARs) fut définie comme un premier objectif, et la TFEDMA (tetrafluoroethyl-*N*,*N*-dimethylamine, ou réactif de Petrov) fut définie comme un FAR modèle. L'étude de sa réactivité a été réalisée sur de nombreux substrats. Deux autres FARs (les réactifs de Yarovenko et d'Ishikawa) furent utilisés à partir de sources commerciales.
Par ailleurs, le développement de nouvelles méthodes pour la préparation de building blocks de type pyrazoles contenant des groupés fluorés émergents était visé. Deux méthodes ont été développées, la première étant la voie azine, la seconde étant la voie cétimines.

A. Réactivité de la TFEDMA

Les FARs possèdent une réactivité spécifique. Après activation avec un acide de Lewis, ces réactifs sont convertis en sels d'iminiums hautement électrophiles (Figure 7) :

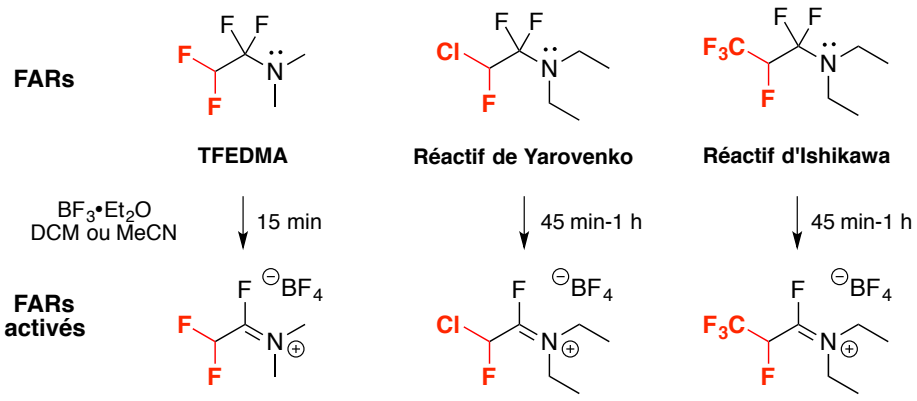


Figure 7: Procédé d'activation des FARs à l'aide d'un acide de Lewis (BF_3•Et_2O)

L'étude de la réactivité de la TFEDMA sous sa forme activée a été réalisée avec une grande variété de substrats (hétérocycles et arenes riches en électrons, éthers vinyliques et dérivés, éthers d'énol silylés, composés CH-acides).
La difluoroacylation d'hétérocycles riches en électrons (pyrrole, furane, thiophène, etc.) a permis la préparation des produits difluoroacylés correspondants. Cette transformation était auparavant très rarement décrite, et aucune méthode directe n'était référencée [a), Figure 8].
Par la suite, la difluoroacylation d'arenes riches en électrons a été développée et a permis la préparation de composés difluoroacylés auparavant difficiles à préparer [b), Figure 8]. Une méthode régiosélective a également été développée à l'aide d'un échange halogène/métal. Les produits préparés étaient également peu décrits dans la littérature précédemment. [c), Figure 8].

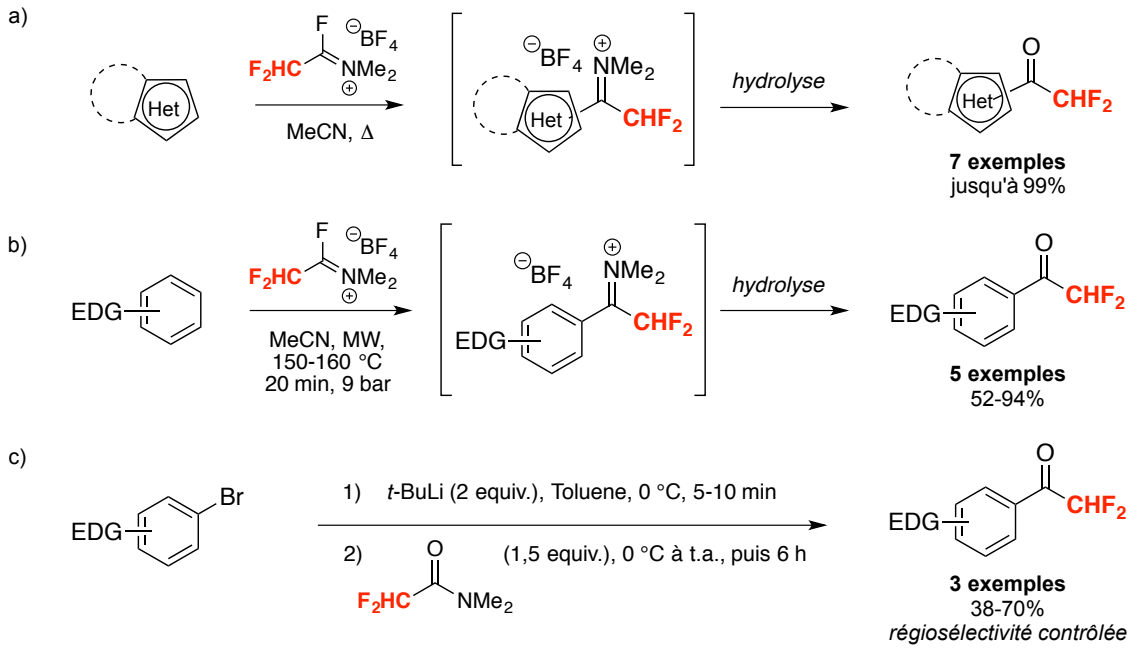


Figure 8: Résultats pour la difluoroacylation d'hétérocycles et d'arènes riches en électrons

La TFEDMA activée a ensuite été confrontée à des composés d'éthers vinylogues, des éthers d'énols silylés ou des composés CH-acides. Une large variété de pyrazoles et d'isoxazoles difluorométhylés en position 3 a été préparée à l'aide de méthodes régiosélectives avec des rendements allant de bons à excellents (Figure 9).

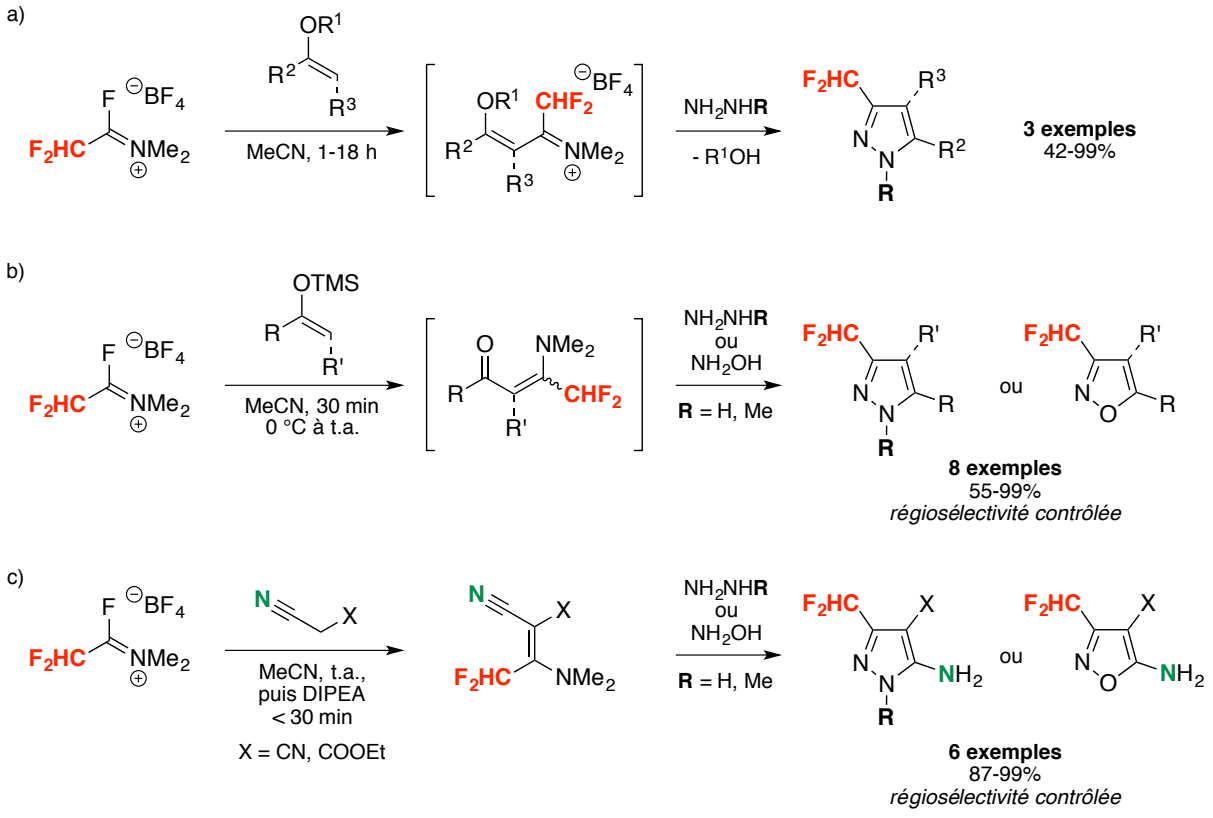


Figure 9: Préparation régiosélective de pyrazole et d'isoxazoles substitués par un CHF_2 en position 3

B. Développement d'un nouveau FAR

À la suite de ce projet, nous avons décidé de réaliser la préparation d'un nouveau FAR à l'aide d'un réactif gazeux disponible commercialement, le trifluoromethyl trifluorovinyl ether (Figure 10). Le rendement global basé sur la quantité de dimethylamine introduite est de 85%.

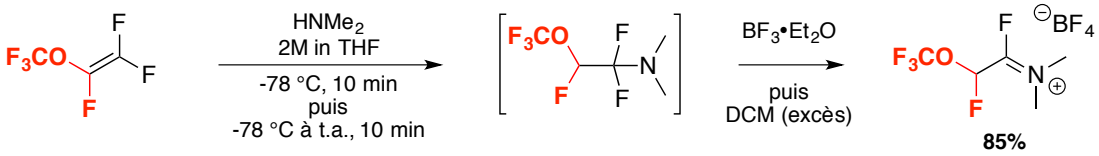
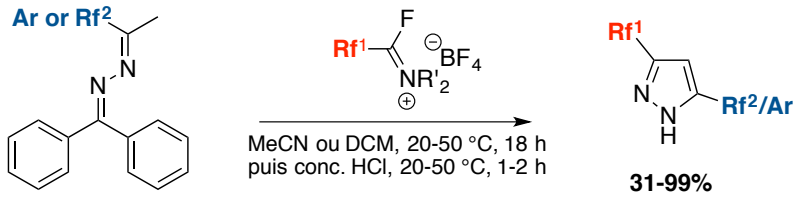


Figure 10: Procédé pour la préparation du nouveau FAR

Ce FAR possède une réactivité similaire à la TFEDMA après activation, et son utilisation sera décrite dans la partie D de ce chapitre.

C. Synthèse de Hétérocycles à 5 chainons Bis-Fluoroalkylés

Un objectif prioritaire de ce projet de thèse fut le développement de building-blocks de type pyrazoles 3,5-bis(fluoroalkylés). Une méthode a été récemment publiée par notre groupe avec un accès final à ces composés, *via* une séquence en 3 étapes (préparation des carboxylates de pyrazole en position 4, saponification et décarboxylation sous conditions sévères). Le développement d'une méthode directe et simple était fortement désiré. Nous sommes parvenu à établir une approche efficace basée sur l'utilisation d'azines fluorées donnant accès aux building-blocks souhaités en une étape. Aucune autre alternative n'avait été décrite auparavant pour préparer ces composés (Figure 11).



Rf^1 = CHF_2, CHFCl, $CHFCF_3$
Rf^2 = CH_2F, CHF_2, CF_3, CHFCl, C_2F_5 Ar = C_6H_4F, $C_6H_4(CF_3)$, $C_6H_4F_2$, $C_6H_3(CF_3)_2$

Figure 11: Préparation de pyrazoles 3,5-bis(fluoroalkyls) par la voie azine

Cette méthode présentant néanmoins quelques désavantages, comme la difficile purification des composés formés, et principalement l'élimination de benzophénone reformée en fin de réaction, une méthode alternative et au fort potentiel a été développée par la suite. Cette alternative est basée sur l'utilisation de cétimines fluorées, préparées à partir de benzylamine. À l'issue de la réaction, cette dernière est bien plus aisée à séparer des produits formés. D'autre part, l'addition d'hydrazines durant la réaction a permis d'introduire une grande diversité de substituants en position 1 du pyrazole.
Cette méthode a également démontré la possibilité de contrôler la formation d'un régioisomère spécifique, dû à une réactivité spécifique des deux intermédiaires clés impliqués dans cette méthode (sel de vinamidinium dans la méthode α, ou vinamide dans les méthodes β ou δ). De plus, la fonctionnalisation de la position 4 du pyrazole a été largement étudiée, avec l'introduction d'un grand nombre de groupes

fonctionnels (voir R'', Figure 12). Enfin, les temps réactionnels ont été fortement raccourcis, et l'étape de purification fortement simplifiée.

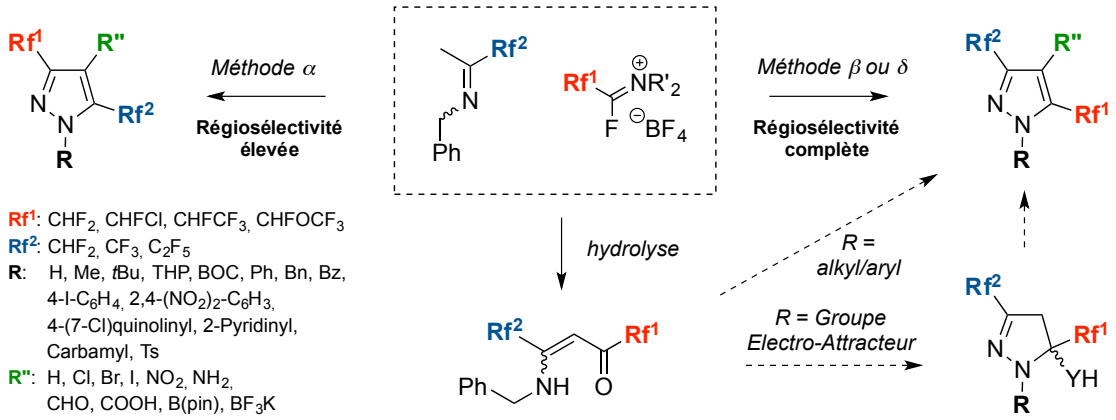


Figure 12: Développement d'une methode donnant régiosélectivement accès à des pyrazoles 3,5-bis(fluoroalkyls)

D. Préparation d'Hétérocycles comportant le motif –CHFOCF$_3$

Le nouveau FAR a été utilisé similairement à l'étude de la TFEDMA, dans la préparation d'hétérocycles comportant le motif -CHFOCF$_3$, très peu décrit dans la littérature. La préparation des adduits clés fut moins efficace que pour la TFEDMA, cependant la préparation des pyrazoles et isoxazoles a fournit des rendement satisfaisants (Figure 13).

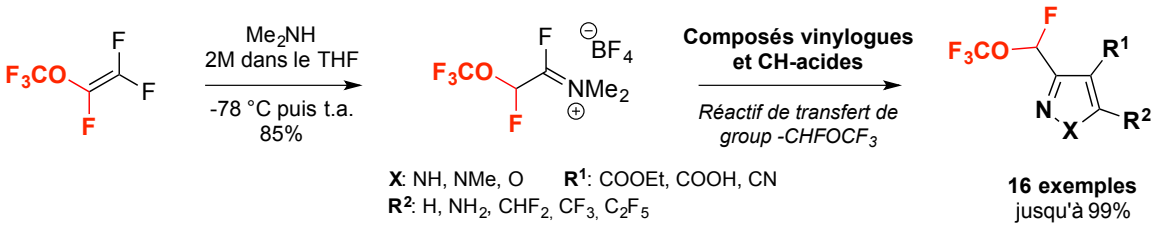


Figure 13: Préparation d'hétérocycles à 5 chaînons à l'aide du nouveau FAR

Par la suite, la synthèse d'analogues d'un intermédiaire clé de la production d'un fongicide SDHI de dernière génération (commercialisé par Bayer CropScience) a été réalisée efficacement avec ce nouveau FAR (Figure 14).

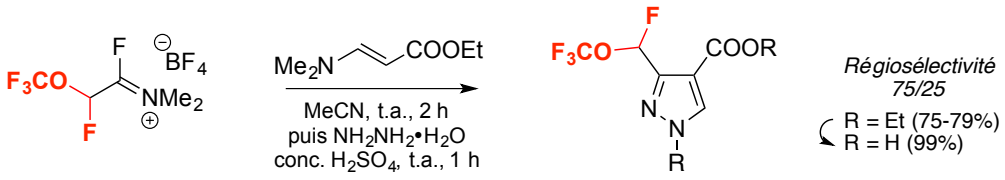


Figure 14: Préparation d'un analogue d'un intermédiaire clé dans la production de Bixafen

E. Préparation d'Hétérocycles Fluoroalkylés sans l'aide des FARs

La préparation de pyrazoles comportant des groups fluorés émergents à partir de FARs a été réalisée efficacement, néanmoins ces réactifs ne sont pas encore répandus dans la communauté scientifique, et la synthèse de composés similaires réalisée sans l'aide des FARs fut attentée. Deux approches ont été développées, une à partie de cétimines fluorées et d'anhydrides fluorés, tous deux faciles d'accès, et l'autre à l'aide de cétimines fluorées et de chlorures d'oxalyle alkylés également répandus. Dans le premier cas, l'accès facile aux pyrazoles 3,5-bis(fluoroalkylés) a été reproduit et amélioré. Dans le second cas, une nouvelle approche a été développée pour la préparation de carboxylates de pyrazoles fluoroalkylés en position 3. Ces composés représentent un intérêt important pour l'industrie, et cette méthode a été protégée dans un brevet (Figure 15).

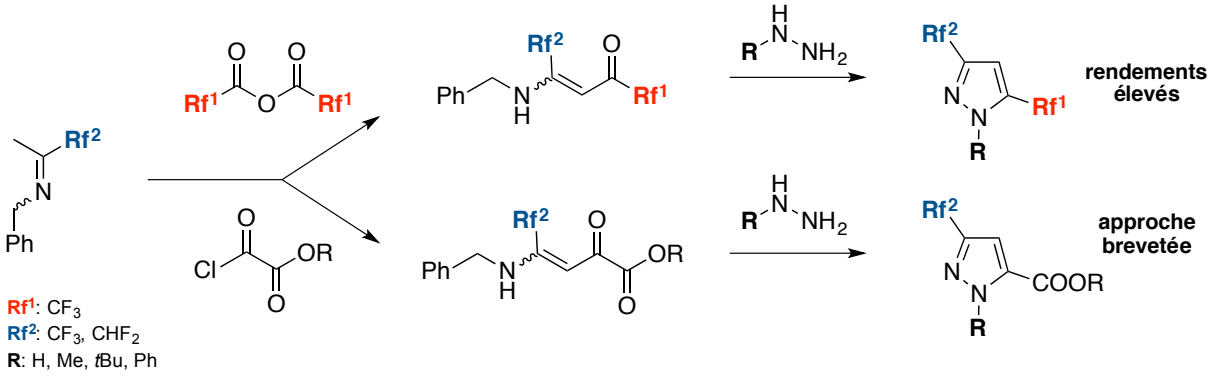


Figure 15: Préparation de pyrazoles fluoroalkylés sans utiliser de FARs

Chapitre III

Les FARs comme Nouveaux Outils pour la Synthèse de Pyrimidines et Pyridines Comportant des Groupes Fluorés Emergents

Dans le chapitre III, l'intérêt a été placé sur la préparation de building blocks de type pyrimidines, puisque la synthèse de pyrimidines comportant des groupes fluorés émergents est extrêmement peu décrite dans la littérature.
Lors du projet précédemment publié dans notre groupe sur la synthèse de carboxylates de pyrazoles 3,5-bis(fluoroalkylés), un intermédiaire sembla posséder un potentiel encore non exploité, et il fut décidé de tenter son isolation. Par la suite, la synthèse de pyrimidines pourra potentiellement se faire par condensation avec des amidines.

A. Synthèse d'Hétérocycles à 6 chainons Mono- et Bis-Fluoroalkylés

La première avancée de ce projet fut l'isolation des intermédiaires clés, auparavant impossible à préparer et conserver.

1. Préparation des Intermédiaires Clés

Les énaminocétones bis(fluoroalkylées) ont été préparées à partie d'acétoacétates fluorés et de FARs activés en présence de pyridine en excès, suivant la procédure récemment développée au sein de notre équipe. Une procédure basée sur des techniques de filtration et d'évaporation de mélanges azéotropiques a pu permettre de préparer cette série d'intermédiaires clés avec des rendements et des puretés élevés.

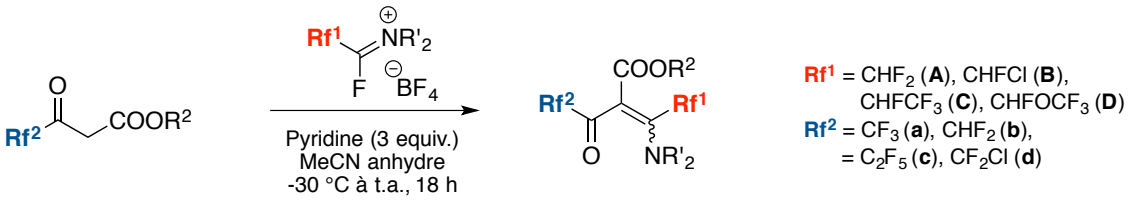


Figure 16: Préparation efficace des intermédiaires clés pour la synthèse de pyrimidines

2. Synthèse des Pyrimidines

Avec ces intermédiaires à disposition, l'optimisation des conditions réactionnelle a pu être réalisée pour la préparation d'un carboxylate de pyrimidine bis(fluoroalkylé) modèle. Les ratios de réactifs engagés, la température et le type de solvant ont été optimisés, et l'utilisation d'irradiation microondes a démontré un impact important et positif. Par la suite, l'utilisation des autres intermédiaires clés a permis la préparation d'exemple de carboxylates de pyrimidines bis(fluoroalkylés) non-symmétriques en série 2-méthyl et 2-phenyl.
L'utilisation d'une grande variété d'amidines a permis d'introduite autant de groupes fonctionnels différents en position 2 en plus des groupes méthyl et phenyl. Des groupes alkyls, aryl, hétéroaryl et même des hétéroatomes fonctionnalisés ont pu être introduits. Les carboxylates de pyrimidines ont pu être saponifiés aisément pour permettre la préparation des acides carboxyliques correspondants. Dans une majorité des cas, les rendements de saponification furent excellents. Quelques exceptions subsistent dans

des cas spécifiques, où une instabilité du substrat sous conditions aqueuses basiques fut observé. Globalement une grande variété de nouveaux composés bis(fluoroalkylés) a été préparée à l'aide d'acétoacétates fluorés et de FARs (Figure 17).

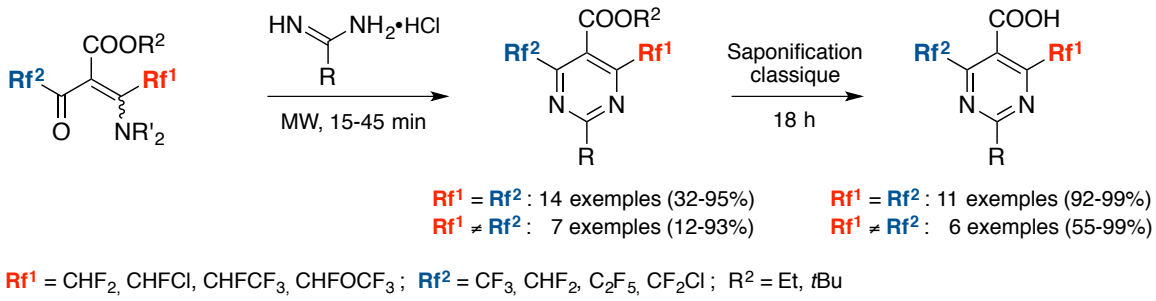


Figure 17: Résumé des résultats pour la preparation de pyrimidines 4,6-bis(fluoroalkylées) comportant un ester ou un acide carboxylique en position 5, et un substituent R en position 2

La combinaison de résultats obtenus dans le chapitre précédent avec ces derniers résultats a permis d'accéder à des composés similaires, de type pyrimidines mono(fluoroalkylés). L'utilisation d'intermédiaires clés utilisés pour la préparation de pyrazoles a également permis de produire des pyrimidines. Ce type de composé est également très peu décrit dans la littérature par construction de cycle. Le champ d'application de cette réaction est actuellement à l'étude dans notre groupe (Figure 18).

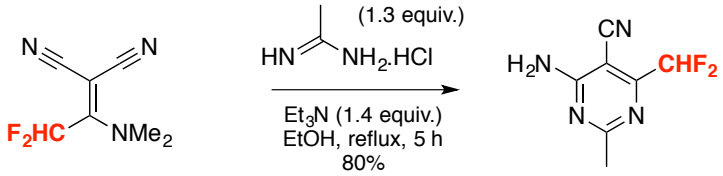


Figure 18: Premier accès à des derives de pyrimidines mono(fluoroalkylées) à l'aide de FARs

Durant ce projet, la préparation d'un intermédiaire clé à l'aide du réactif d'Ishikawa a donné lieu à la formation d'un sous-produit extrêmement intéressant. Par la suite, d'autres exemples ont pu être préparés avec d'excellents rendements. Ce réarrangement donnant lieu à la formation de cyclobutènes hautement fonctionnalisés se déroule selon un mécanisme pas encore prouvé. Cependant, des suppositions ont pu être faites, notamment sur l'aspect thermique du mécanisme, qui pourrait avoir lieu *via* une electrocyclisation conrotatoire. Ce sujet pourrait constituer un thème de recherche fondamentale intéressant (Figure 19).

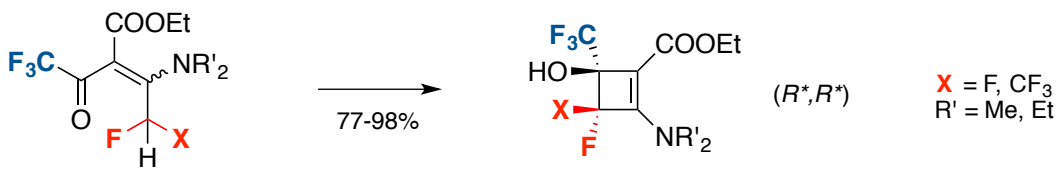


Figure 19: Réarrangement donnant lieu à la formation de cyclobutènes hautement fonctionnalisés

B. Concept de FAR vinylogue

Dans ce chapitre III, un dernier sujet a été approché et des résultats intéressants obtenus. Le développement du concept de FAR vinylogue a été envisagé. Cette idée résulte de travaux publié en 1986 décrivant la préparation d'enamines possédant une chaine perfluoroalkyle. En considérant la réactivité des FARs, on peut concevoir l'introduction d'un groupe alcène entre l'azote et le groupe difluoromethyl, donnant lieu à un FAR vinylogue (Figure 20).

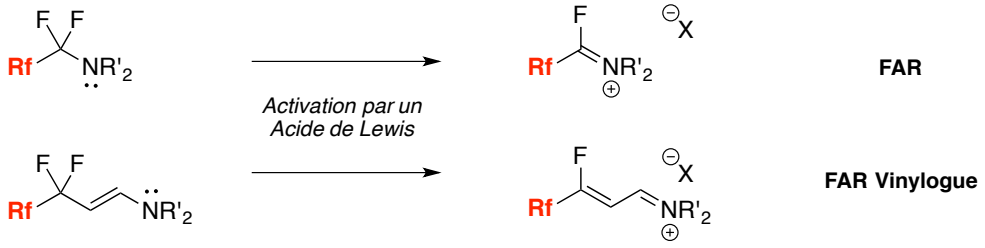


Figure 20: Concept de FAR vinylogue développé et illustré

Après quelques essais préliminaires, il a été possible de développer un procédé *in situ* combinant (1) la préparation du FAR vinylogue, (2) son activation, (3) sa réaction avec un nucléophile, le *N*,*N*-dimethylaminoacrylate d'éthyle, (4) la cyclisation de l'intermédiaire formé en présence d'ammoniaque. Cette séquence a pu fournir le 4-perfluoropropylnicotinate d'éthyle, jamais reporté auparavant. La saponification de ce produit a permis la synthèse de l'acide 4-perfluoropropylnicotinique également jamais décrit (Figure 21).
La procédure a permis d'obtenir un rendement de 38% pour la 1ère étape, et cette dernière pourrait faire l'objet d'une optimisation ultérieure. D'autres iodures de perfluoroalkyle (notamment avec un chlore terminal, et de longueur variables) sont disponibles commercialement, et il pourrait être possible de préparer d'autres analogues d'acide nicotinique.

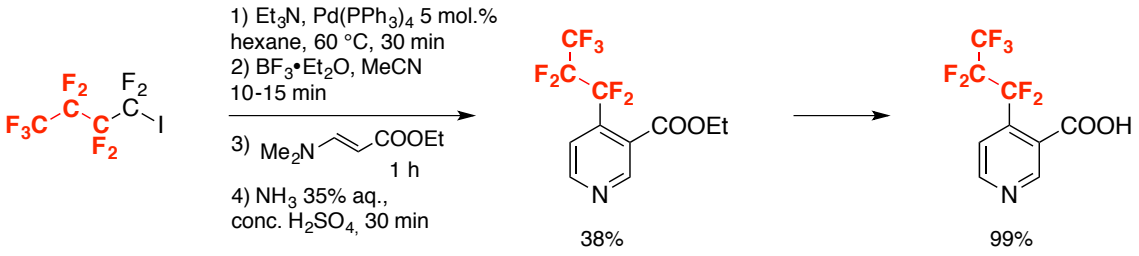


Figure 21: Préparation des formes ester et acide du 4-perfluoropropylnicotinate

Chapitre IV

FARs pour la Synthèse de Pyrazoles Rares Comportant les Groupes Emergents CHF_2 et OCF_3

Dans le chapitre IV, un nouvel objectif a été désigné. L'introduction du groupe OCF_3 étant très rarement décrite sur les pyrazoles, spécialement par construction de cycle, nous avons souhaité nous y intéresser. Un nombre limité de publications récentes a décrit ce type de stratégies à partir d'aryl-acétophénone substituée an *alpha* par un groupe OCF_3, dont la préparation a été récemment facilitée par plusieurs nouvelles méthodes.

Notre défi a été d'utiliser ce type de composés carbonylés en combinaison avec la TFEDMA pour parvenir à introduire à la fois les groupes OCF_3 et CHF_2 sur un pyrazole. Pour ce faire, nous avons utilisé des arylcétones trifluorométhoxylées dont le prix d'achat reste prohibitif, et les avons utilisées avec précaution. La préparation d'intermédiaire clés a été réalisée *via* la préparation des éthers d'énols silylés correspondants. Ce type de substrat a démontré plus tôt dans ce résumé une excellente compatibilité avec les FARs activés, et les essais de transformation directe des aryl-cétones en énaminocétones n'ont pu être réalisés.

A. Préparation des Intermédiaires Clés de type Enaminocétones

Après une phase d'optimisation des conditions réactionnelles, les aryl-énaminocétones correspondantes ont été préparées avec des rendements fortement dépendants de la pureté des réactifs de départ, ainsi que de l'échelle sur laquelle la réaction est lancée (Figure 22). Le rôle de la combinaison d'hydrchlorure d'acétamidine et de triéthylamine n'a pas encore été complètement expliqué. Cependant, seules ces conditions réactionnelles ont pu permettre la préparation efficace de ces intermédiaires. Par ailleurs, ces énaminocétones ont démontré une grande sensibilité, et leur utilisation rapide est nécessaire pour des résultats satisfaisants dans les étapes ultérieures de synthèse d'hétérocycles.

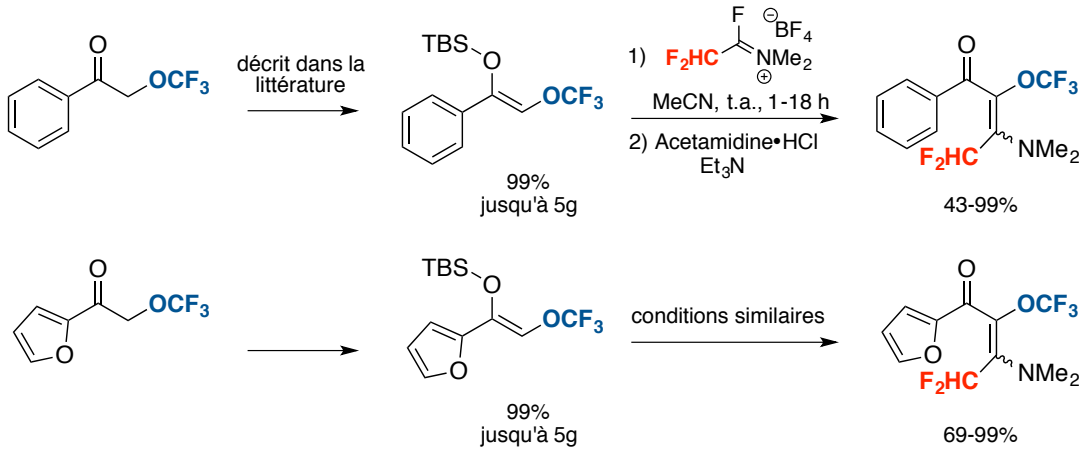


Figure 22: Préparation des intermédiaires clés à partir d'arylcétones trifluorométhoxylées

B. Synthèse d'Hétérocycles Possédant les Groupes OCF_3 et CHF_2

Après avoir préparé les intermédiaires clés de type énaminocétones, leur réactivité de type 1,3-diéletcrophiles ont permis de les convertir en pyrazoles et isoxazoles à l'aide d'hydrazines ou d'hydroxylamine (1,2-dinucléophiles). L'intermédiaire phényl-énaminocétone a été efficacement converti en plusieurs exemples de pyrazoles substitués en position 1 par les groupes méthyl, phényle et *tert*-butoxycarbonyle (ou BOC). Dans le cas du phényl-pyrazole, une proportion de pyrazole possédant un hydrogène en position 4 a été isolée. Dans le cas du BOC-pyrazole, un mélange de diastéréoisomères de pyrazolines a d'abord pu être isolé sans séparation possible. La déshydratation de ce mélange a permis d'isoler le BOC-pyrazole avec un rendement de 35% sur 2 étapes. L'utilisation d'hydroxylamine a conduit à la formation quantitative de l'isoxazoline stable correspondante, qui a fourni une confirmation structurale pas cristallographie. Une étape de déshydratation a conduit à la préparation de l'isoxazole correspondant avec un bon rendement (Figure 23). La régiosélectivité de l'addition d'1,2-dinucléophiles est inversée par rapport aux travaux présentés jusqu'alors. Par ailleurs, une réaction très proche a été publiée récemment à partir d'énaminocétones identiques possédant un hydrogène à la place du groupe CHF_2. La régiosélectivité obtenue était alors l'inverse de celle observée ci-dessous. Ce point reste à résoudre lors d'études ultérieures. De plus, la préparation du *N*H-pyrazole ou de l'analogue de type pyrimidine n'a pu être réalisée.

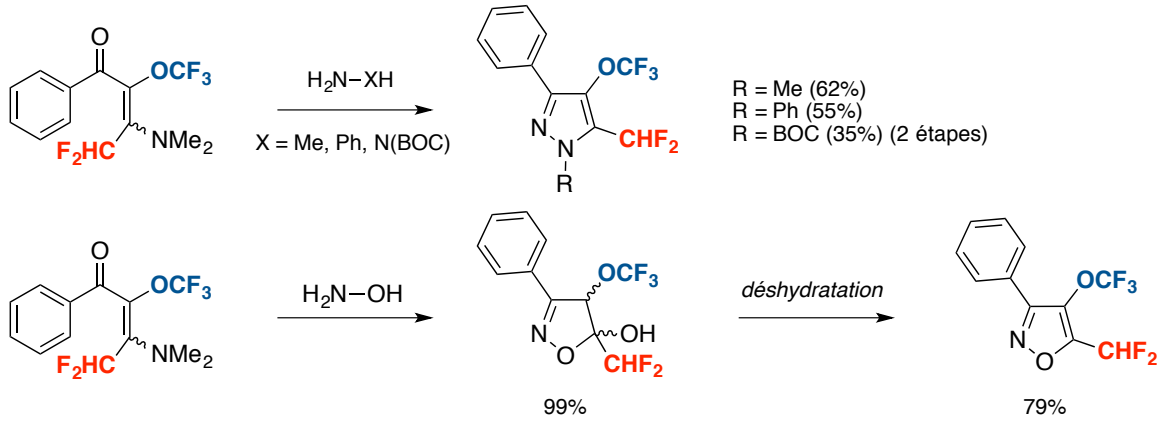


Figure 23: Synthèse d'hétérocycles comportant les groups OCF3 et CHF2 à partir des énaminocétones clés

Enfin, l'intermédiaire furyl-énaminocétone a permis la préparation d'un seul pyrazole possédant un méthyle en position 1. Cet intermédiaire s'est révélé plus difficile à convertir en hétérocycles que l'analogue phényle. Néanmoins, le 3-furyl-pyrazole correspondant a été préparé avec un rendement de 87%. Encore une fois, la pureté des réactifs de départ (notamment l'énaminocétone) a une influence importante sur le rendement et la régiosélectivité à l'issue de la réaction. Le produit correspondant a été converti en acide carboxylique à l'aide d'une méthode connue pour être efficace sur ce type de pyrazoles. La dégradation oxydante du cycle furanique a permis d'accéder pour la première fois à un pyrazole possédant les groupes OCF_3 et CHF_2 en position 4 et 5, et un acide carboxylique en position 3. Cette structure a été confirmée par cristallographie (Figure 24).

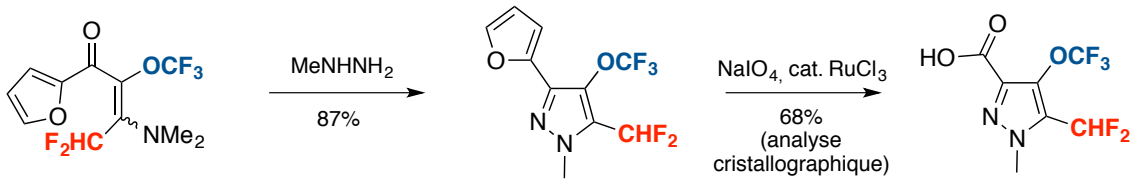


Figure 24: Préparation de l'acide 5-(CHF_2)-1-methyl-4-(OCF_3)-1*H*-pyrazole-3-carboxylique

Perspectives

Concernant les perspectives futures de recherche, la première option est le développement d'autres FARs à partir de précurseurs de type (per)fluoro-alcènes. Une série de réactifs (souvent gazeux) est disponible commercialement, et l'application de la procédure utilisant un gaz liquéfié pourrait être appliquée au développement de futurs FARs (a, Figure 25).

D'autre part, certains intermédiaires ou produits de réactions ont probablement le potentiel de fournir d'autres types d'hétérocycles d'intérêt, notamment les énaminocétones préparées dans le projet cétimine. Ces 1,3-diélectrophiles pourraient potentiellement être condensées avec des amidines, pour donner accès à des building-blocks de type pyrimidine avec une position 5 non-fonctionnalisée, ouvrant le champ aux réactions de métallation, entre autres (b, Figure 25).

Un type de sous-produit obtenu lors de la préparation d'intermédiaires énaminocétones clés (pour la préparation d'hétérocycles fluoroalkylés sans utiliser de FARs) pourrait se révéler utile dans la synthèse de pyridines fluoroalkylées. Cependant, il serait nécessaire de procéder au clivage du groupement benzyle *in situ* pour permettre une aromatisation du cycle (c, Figure 25).

D'autres substrats pourraient se révéler compatibles avec la préparation d'hétérocycles en combinaison avec les FARs, notamment le 2-(dimethylamino)acrylate d'éthyle et ses dérivés (d, Figure 25).

La préparation de pyrimidines mono(fluoroalkylées) comportant des fonctions modifiables en position 4 et 5 ouvre la voie à des transformations possibles menant à de possible dérivés fluoroalkylés de purine, un type de composés quasiment absent de la littérature, et pourtant très « drug-like » (e, Figure 25).

L'étude de la préparation, de l'influence des conditions réactionnelles, du mécanisme réactionnel et des transformations ultérieures des produits de type cyclobutènes obtenus lors du projet Pyrimidines est un projet qui mériterait une attention toute particulière. Ces composés sont totalement absents de la littérature, et leur potentiel dans la découverte de composés biologiquement actifs est totalement inconnu. De plus, cela pourrait être un thème de recherche fondamentale puisque les cycles tendus comportant du fluor sont un sujet actuellement largement étudié (f, Figure 25).

Enfin, le concept de FAR vinylogue a été tout juste débuté, et pourrait donner lieu à de futures recherches sur l'introduction de chaines perfluoroalkyles sur une variété d'hétérocycles azotés et leur effet (g, Figure 25).

D'autres perspectives pourraient être formulées, tant la chimie des FARs est maintenant sur une dynamique nouvelle, et ouvre le champ des possible dans la chimie organofluorée.

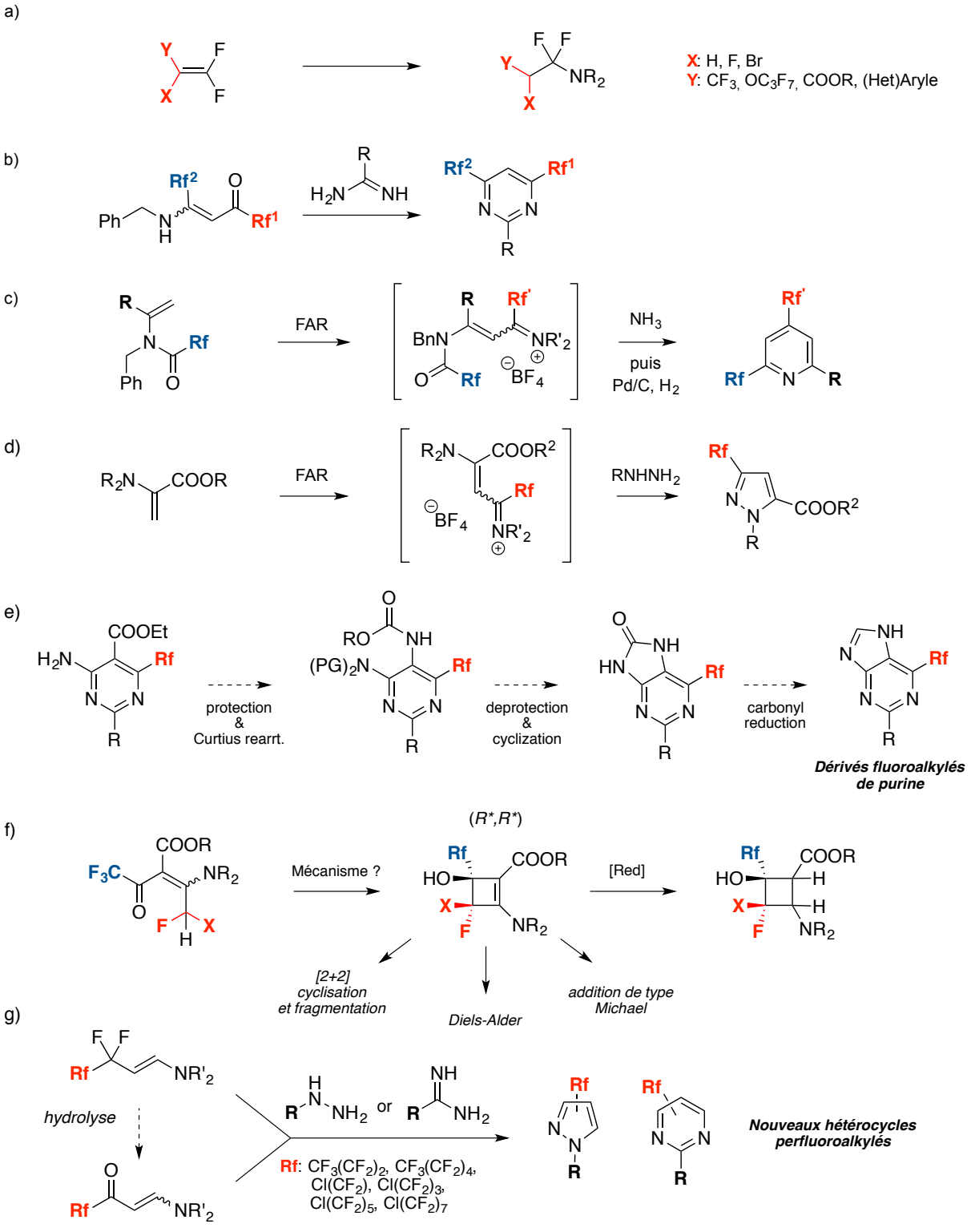


Figure 25: Sommaire des perspectives possibles de l'utilisation des FARs, de leurs produits, ou des FARs vinylogues

Chapter I

Organofluorine Chemistry in Agrochemistry and Pharmaceutical Research

Table of contents

A. Properties of Fluorine

Fluorine is a chemical element with the symbol F and the atomic number Z = 9. It is the 13th most abundant element on earth, generally under mineral form. Its name comes from the Latin verb fluo meaning "to flow", due to the use of Fluorite (CaF_2 also called fluorspar, the primary mineral source of fluorine, firstly described in 1529) as metallurgical flux in smelting processes.

Under standard conditions, fluorine exists as a highly toxic and strongly oxidizing diatomic gas. During the 19th century, many scientists attempted to isolate this element but were either severely injured or even killed by hydrofluoric acid after the experiments. In 1886, the French chemist and pharmacist Henry Moissan successfully isolated fluorine by means of electrolysis at low temperature after a long optimization of the equipment. He was awarded of the Nobel prize in 1906 for this important breakthrough, which led to the introduction of the electrical furnace.[1]

Fluorine is the first most abundant halide on earth, however the majority resides in insoluble minerals [fluorspar (CaF_2) and cryolite (Na_3AlF_6)] and its delivery to aqueous biological systems is limited. As a comparison, the concentration of fluoride in sea water is 1.3 ppm whereas chloride is found at 19000 ppm.[2] Even though massive release of HF in the atmosphere was demonstrated during volcanic eruptions,[3] this atomic element is almost completely excluded from metabolic processes in living organisms.

An explanation resides in the fact that all possible enzymatic mechanisms that would allow the introduction of fluorine are not compatible with its extreme properties (discussed in *atomic properties* section):

- Common enzymatic halogenations usually involving vanadium-dependent halogenases and H_2O_2 are excluded due to the extremely high ionization energy of fluorine (402.15 kcal/mol), which prevents efficient redox transformations to occur.
- Another general enzymatic incorporation of halogens using nucleophilic opening of epoxide intermediates with halide anion cannot occur due to the extraordinary high hydration energy (117 kcal/mol) of fluoride, which behaves as a very poor nucleophile under aqueous biological conditions.
- Another possible pathway for biological halogenation involving radical mechanism could be considered with the fluorine radical, but they are extremely difficult to generate and their violent reactivity would prevent any regio- or chemoselectivity.
- The strength of the C–F bond would require extremely activated intermediates for a facile formation or cleavage, but they would be difficult to generate under biological conditions.[4, 5]

As a consequence, only a dozen of natural compounds or metabolites containing fluorine have been identified, with several of them being highly toxic (*e.g.*: fluoroacetate). A very limited number of plants demonstrated the ability to synthesize fluorinated metabolites from mineral sources of fluorine,[6, 7] explaining the lack of natural sources of fluorinated synthons for research. Recently, the discovery of organofluorine-producing bacterium, *S. cattleya*, has allowed for the elucidation of a biosynthetic pathway for fluoroacetate and fluorothreonine, two important biogenic organofluorines. However, most of the questions concerning natural sources of fluoroorganics remain to elucidate.[4]

The synthetic introduction of fluorine into organic molecules began in the 1890's with the preparation of polyhalogen compounds containing fluorine by the Belgian chemist Frédéric Swarts, who also developed a trifluoromethylation protocol using antimony trifluoride (SbF_3, Swarts reagent). After this initial progress, organofluorine chemistry remained relatively undeveloped until the 1920's due to great difficulties in handling highly reactive and corrosive reagents. Further achievements were made, such as the use of Freons® as new generation of refrigerants in the 1930's, the serendipitous discovery of Teflon (PTFE,

polytetrafluoroethylene) in 1938 followed by huge applications, or the first aromatic fluorination reaction (Balz-Schiemann, 1927), etc.
In the late 1940's, several areas (inhalation anaesthesia, anti-inflammatory agents, central nervous system medication and anti-cancer drugs) used fluorinated compounds with great success, which helped the following development of organofluorine chemistry, especially during and after World War II. Several factors helped in this way, such as the availability of new fluorochemicals, the better handling of F_2 and HF, the development of many new and safe fluorination reagents, and also the success of CF_3-substituted aromatic compounds in medicinal chemistry.[8, 9]

Since the first approval in 1955 by the U.S. Food and Drug Administration (FDA) of a fluorine-containing drug, the steroid fludrocortisone, one to three candidates were launched per year until the early 1980s, and nearly 150 fluorinated molecules have succeeded in reaching the market in pharmaceutical industry.[10, 11]
In the last 10 years, 27% of all approved small molecule drugs contain fluorine,[12, 13] and this figure increased up to 36% in the last 3 years. Fluoroorganic drugs are effective against a very large diversity of diseases, as recently reviewed.[5, 13]

In a context of high global population rising, agrochemicals are more and more significantly considered as a modern solution to improve crop production rates, even though facing new challenges, such as increased efficacy (lower g/ha), reduced environmental impact, etc. The introduction of halogens into agrochemicals has become an important concept in the quest for a modern agrochemical with optimal efficacy, environmental safety, user friendliness and economic viability.[14]

Fluorine plays a critical role in this research,[15, 16] as illustrated by the dramatic increase in the number of fluorinated agrochemicals marketed in the past three decades: from 4% of all listed agrochemicals in 1977, it rose to 15.4% in 2009 [908 compounds, F-containing 140 (15,4 %), The Pesticide Manual, XV Edition], and up to 17.7% in 2014 [920 compounds, F-containing 155 (17,7 %), The Pesticide Manual, XVII Edition].
Interestingly, a differentiation with regard to the level of fluorination shows a statistical pattern:

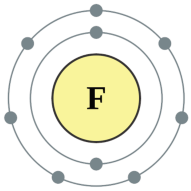
- Fungicides often have about two fluorine atoms,
- Insecticides/acaricides tend to contain four or more fluorine atoms,
- Herbicides often contain three or more fluorine atoms.[17]

To illustrate this, almost 25% of the licensed herbicides (56 compounds from 229) contain at least one fluorine atom, most often present as aryl-F, aryl-CF_3 and aryl-OCF_3 substituents, although aliphatic fluorinated motifs are also represented.[15] The current trend indicates a definite growth to be expected in fluorine-substituted agrochemicals throughout the 21st century.

The most common fluorine-containing groups of agrochemicals are aromatic fluorine, (32%) and aromatic trifluoromethyl (43%) (The Pesticide Manual, XVIIth Edition, 2014). The large development of synthetic techniques for these two fluorinated groups explains this trend, but many other fluorinated substituents are still suffering of under-developed synthetic strategies to prove a larger potential in the development of novel agrochemicals and drugs.

Many reviews and articles discuss the various properties of fluorine. A short summary of the most important points is given below, without being exhaustive.

1. Atomic properties.



Fluorine is the lightest halide of the periodic table, with the electronic configuration $1s^2 2s^2 2p^5$. With a small atomic radius (64 pm) due to its high nuclear charge (9 protons) and a low nuclear shielding, the valence electrons are highly attracted by the nucleus. Consequently, Fluorine has the highest electronegativity of all elements (Pauling's scale: 3.98).[18] Fluorine tends to capture an electron to become isoelectronic to Neon, with a high electron affinity (79.6 kcal/mol).[19] This electron fills the 2p orbital in a compacted atom, and the resultant negative charge is stabilised by the electropositive nucleus, much larger than electrons in more expanded valence orbitals with smaller nuclear charges.[20] The first ionization energy is also very high (402.15 kcal/mol, third-highest among all elements), making it almost non-oxidizable.[21] Fluorine also has the lowest polarizability of all elements,[22] implying very low intermolecular interactions, low surface energies and low refractive indexes for perfluorocarbons.[23] An illustration of this can be observed by comparing the boiling point of iodine (I-I, 184 °C), much higher than the boiling point of fluorine (F-F, –188 °C). Due to a small anionic radius and high negative charge density, the fluoride anion is the smallest anion. It is also the hardest and strongest base of all halides. The nucleophilicity of fluoride is largely influenced by the solvent, especially in SN_2-type reactions. F^- is a poor nucleophile in polar protic solvents (R-OH, etc.) due to high solvation effect, but is a good nucleophile in polar aprotic solvents (MeCN, acetone, DMF, DMSO, etc.) with a much weaker solvation effect.

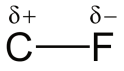
2. Isotopes

Fluorine exists as a single stable isotope (^{19}F with 10 neutrons), and due to a high gyromagnetic ratio, it shows an excellent sensitivity towards magnetic fields. A nuclear spin of ½, a 100% natural abundance, a high sensitivity (83% of proton's case) and a large chemical shift range (500 ppm) offer excellent parameters for NMR spectroscopy.[24]

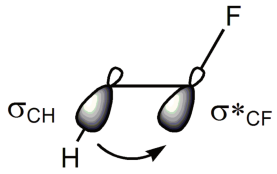
However, ^{18}F (9 neutrons) is an important positron-emitting isotope (half-life of 110 min), produced in a cyclotron after bombardment of ^{18}O-enriched water by high-energy protons (~18 MeV protons). ^{18}F tracers are advantageous because of their longer half-lives compared to the other commonly used radionuclides (^{15}O, 2.07min; ^{13}N, 9.96min; ^{11}C, 20.04min). Positron Emission Tomography (PET) imaging using ^{18}F tracers is a very rapidly developing area in medicinal chemistry. PET can show biological processes, giving metabolic information, but is also an *in vivo* pharmacological imaging tool in drug development, particularly in the areas of biodistribution and drug occupancy studies.[8, 9]

B. Organofluorine chemistry

Nowadays, fluoroorganic chemistry has become essential in the evolution of many different but interconnected research fields (new materials with broad range of applications, *e.g.*: photovoltaic solar cells; diagnostic tools, *e.g.*: positron emission tomography (PET) employing radiotracers labelled with ^{18}F nuclei as previously mentioned; ^{19}F magnetic resonance imaging (MRI) relying on the design and synthesis of polyfluorinated molecules, etc.).[25] The largest impact of fluorine is however observed in medicinal research[5, 8-13, 26] and agrochemistry[15, 17, 26-31].



This is due to the inherent atomic properties of this element. The C-F bond is a polar covalent bond and the second strongest bond in organic chemistry (114.7 kJ/mol) behind Si-F single bond. The high electronegativity of fluorine confers to the C-F bond a significant dipole moment. The electronic density is mostly located on the fluorine atom, while the carbon atom is rather electron-poor, introducing partial charges ($C\delta^+$---$F\delta^-$), which are attractive and contribute to the bond strength. Consequently, the length of C-F bond is short (around 1.35-1.40 Å).[22]



The addition of geminal fluorine atom(s) on the same carbon increase the partial charges involved in the electrostatic interactions as well as the ionic character of the bonds, increasing their strength. This phenomenon is called the bond strength effect of geminal bonds. In the case of vicinal fluorine atoms located in an alkyl chain, a *gauche effect* has been described as a phenomenon of stabilization of gauche conformers (2.4 to 3.4 kJ/mol more stable than *anti* conformers, usually more stable) due to hyperconjugation and bent bonds.[32, 33]

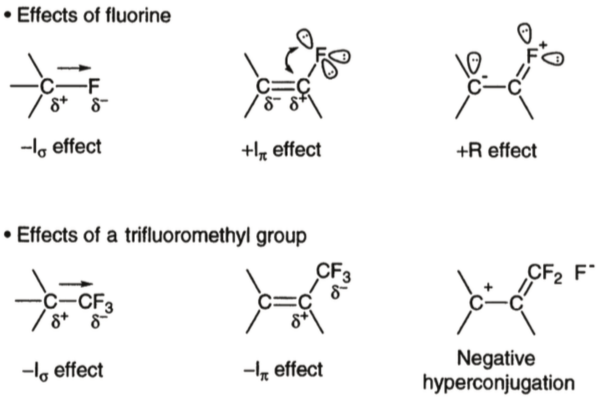


Figure I.1: Electronic effects of fluorine-containing substituents.

The presence of fluorine-containing substituents has peculiar electronic effects on the adjacent bonds. The fluorine substituent having three non-bonding electronic pairs, tightly bound to the nucleus, is responsible of electronic effects of two types:

- "Push" effects: +M or +Iπ effects in aromatic systems, Stabilization of α-carbocations ($^{+}CHF_2 > {}^{+}CH_2F > {}^{+}CF_3 > {}^{+}CH_3$)
- "Pull" effects: Destabilization of β-carbocations, possible negative (or anionic) hyperconjugation.

Adjacent C-C single bonds are strengthened by fluorination, whereas allylic C=C double bonds are weakened. Fluorination of acetylenes is always highly destabilizing (Figure I.1).

Due to very high C-C and C-F bond strength, polyfluorocarbons possess enhanced thermal and chemical stabilities in comparison with their non-fluorinated analogues. The small size of the fluorine atom [Van der Waals radius of 1.47 Å, between oxygen (1.57 Å) and hydrogen (1.20 Å)] close to the size of hydrogen (1.2 Å) combined with short C-F bond length causes little steric strain in polyfluorinated compounds (Figure I.2). The effect of fluorination on bond strengths, stabilities of reactive intermediates and steric interactions is a question already discussed in the literature,[23] but one can understand that these effects can in certain cases be highly profitable in the tuning of specific electrostatic interactions or pharmacokinetic properties of drug candidates or agrochemical candidates.

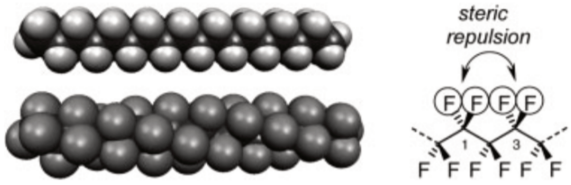


Figure I.2: Zigzag conformation of octadecane (top) versus helical conformation of perfluorooctadecane (bottom)

The overall electronic distribution and also the global dipole moment are significantly altered, due to high electronegativity of fluorine (Figure I.3).

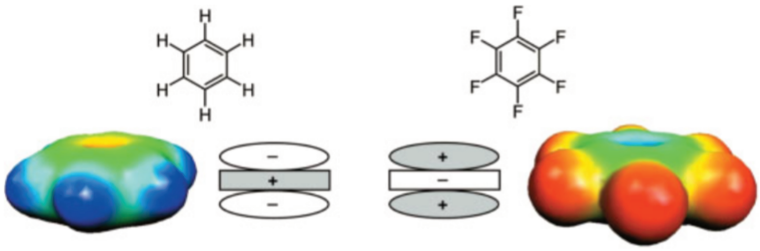


Figure I.3: Illustration of the impact on the electronic distribution of the replacement of Hydrogen by Fluorine into a molecule (largest negative charge density coded in red, positive partial charge coded in blue).[22]

Generally, fluorination of aromatics or of positions engaged in π-electrons systems *increase* lipophilicity, whereas fluorination/trifluoromethylation of saturated aliphatic chains *decrease* lipophilicity due to higher dipole moments and thus polarity. The presence of ω-fluoroalkyl groups (with one uncompensated C–F dipole moment) *decrease* lipophilicity, similarly to compounds with α-fluorocarbonyl groups (with increased electrophilicity of the carbonyl carbon atom), which can form more easily stable and polar hydrates.

The modification of global or local dipole moment(s) of the molecule combined with steric variations can have an effect of conformational modification(s); Methoxybenzene and trifluoromethoxybenzene do not

adopt similar ground state conformations (methoxy is planar while trifluoromethoxy is out of the plane, dihedral angle for C–C–O–C up to 90°).[34]

In modern agro- and medicinal chemistry, bioisosteres have been adopted as a fundamental tactical approach useful to tune various characteristics of a candidate (size, conformation, electronic distribution, polarizability, dipole, polarity, lipophilicity, pKa), thus playing a key role in molecular recognition and mimicry, improving potency, selectivity and physical properties, reducing or redirecting metabolism, eliminating or modifying toxicophores, as well as acquiring novel intellectual property. A careful selection and tailoring of an isostere is necessary as one modification can be beneficial for one target and deleterious for another.

Some groups are metabolically unstable or degrade to toxic metabolites. They can be ‘‘mimicked’’ by F-containing analogues using suitable ‘‘bioisosteric’’ replacements. This not only mimics the geometry of another functional group but also models the polarity and electrostatic charge distribution of the “original”. The biological target structure should not discriminate between the congener and the bioisosteric mimic. The electronic effect of a selection of these fluorinated mimics is listed above (Figure I.4) and can be compared with non-fluorinated substituents.

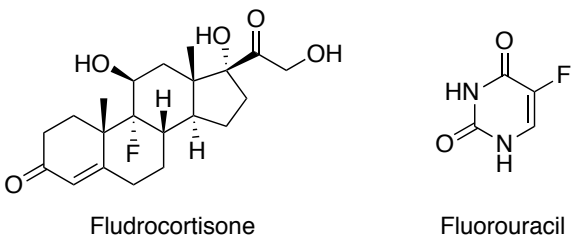
Substituent X	σ_m	σ_p	σ_I	σ_R	Π_p
*t*Bu	-0.10	-0.20	-	-	+1.68
CH_3	-0.07	-0.17	-	-	+0.56
H	0	0	-	-	0
OCH_3	+0.12	-0.27	-	-	-0.04
OH	+0.12	-0.37	-	-	-
F	+0.34	+0.06	-	-	+0.14
Cl	+0.37	+0.23	-	-	+0.71
$COCH_3$	+0.38	+0.50	-	-	-
OCF_3	+0.38	+0.35	-	-	+1.04
Br	+0.39	+0.23	-	-	-
CF_3	+0.41	+0.53	+0.39	+0.12	+0.88
SCF_3	+0.44	+0.48	+0.41	+0.07	+1.44
CN	+0.56	+0.66	-	-	-
SF_5	+0.61	+0.68	+0.55	+0.11	+1.23
trans-SF_4CF_3	-	+0.68	-	-	+2.13
OSF_5	-	+0.44	-	-	-
NO_2	+0.71	+0.78	-	-	-0.28
$SOCF_3$	+0.77	+0.85	+0.69	+0.16	-
SO_2CF_3	+1.01	+1.17	+0.84	+0.34	+0.55
$S(CF_3)NSO_2CF_3$	+1.27	+1.39	+1.15	+0.24	-
$SO(CF_3)NSO_2CF_3$	+1.36	+1.55	+1.17	+0.38	-
$SF(NSO_2CF_3)_2$	-	+1.78	+1.37	+0.41	-

Figure I.4: Comparison of Hammet’s constants (σ) and lipophilicity increments (π) for various substituents[35]

Due to the properties of fluorine,[36] organofluorine chemistry has become essential in the development of bioactive small molecules, and the interest for emergent fluorinated groups (EFSs) is becoming more and more important. Several fluorinated substituents (F, CF_3, OCF_3, SCF_3, etc.) have been studied and their influence into a molecule has been partially addressed.[23] Many EFSs are not included in the tables describing related physico-chemical properties, as the introduction of groups such as CHF_2, $CHFCF_3$, CHFCl, CF_2Cl, CF_2Br, etc. is very often challenging; consequently, no systematic study has ever been produced for these groups. Emergent fluorinated substituents (EFSs) will be included in the bioisostere toolbox for agro- and medicinal research after a period of technical development to facilitate their introduction in various substrates. The content of this manuscript will try to contribute to this aspect.[37]

1. Interest of fluorinated compounds in Life Science

In late 1940–1950s, the introduction of fluorine into molecules for pharmaceutical or agrochemical research was not considered at all, as the element was excluded from biological mechanisms and known as highly dangerous, scientists using fluorine for military and special materials applications only. The first drug containing fluorine - fludrocortisone, was developed in 1955 (displaying high glucocorticoid activity), followed in 1957 by 5-fluorouracil, an antimetabolite of uracil showing tumour inhibitory properties.[38]



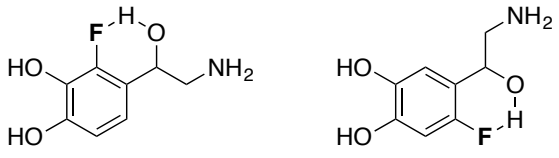
Fludrocortisone Fluorouracil

Figure I.5: First fluorinated drugs commercialized

These two drugs triggered a new era in the research of biologically active compounds, after understanding that fluorine could be a powerful tool to tune the properties of bioactive molecules (Figure I.5). Presently, in pharmaceutical industry, one third of the top 30 best selling pharmaceutical products contain at least one fluorine atom (US Sales in 2008), and 30% of the leading blockbuster pharmaceuticals contain fluorine. Lipitor (Atorvastatin) is currently the biggest selling pharmaceutical with sales of 5.9 billion $ in 2008.[12] In agrochemistry, as previously mentioned, up to 17,7% of the reported agrochemicals contain fluorine (The Pesticide Manual, XVII Edition). But why introducing fluorine into a bioactive molecule can lead to such beneficial outcomes?

In pharmaceutical industry, fluorine is often introduced into organic structures during lead optimisation studies as a strategy to block metabolism, to increase lipophilicity (logP) or to tune pharmacokinetic properties. The presence of fluorine atom(s) into a molecule has important effects:

- pKa values of neighbouring acidic groups (alcohols, carboxylic acids, amides) are decreased, and increased for neighbouring basic functional groups (amines, ethers, carbonyls).[23]
- Water solubility is consequently influenced by polarity and/or pKa changes.
- The presence of C-F bond(s) generally increases the lipophilicity, which often governs the absorption, transport and receptor binding affinity.
- The bioavailability is increased due to a facilitated transport through cell membranes.
- For bioactive molecules, the change in dipole moment alters the binding affinity for a receptor due to modified electrostatic interactions.
- The C–F bond can participate in weak hydrogen bonding, as it is highly non-polarizable. To illustrate this, we can observe the different modes of actions of two isomers of fluoronorepinephrine (F-NE). The 2F-isomer is an α-adrenergic agonist, whilst the 6F-isomer is a β-adrenergic agonist (see below).



2F-NE: β-agonist 6F-NE: α-agonist

- The metabolic stability is potentially increased, mainly by lowering the neighbouring moieties' susceptibility to cytochrome p450 enzymatic oxidation (Figure I.6).[10]

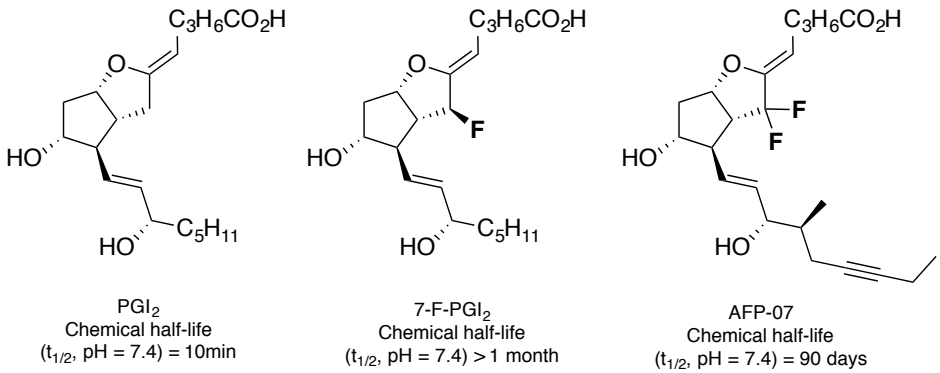


Figure I.6: Influence of the introduction of fluorine in positions susceptible to metabolic oxidation

The introduction of a suitable fluoroalkyl group (e.g.: CF_3) onto a likely site of metabolic degradation has been described as a strategy to destabilize the necessary protonated transition state, preventing the decomposition and increasing dramatically the bioavailability of the compound.[39]

Oxidative metabolism of phenyl rings is a common problem, and fluorine substitution, usually at the *para*-position, has become a widespread practice to increase stability in various substance classes. Trifluoromethyl and trifluoromethoxy groups (CF_3 or OCF_3) are known to be very stable and enhancing the degradative stability of biologically active molecules or fragments. The presence of electron-withdrawing groups such as CCl_3, CF_3, OCF_3, $OCHF_2$, $C(O)CF_3$ or $S(O)_2CF_3$ may stabilise an aromatic ring towards oxidative (or electrophilic) attacks, but their excessive presence may cause nucleophilic attack.

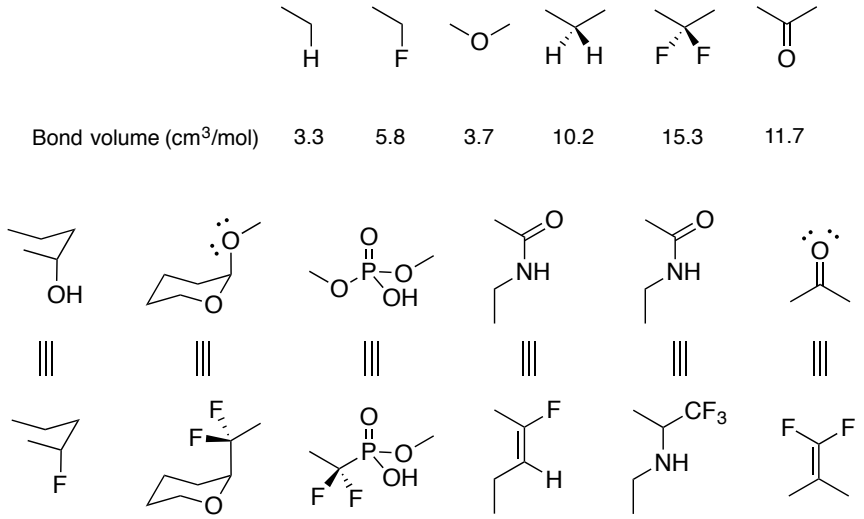


Figure I.7: bond volumes of several common bond (top) and known related bioisosteric mimicking (bottom)

Introducing fluoroalkyl groups is used to mimic functional groups that present specific disadvantages, such as weakness towards metabolic degradation, undesired influence on the physicochemical properties of a candidate, toxicity, etc. Selected functional group replacement can be achieved to improve the physico-chemical properties of the candidate, with little spatial modification (by maintaining the size and polarity of the replacing group) (Figure I.7). Developing new EFSs could lead to new bioisosteres, which could be used for random screening in lead optimization stages.

2. Safety concerns about fluorinated organic compounds

The introduction of fluorine and fluorinated groups has demonstrated great potential in the discovery of new bioactive molecules or analogues of natural products and already marketed ingredients. However, despite the huge interest of scientists for new fluorinated (and non-fluorinated) bioactive molecules in medicinal and agrochemical research, the extreme properties of fluorine, such as the strength of C-F bond, and consequently the longer lifetime of these compounds in the environment, it is important to open the question of biopersistance and environmental effects of these new molecules.

The use of low-boiling chlorofluorocarbons and perfluoroalkanes (potent greenhouse gases) has been covered by Montreal and Kyoto protocols, limiting and even diminishing the atmospheric concentrations of these important greenhouse and ozone-depleting gases.

However, some perfluorosurfactants (PFS) [such as persistent perfluoroalkyl carboxylates (PFCAs) and perfluoroalkyl sulfonates (PFSAs)] have caught the attention of regulatory agencies, because of their capacity to bioaccumulate in living organisms, toxicity, and widespread occurrence in the blood of populations[40] and wildlife. Many scientists suggest a constant monitoring of these PFSs and PFSAs, even though a lack of knowledge concerning the transport, accumulation, biodegradation, temporal and spatial trends and PFS precursors has been identified.[41, 42]

Concerning fluorinated pharmaceuticals (antibiotics, antidepressants), they have been found in treated city sewage and wastewater.[43] The evolution of several agrochemicals in the soil has been studied and a limited degradation process was observed with fluorinated substituents such as trifluoromethyl, etc. [44]
The toxicity of pesticides is nowadays a critical aspect of agrochemistry business, as the public demands more and more ecological and environmentally friendly products. The toxicity is evaluated for any new active ingredient to be marketed, and new analytical methods are also developed. This aspect is no longer negligible in a context of global warming and ecology-oriented public opinion.[45-47]
All the fluoroorganic compounds deserve the same risk assessment than any other anthropogenic chemical being used in a sufficient quantity to represent a risk equally for humans or wildlife.

3. Fluorinated compounds in Agrochemistry

Agrochemical products are extensively studied and employed in modern agriculture to satisfy increasing demands (strict regulatory requirements, growing population). Insecticides/acaricides, herbicides, and fungicides play an important role in modern agriculture by increasing crop qualities and yields (*e.g.*: rice, corn, fruits, and vegetables), and diminish labour costs. New agrochemicals have to be more efficacious, and to possess better safety profiles and novel modes of action (MoA) (to avoid resistance phenomenon), and this requires new chemical substructures. Similarly to Lipinski's rule of five in pharmaceutical research,[48] bioavailability guidelines for agrochemical leads discovery was developed by Briggs (and reported by Tice)[49]. An analysis of bioavailability parameters of marketed agrochemicals was achieved and a 'Rule of Three' was proposed for the selection of compounds for high throughput *in vivo* screening.[50] Compounds are likely to be active in *in vivo* agrochemical screening if:

- MWt = 300 ± 100 g/mol
- log P = 3 ± 3
- ΔlogP ≤3
- Number of H-bond donors: ≤3
- M.p. ≤ 300 °C
- Equivalent hydrocarbon (EH) number = 30 ± 5.

New agrochemical discovery is based on the exploitation of a bioactive lead compound. The existing methods for discovering bioactive lead compounds are:

- "Me too chemistry" (molecules with structures similar to those of existing products)
- Random synthesis and screening
- Modification of natural compounds
- Combinatorial chemistry (based on pre-screening of virtual libraries prior to synthesis and HTS)
- Rational design (Protein structure based design)

From 2000 to 2013, 70% of 126 new synthetic agrochemicals were developed by "me too chemistry" and 30% by random synthesis and screening. For example, Diflufenicanil (herbicide) and Flonicamid (insecticide), discovered by Random Synthesis and Screening, and Haloxyfop (herbicide), discovered *via* "Me Too Chemistry", are examples of fluorinated agrochemicals discovery using general methods (Figure I.8).[51]

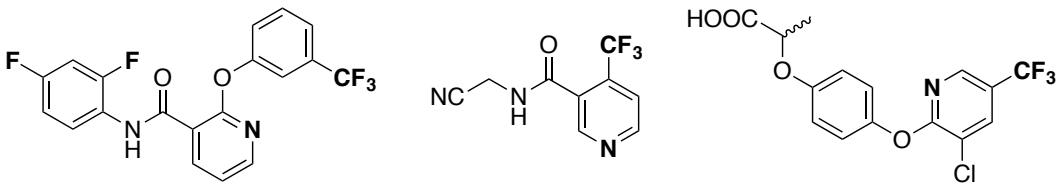


Figure I.8: Recently developed fluorinated agrochemicals

Both methods require high investment in time and human resources, with decreasing success rates for new agrochemical discovery. Furthermore, agro- and pharmaceutical companies tend to protect more severely than ever their intellectual properties, and "me too chemistry", which is often based on bioisosteric replacement, becomes more and more difficult to exploit.[52] The development of new fluorinated structures could give a new breath to this field. Combinatorial technology proved poor efficacy in the past years, but has enormously evolved with much greater emphasis for biology-oriented library design. Reports describing commercial pharmaceuticals discovered by means of combinatorial

approaches are starting to appear,[53] but one can only find reports of field candidates discovered using this method in agrochemistry.[54] The poor results of rational design strategies is related to the lack of reliable models for targeted active sites, a known issue in this research field. However, as genetic sequencing of increasing numbers of organisms is being performed, more readily accessible structural data could help structure-based inhibitor design to become a common approach to lead generation in agrochemistry.[55]
New methods were recently imagined to increase the efficiency of innovative agrochemicals design, combining conventional techniques and recent novel methods reported in the pharmaceutical field:

- Common Intermediate Method (CIM): Modification of key building blocks.
- Terminal Group Replacement Method (TRM): Modification of key intermediates by replacing terminal moieties
- Active compound Derivatization Method (ADM): Modification of known active compounds bearing specific tuneable functional groups.

Modern techniques (fragment-based design, virtual screening, and genome sequencing, developed primarily in the pharmaceutical or biotechnology industries) have been successfully applied for the generation of drug leads, but published examples of fragment-based design in the agrochemical context have been comparatively rare.[56] The overall remark is that researchers seek intensively for new ideas and methods for designing valuable compounds. The development of novel synthetic strategies for the introduction of new functional groups (*e.g.*: emergent fluorinated groups), potentially providing enhanced physico-chemical properties and original alternatives in the researchers' toolbox, can be of great help in this field.

While pharmaceutical leads usually have inhibitory activity against an enzyme or (ant)agonistic activity against a receptor, *i.e. in vitro* activity, agrochemical leads are expected to show activity against a (living) target organism, *i.e. in vivo* activity. It is therefore unnecessary to achieve costly *in-vitro* evaluations, as required before pharmaceutical leads can be tested in humans (their target organisms). The transition to field tests is a significant barrier which most of leads fail to pass even after optimisation work. Early *in vivo* activity studies (under glasshouse conditions or in artificial *in vivo* HTS) are used as an initial 'filter', before *in vitro* activity studies being carried out at a later stage (under greenhouse conditions). The dramatic effect of fluorine on the biological activity of numerous herbicides, insecticides, and fungicides has earned fluorine a unique place in the toolbox of the agrochemist.

Another critical aspect of the discovery of agrochemical leads is that their (biochemical) mode of action (MoA) has to be established for the registration of a new agrochemical product,[55] and this requires isolation and characterisation of the molecular target, *i.e.* an enzyme or receptor. Several MoAs where fluorination (or halogenation) showed a great influence are described below:[14]

- **Insecticides**
  - Voltage-gated sodium channel (vgSoCh), targeted by pyrethroids (*e.g.*: Flumethrin[57]) and oxadiazines (*e.g.*: Indoxacarb[58]), which block the nerve signal by prolonging the sodium channel's opening. Insect and vertebrate channels are pharmacologically distinguishable.[59, 60]
  - Nicotinic acetylcholine receptors (nAChRs), targeted by the well-known neonicotinoids (usually non-fluorinated),[28, 59-62] which in high doses overstimulate and block insects' nAChRs causing paralysis and death.
  - Ryanodine receptor (RyR), targeted by ryanoids such as diamides (*e.g.*: flubendiamide, completely inactive on mammalian RyR subtypes, Figure I.17).[63] RyRs are ligand-gated calcium channels controlling the release of calcium from intracellular stores, controlling muscles contraction.
  - Chitin biosynthesis, targeted by Insect Growth Regulators (IGRs, *e.g.*: hexaflumuron, Figure IV.3); IGRs prevent an insect from reaching maturity by interfering with the molting process by mimicking/inhibiting the juvenile hormone (JH), one of the two major hormones involved in insect molting.
  - Etc.
- **Fungicides**
  - Sterol biosynthesis (sterol-C14-demethylase); targeted by De-Methylation Inhibitors (or DMI's), a class of azoles [*e.g.*: epoxiconazole, tetraconazole (Figure IV.3)] targeting cell membrane integrity by inhibiting C14 demethylation during sterol formation.[64-66]
  - Respiratory chain:
    - Q_o-site of complex III or cytochrome bc_1 complex; targeted by Q_0 inhitors (or Q_0I's) strobilurins [*e.g.*: Picoxystrobin (Figure I.10), or related Trifloxystrobin] inhibiting mitochondrial respiration.[67]
    - Complex II, succinate dehydrogenase, targeted by Succinate Dehydrogenase Inhibitors (SDHIs) of *cis*-crotonanilide type, or more recently *N*-methyl pyrazole carboxamides (*e.g.*: Bixafen, Bayer CropScience, further discussed in this manuscript). All these carboxamides interfere with ubiquinone binding and affect three subunits of succinate dehydrogenase.[68]
  - Spectrine-like protein; affected by acylpicolides (*e.g.*: Fluopicolide, Bayer CS), with an unknown MoA.
  - Etc.
- **Herbicides**
  - Carotenoid biosynthesis: targeted by PDS (phytoene desaturase) inhibitors (*e.g.*: Diflufenicanil, Figure I.8). A lack of carotenoids - photo-protecting agents quenching singlet oxygen - damages chlorophyll.[69]
  - Cell growth and division: targeted by "K_3 herbicides" oxyacetamides (*e.g.*: Flufenacet, 1998, Axiom®) and tetrazolinones; inhibition of Very Long Chain Fatty Acids (VLCFAs) biosynthesis *via* covalent binding between the herbicide and the membrane-bound multienzyme acyl-CoA elongase system, the target enzyme.[70, 71]
  - Acetolactate synthase (ALS) [also known as Acetohydroxyacid synthase (AHAS)]: targeted by sulfonylureas (*e.g.*: Prosulfuron), extremely potent inhibitors of ALS, a key enzyme for the biosynthesis of branched amino acids such as leucine (Leu), isoleucine (Ile) or valine (Val).
  - Protoporphyrinogene oxidase (PPO): targeted by PPO (or Protox) inhibitors like fluoro-substituted uracil [*e.g.*: uracil derivatives (Figure I.13), triazolinones and pyrazoles (Figure I.14)]. After PPO inhibition, highly reactive oxygen radicals are formed in plants, causing cell membrane breakage.
  - ACCase (Acetyl CoA carboxylase): targeted by ACCase inhibitors like Haloxyfop-P-methyl (Figure I.8). This essential enzyme is involved in the biosynthesis of essential fatty acids.
  - 4-Hydroxyphenylpyruvate dioxygenase (HPPD); targeted by HPPD inhibitors (*e.g.*: Bicyclopyrone). This crucial enzyme catalyses the catabolism of tyrosine.
  - Etc.

Other fluorinated active ingredients possessing different MoA are referenced, an exhaustive list cannot be proposed in this manuscript, the objective being only to expose the opportunities given by the introduction of known fluorinated groups, and to outline the potential of unknown emergent fluorinated substituents.

Emergent fluorinated substituents could bring new MoA, high potency, enhanced physicochemical properties, increased metabolic stability if introduced in a bioactive candidate, or even in a new structure. The complexity of the Structure-Activity Relationship (SAR) in the field of agrochemicals makes predictions of sites where fluorine (or halogens) will increase biological efficacy very difficult.
These emergent groups could also provide new compounds for pharmaceutical research.

To illustrate the potential of new fluorinated substituents in agrochemical research (and by extension medicinal research), a few examples of marketed bioactive compounds bearing classical or more "exotic" fluorinated groups are described below:

For example, the use of a common fluorinated building block (3-chloro-5-trifluoromethyl-2-pyridinyl residue) on different structures showed bioactive molecules having different MoA and targeting different organisms (Figure I.9):

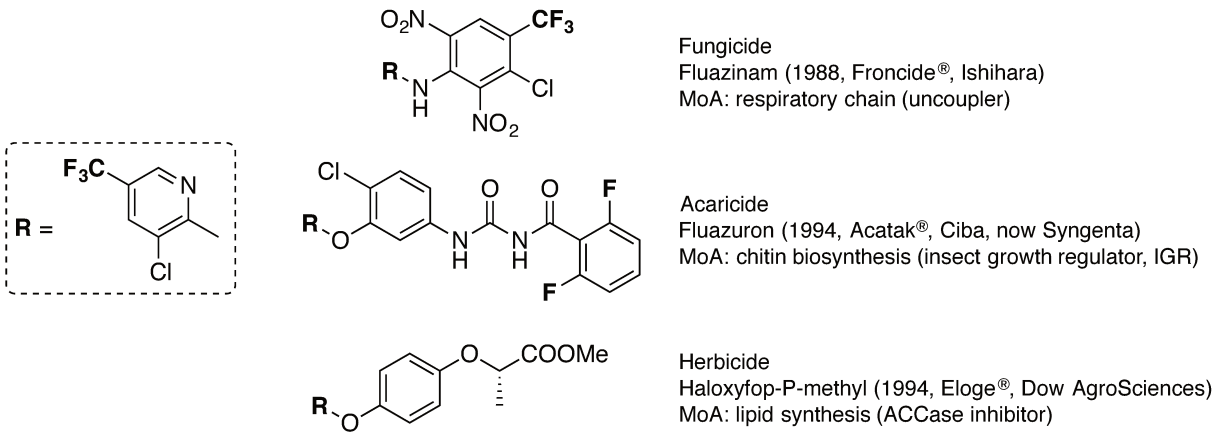


Figure I.9: Active ingredients with different biological activities and MoAs containing a common residue.

Similarly, the replacement of defined position(s) of bioactive structures by fluorinated substituents has demonstrated possible critical modifications of the MoA of the initial structure (Figure I.10).[14] This opens a scope of applications if one considers the introduction of emergent fluorinated substituents, with hardly predictable but promising effect(s). Fluorinated 5-amino-4-pyrazole carbonitriles will be notably discussed in Chapter II.

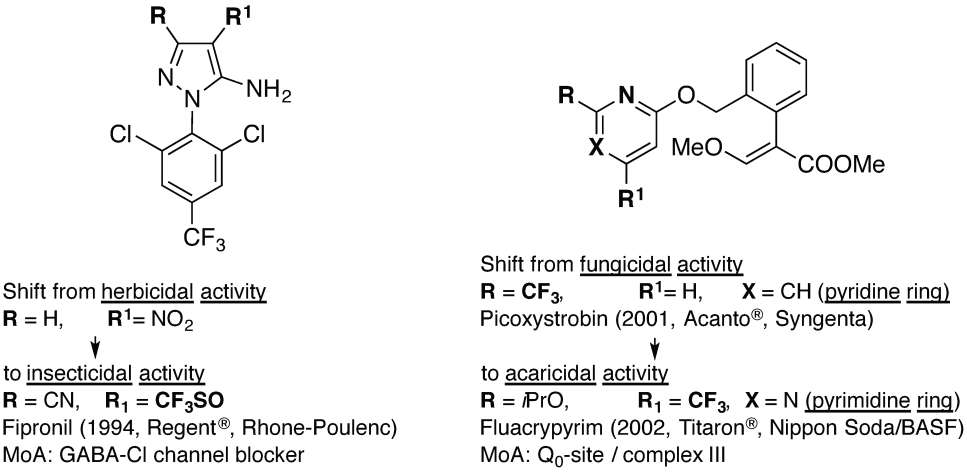


Figure I.10: Herbicidal *N*-aryl-pyrazoles and fungicidal methoxyacrylates for halogen-group-induced shift in biological activity.

Another important observation, relative to the discovery of new active ingredients, is the occurrence of pharmaceuticals and agrochemicals built around heteroaromatic rings, like diazines (pyridines, pyrimidines, etc.) and diazoles (pyrazoles, imidazoles, etc.).

In medicinal chemistry, fluorinated-diazines have already proven their potential, with more than 1150 hits possessing fluorine-containing diazines. 30% of these are anti-cancer agents; the remaining is spread among other classes (more than 100 examples) including antiviral (mainly anti-HIV) and antiarthritic activity (Figure I.11). According to MDDR (MDL Drug Data Report), 106 fluorinated-diazine compounds have entered pre-clinical studies, 40 of them have reached clinical phase, and 12 of these have become drug substances.[26]

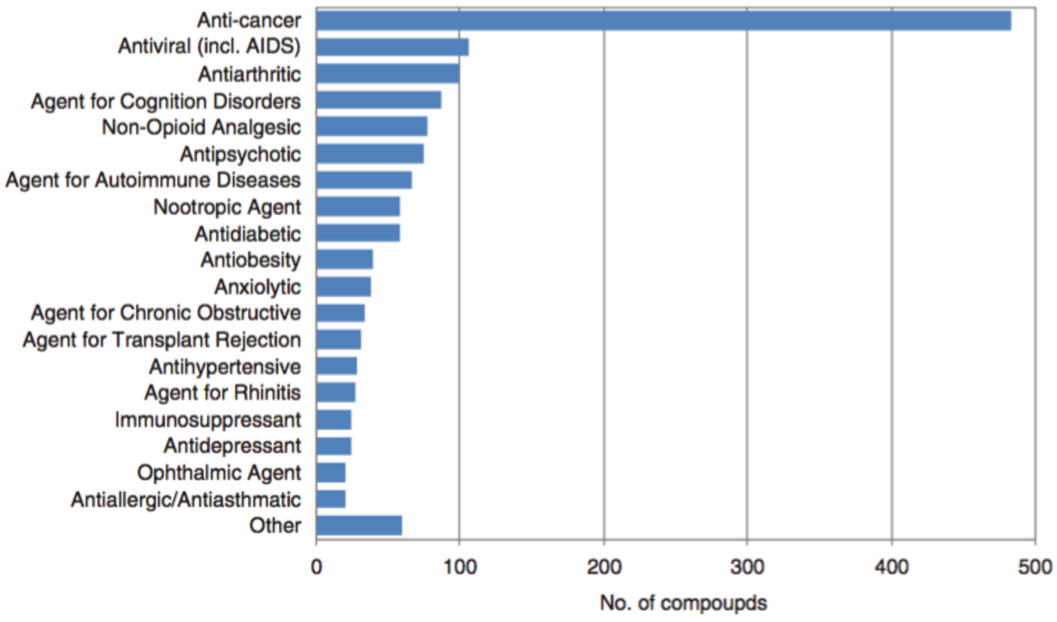
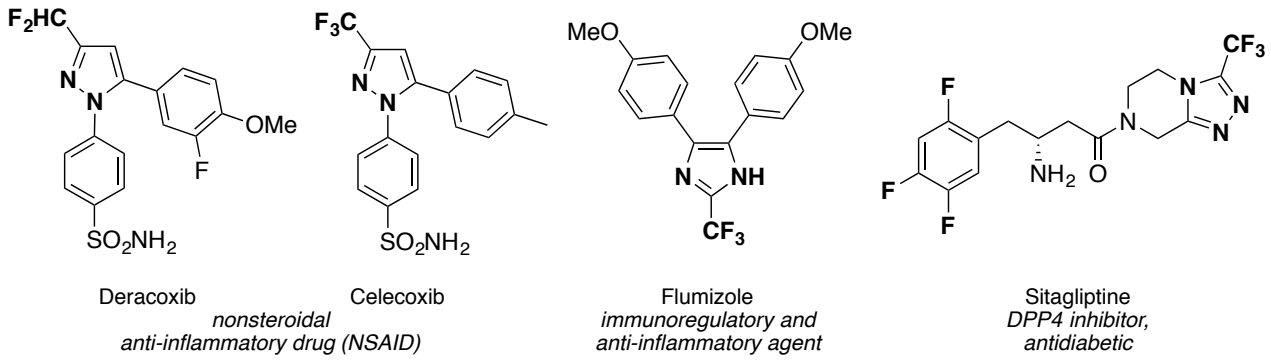


Figure I.11: Distribution of biological activity for fluorine-containing diazines in MDDR (MDL Drug Data Report)[26]

In agrochemistry, fluorinated diazines have also led to eleven marketed agrochemicals. One can notice the high potential of fluorinated pyrimidinyl systems (pyrimidines, uracil-derived pyrimidine-diones, triazole-fused pyrimidines, etc.) in various applications (Herbicides, etc.):
- Triazolopyrimidine sulfonanilides are extensively adopted herbicides in the control of broad-leaf weeds and grasses (soya beans, peas and maize). However, because of its high herbicidal activity and slow degradation rate, trace residues in soil can have adverse effect on the quality and yield of following crops.[72]
- Sulfonyl urea type herbicides are equally interesting examples of pyridinyl and triazinyl-containing modern low-dose agrochemicals providing a 50–100-fold greater herbicidal activity than earlier classes of active ingredients (typical crop-selective weed control at 2–75 g/ha). Such low doses reduce the environmental impact, in parallel with non-toxicity towards vertebrate and invertebrate animals and soil microorganisms. Finally, the degradation products have low potential to accumulate in non-target organisms. More than 30 sulfonylurea herbicides are used in a wide variety of crops.[73]

Fluorinated azoles play also a critical role in pharmaceutical research, and many drugs containing a fluorinated di- or triazole are described.[74] Deracoxib, Celecoxib or Flumizole are famous examples of CF_3-substituted pyrazole and imidazole drugs, while Sitagliptine is a triazole ranked at the 14th position of top-selling drugs ($5.0 billion sales in 2014) (Figure I.12).



Deracoxib — Celecoxib
nonsteroidal anti-inflammatory drug (NSAID)

Flumizole
immunoregulatory and anti-inflammatory agent

Sitagliptine
DPP4 inhibitor, antidiabetic

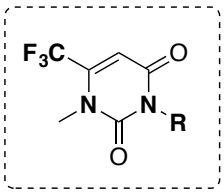
Figure I.12: Commercialized fluorinated pyrazoles (Celecoxib), Imidazole (Flumizole) or triazole (Sitagliptine)

Interestingly, several herbicides contain emergent fluorinated groups ($OCHF_2$, OCH_2CF_3, $CH_2CH_2CF_3$). Primisulforon-methyl is one interesting example of bis($OCHF_2$)-pyrimidine system active as herbicide (Figure I.13).

In agrochemistry, azoles (pyrazoles, triazoles, thiadiazoles, etc.) are also a very important class of scaffolds, and several examples containing fluorinated substituents are available on the market (Figure I.14).
Fluorinated pyrazoles have more recently attracted considerable attention due to their potentially enhanced biological properties, and great effectiveness as new generation succinate-dehydrogenase inhibitor (SDHI) fungicides. In particular, a huge interest was accorded to (CHF_2)-pyrazole-carboxamides, as at least four different new SDHI compounds were recently introduced in the crop-protection market (Figure I.15). [75, 76]

Herbicides:

Uracil derivatives
(protoporphyrinogen oxidase inhibitors)



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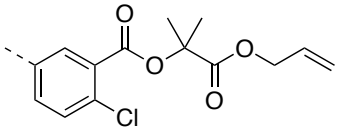
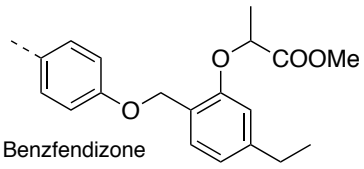
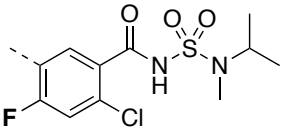


Butafenacil

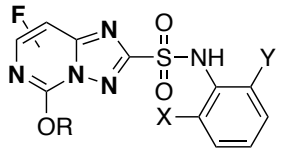


Benzfendizone



Saflufenacil

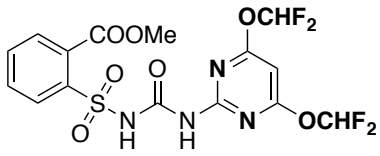
Triazolopyrimidine sulfonanilides [acetohydroxy acid synthase (AHAS) inhibitors]



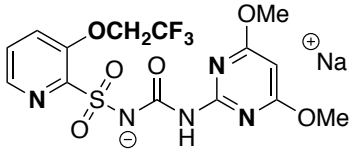
7-F: (R = Et)
Cloransulam-methyl
(X = Cl, Y = COOMe)
Diclosulam
(X = Y = Cl)

8-F: (R = Me)
Florasulam
(X = Y = **F**)

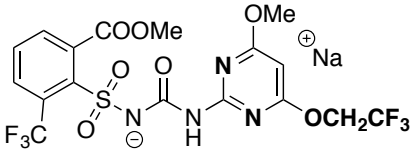
Sulfonyl ureas [acetohydroxy acid synthase (AHAS) inhibitors]



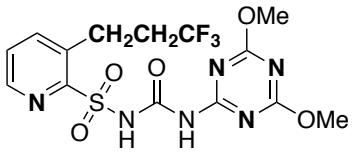
Primisulfuron-methyl



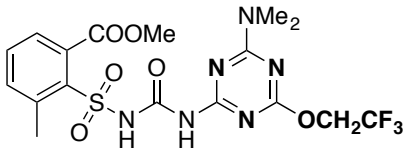
Trifloxysulfuron-methyl-sodium



Flupyrsulfuron-methyl-sodium

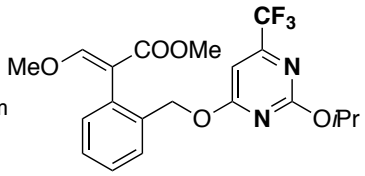


Prosulfuron

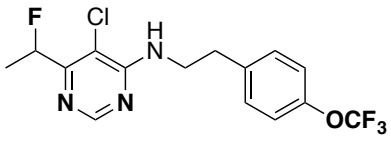


Triflusulfuron-methyl

Other agrochemicals:



Fluacrypyrim
acaricide



Flufenerim
insecticide

Figure I.13: Agrochemicals derived from fluoro-containing diazines (and triazines) – presence of emergent fluorinated substituents.

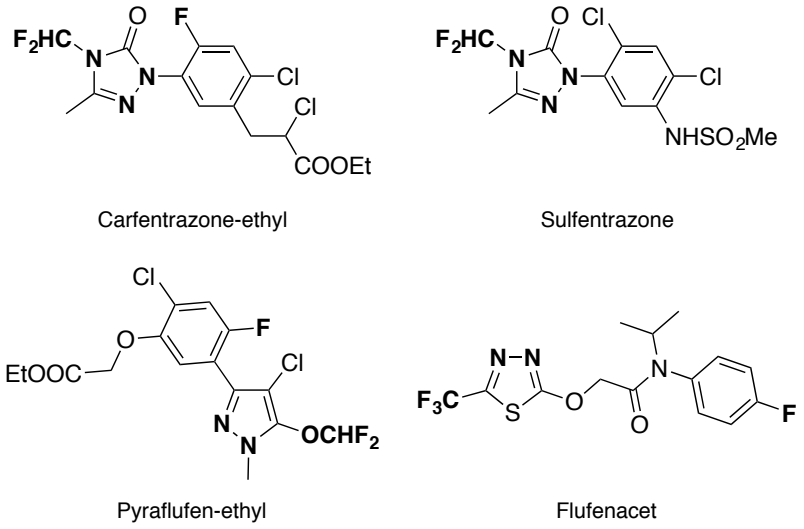


Figure I.14: Fluorinated PPO-inhibitor herbicides with triazolinone-, pyrazole- or thiadiazole core

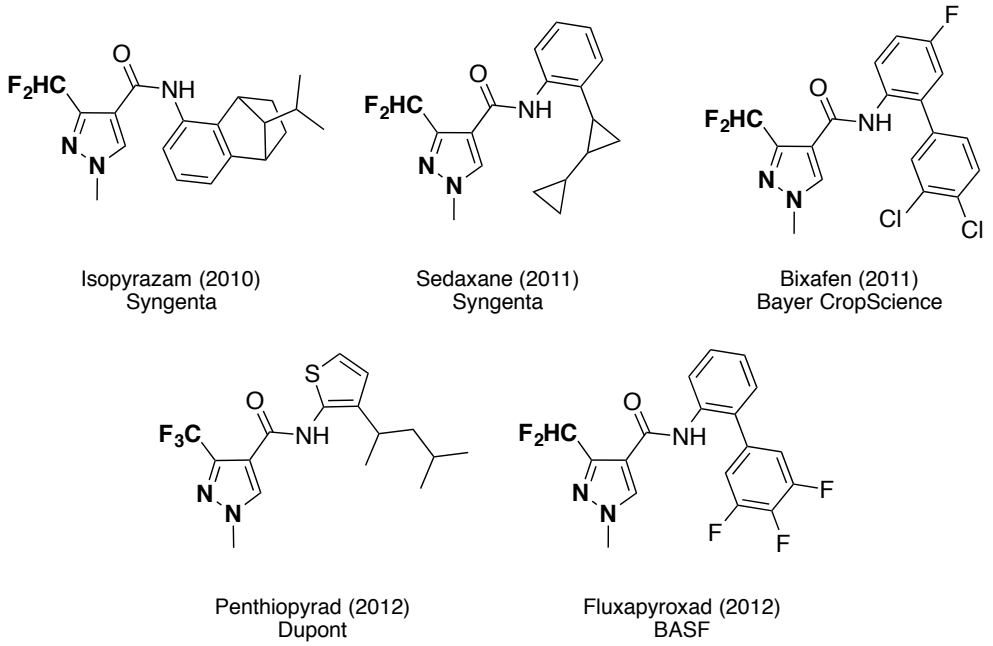


Figure I.15: Recently marketed new-generation SDHI fungicides containing mostly CHF_2 substituent

One can conclude that the combination of fluorinated substituents (F, CF_3, emergent groups such as CHF_2, etc.) with arenes or nitrogen-based heterocycles has already demonstrated great potential in new bioactive ingredients discovery, and a further development of synthetic strategies to access novel fluorinated structures can lead to huge applications, either in pharmaceutical- or in agrochemical research. This doctoral fellowship focused mostly on the introduction of emergent fluorinated substituents in arenes, diazines, diazoles and other heterocycles. Their characteristics will be briefly described in the next paragraph.

C. Emergent fluorinated substituents – State-of-the-art

As previously discussed, the introduction of new fluorinated substituents has proven great potential in the discovery of new bioactive ingredients in agrochemistry (and in pharmaceutical research,)as illustrated by the occurrence of emergent fluorinated substituents in recently developed fluorinated agrochemicals.

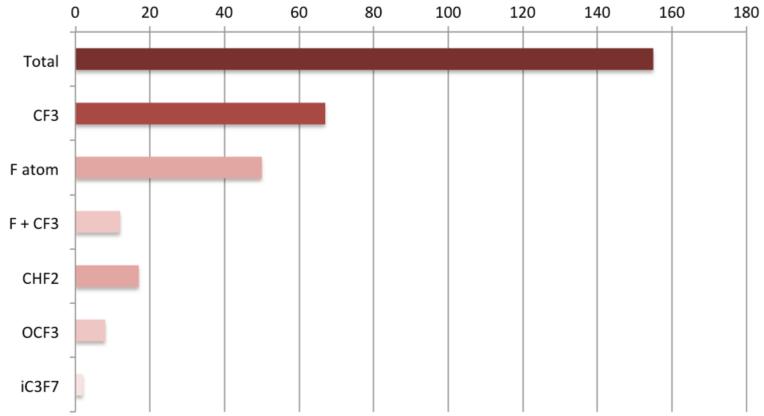


Figure I.16: Occurrence of emergent fluorinated substituents in fluorinated agrochemicals up to 2014. The Pesticide Manual, XVIIth Edition.

The major part of fluorinated agrochemicals are F- and CF_3-substituted aromatic or heteroaromatic compounds [83% contain either F (32%), CF_3 (43%) or both combined (7%)], but the presence of OCF_3- and CHF_2-substituted examples is remarkable due to the very recent development of synthetic techniques to introduce these groups. This gives a hint of their great potential in life science research.
Similarly, in pharmaceutical research, the introduction of emergent fluorinated groups (EFSs) led to many active drugs, but the most represented fluorinated substituents are F and CF_3. This is due to a former lack of synthetic strategies to introduce these EFSs.
Surprisingly, very few drugs contain the CHF_2 motif, in comparison with agrochemicals where this EFS is the most prevalent. Emergent fluorinated groups could be more present in the next decades, if the development of synthetic techniques allows for the evaluation of diversely fluoro-substituted candidates in both agro- and pharmaceutical research. There is in any case a need for developing new chemical structures, and emergent fluorinated groups could be a part of the solution.

1. Effect(s) of fluorinated substituents

For the most commonly introduced groups, the main influence is rather well documented:

F
Increases lipophilicity [π_x(F)= +0.14]. Fluorine is an isostere of Hydrogen or tertiary OH groups, while the fluoro-alkene group is an isostere of an amide bond. The construction of a single C-F bond has been nicely reviewed recently.[77, 78]

CF_3
Highly lipophilic group [$\pi_x(CF_3)$ = +0.88]. The CF_3 motif is an isostere of *i*Pr or *i*Bu groups,[79] whereas trifluoroethylamines were identified as isosteres of amides. Trifluoromethylation reactions have been broadly studied and are state-of-the-art.[80-89]

Another fluorinated group has been at the centre of many researches over the past decades, as it proved great effect in many pharmacophores and agrophores, the difluoromethyl group (CHF_2). The introduction of the CHF_2 group will be central in this manuscript, as it possesses many special features and mimicking ability (see below):

CHF_2

The difluoromethyl group is the most represented emergent fluorinated group in agrochemistry. Almost 11% of all recently marketed fluorinated agrochemicals containing this substituent (Figure I.16). So far, its occurrence is lower in pharmaceutical research, though it possesses high lipophilicity and stability (similar to the CF_3 group) with reduced steric demands and H-bond donor properties, helping drug candidates to cross lipid membranes and prolong their lifetime in the body.[90] CHF_2 presents also radical scavenging capacities.[91] CHF_2 is a lipophilic and membrane permeability-enhancing isosteric and isopolar analogue to OH and SH groups. The difluoromethyl bridge (CF_2) is a bioisostere of methoxy group (OMe),[92] while difluorophosphonate is a bioisostere of phosphate (Figure I.7). The replacement of a carbonyl oxygen by a difluoromethyl group was reported recently (*via* α-dithiane intermediate).[93]
The introduction of the CHF_2 motif has been broadly studied, and will be detailed in the next chapter.

The use of emergent fluorinated groups has already demonstrated a potential for accessing new MoA or tuning physicochemical properties of agrochemical candidates, even in lead optimization stage (Figure I.17):[14]

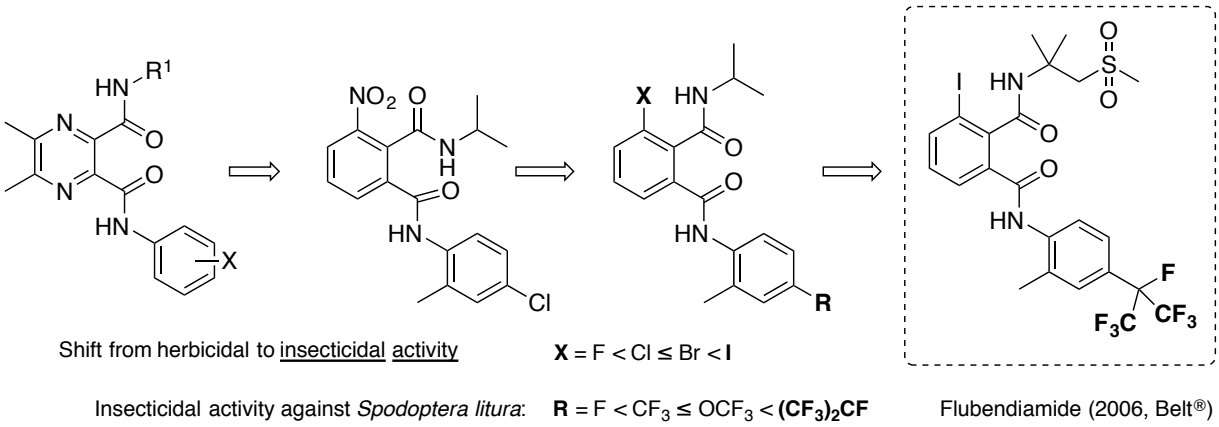
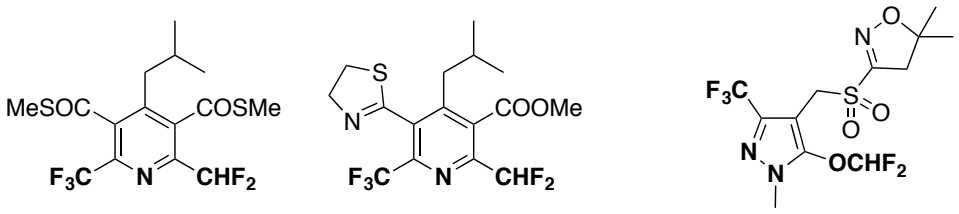


Figure I.17: Evolution of the MoA and target organism of an identified lead after structural modification, and increase of activity after the introduction of emergent fluorinated groups.

Other emergent substituents can be considered. Many less common emergent fluoroalkyl groups exist (*e.g.*: **CHFCl**, **CHFCF$_3$**, **CF$_2$Br**, **CF$_2$Cl**, **CFCl$_2$**, **CFBr$_2$**, **CF$_2$OR**, **CF$_2$SR**, etc.), but the bioactivity of the few related compounds is much less documented. Many patents cite these groups as part of the concerned intellectual property, without systematic analytical proofs of the performed synthesis and/or biological evaluation. These groups have not been studied in detail in terms of physico-chemical properties. Their synthetic introduction will be shortly discussed after the bibliographic study concerning difluoromethylation.

Interestingly, the presence of (bis)fluoroalkyl-heterocycle has also demonstrated a potential in the discovery of bioactive molecules, especially in the context of herbicide research with several bis-fluoroalkylated compounds showing different MoAs [*e.g.*: Primisulfuron-methyl (Figure I.13), Dithiopyr, Thiazopyr and Pyroxasulfone (Figure I.18)]:
In this manuscript, a large part of the work was dedicated to the synthesis of mono- and bis(fluoroalkyl) heterocycles of high potential in agrosciences and drug development. To conclude this short summary of existing emergent fluorinated substituents, there is a need for developing new synthetic methods for the introduction of these groups into various scaffolds, but also with high efficiency, scalability, high atomic efficiency, low waste generation, etc.
The broad diversity of structures observed has no exact correlation with the biological target and/or MoA, thus the development of new structures bearing various emergent fluorinated substituents could bring new solutions to a vast range of biological applications, either in agro- or in pharmaceutical research. In the next part, the state-of-the-art of the introduction of CHF_2 motif into various substrates, especially (hetero)aromatic substrates will be discussed, as well as other EFSs in a smaller extent.



Dithiopyr (*cell growth inhibitor*) | Thiazopyr (*cell growth inhibitor*) | Pyroxasulfone (*VLCFAE inhibitor*)

Figure I.18: Examples of marketed herbicides bearing two fluorinated groups, with at least one emergent fluorinated substituent (EFS)

2. Introduction of the Difluoromethyl motif (-CHF$_2$)

The introduction of the difluoromethyl motif was for decades and up to recently a challenging task, either in arenes or in heterocycles. As it represents an important group in medicinal and agrochemistry, it is necessary to develop scalable and cheap techniques for the preparation of large quantities of the desired products.
A summary of the past synthetic strategies is necessary to understand the technical evolutions for this specific task. The introduction of difluoromethyl group can be achieved *via* various strategies:

- Deoxofluorination of carbonyl compounds,
- Direct difluoromethylation: direct transfer of a CF_2H group into target molecules,
- Stepwise difluoromethylation: introduction of a functionalized moiety into organic substrates followed by its subsequent transformation into H or F atoms

The selective difluoromethylation has been studied on a variety of substrates, and a nice review from the group of Hu *et al.* has already covered the progress in nucleophilic, electrophilic or free radical

difluoromethylations up to 2009.[94] Our group also reported on the progress in metal-catalysed difluoromethylations in 2013.[95] Ritter *et al*. produced an excellent review on the introduction of many fluorinated functional groups (including CHF_2) the same year. More recently in 2015, Liu, Chen *et al.* updated the latest advances in difluoromethylations in another review.[96] These most recent results will be summarized, before describing the preparation of CHF_2-pyrazoles in more details.

i. Deoxofluorination

Deoxofluorination of carbonyl compounds or alcohols using SF_4, DAST or related reagents (Deoxofluor, etc.) is a common way for preparing difluoromethylated products from aldehydes, but suffers some important drawbacks (reagents cost, reagents and substrates stabilities, harsh conditions, poor functional group tolerance). The recently developed alternatives (XTalFluor-E® and -M®, two stable crystalline aminodifluorosulfinium tetrafluoroborate salts) are much easier to handle and can be used under mild conditions (Figure I.19).[97, 98] However, their applications are limited, and starting aldehydes are often rather unstable and difficult to prepare.

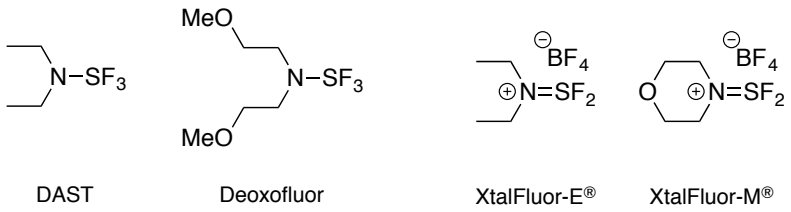


Figure I.19: Examples of deoxofluorination reagents

Other direct difluoromethylation strategies involve the transfer of an equivalent of "$^{-}CHF_2$" into an electrophile. As this anion is highly unstable due to α-elimination of fluoride (Li or MgX complex), alternative techniques were developed, and will be summarized synthetically.

ii. Direct difluoromethylation

Before 2009[94]

Difluoromethyl-metal complexes of Cd, Zn (less reactive than Cd) or Cu (thermally less stable than Cd, but more nucleophilic) were developed and applied to the difluoromethylation of unsaturated substrates (alkenes, alkynes), alkyl halides, etc. These difluoromethylation reagents are not applicable to many other substrates (aldehydes, ketones, imines) due to a weaker ionic character. The Ruppert-Prakash reagent (Me_3SiCF_3) and its CHF_2 analogues (Me_3SiCHF_2 and $PhMe_2SiCHF_2$) were employed for the difluoromethylation of carbonyl compounds under Lewis base activation, with several drawbacks. The first example was only efficient with acyl silanes and unactivated aldimines. Reaction of Me_3SiCF_3 with acyl silanes involved a domino sequence (nucleophilic trifluoromethylation – Brook rearrangement – fluoride elimination) providing 2,2-difluoroenol silyl ethers, further hydrolysed to give difluoroacylated products. Reaction of Me_3SiCF_3 with aldimines provided CHF_2-amines after a similar domino reaction (1,2-H shift – fluoride β-elimination – 1,3-H shift). Me_3SiCHF_2 and $PhMe_2SiCHF_2$ showed limited efficiency due to lower reactivity, and were only applicable with non-enolizable aldehydes, while yields were low with ketones and enolizable aldehydes. All strategies described using CHF_2-silanes possessed drawbacks (substrate limitation and access, yields, substrate scope, etc.).

Two reports not cited in Hu's review described the reductive dehalogenation of halogeno-difluoromethylated aromatics and heterocycles, but the preparation of such substrates is already difficult, and the further reduction presented many drawbacks (residual impurities, etc.). This strategy cannot be considered either for industrial applications.[99, 100]

Between 2009 and 2015

Me_3Si-CHF_2 (analogue of the Ruppert-Prakash reagent) showed great capacity to difluoromethylate efficiently various aldehydes, ketones and imines under mild conditions by using a proper Lewis base (CsF or *t*-BuOK), as reported by Hu *et al*. in 2013.[101] This reagent proved also a great potential in Cu-mediated direct difluoromethylation of aryl and vinyl halides,[102] and later of heteroaryl iodides using optimized conditions, shown respectively by Hartwig's and Qing's groups in 2011 and 2014 (a, b, top, Figure I.20).[103]

Prakash *et al*. developed in 2012 an alternative Cu-mediated direct difluoromethylation of aryl, 2-pyridinyl and styryl halides using tributyl(difluoromethyl)stannane ($^nBu_3SnCHF_2$) as CHF_2 source. This approach displayed a better functional group tolerance (aldehydes, ketones, carbonitriles and esters are tolerated) (c, top, Figure I.20).[104]
Shen *et al.* reported in 2015 the direct difluoromethylation of aryl iodonium, aryl diazonium salts or acid chlorides, using stoichiometric amounts of a thermally stable (NHC)$AgCF_2H$ complex (prepared from Me_3SiCHF_2) in presence of a copper source.[105] Despite the elegant strategy, the use of a stoichiometric amount of silver complex is problematic for large-scale applications. One year earlier, they published the use of the first catalytic bimetallic Pd/Ag difluoromethylation of aryl halides using Me_3Si-CHF_2. This strategy possesses larger substrate scope, functional group tolerance and high yields (d, top, Figure I.20).[106]
These methods recently developed are elegant, efficient, tolerate many functional groups and cover a large substrate scope but require the use of expensive transition metal complexes and/or ligands, with tedious preparation of the substrates. Furthermore, these advances mostly cover the preparation of CHF_2-arenes, but rarely of difluoromethylated heterocycles, especially azoles.

Shibata *et al*. reported in 2015 the first direct difluoromethylation of diaryl-isoxazoles by nucleophilic addition using Me_3Si-CHF_2.[107]
A major breakthrough was reported in 2012 by Baran *et al*., with the development of a new crystalline, bench-top-stable zinc difluoromethanesulfinate reagent ($Zn(SO_2CF_2H)_2$, or DFMS, see below), which has been commercialized by Sigma-Aldrich, for the *t*-BuOOH promoted direct difluoromethylation of various heteroarenes using mild, operationally simple, chemoselective and easily scalable reaction conditions, *via* a radical process (f, top, Figure I.20).[108] Liu *et al*. disclosed in 2013 a Fe-catalysed difluoromethylation of aryl-substituted acrylic acids using DFMS (Baran's reagent), and similarly in 2014, the synthesis of CHF_2-substituted oxindoles by reacting Baran's reagent with *N*-arylacrylamides.[109, 110]
Dilman *et al*. reported in 2014 the direct nucleophilic difluoromethylation of various reactive Michael acceptors, aldehydes and azomethines using an air-stable difluoromethylene phosphabetaine, allowing the introduction of -CHF_2 motif in alkyl chains and aryl benzylic positions only.[111] Goossen *et al*. reported in 2014 a Sandmeyer-type conversion of (hetero-)arenediazonium salts into the corresponding difluoromethyl (hetero-)arenes under mild conditions *via in situ* formed difluoromethyl-copper [$CuCHF_2$] complex.[112] Dolbier *et al*. reported in 2014 the construction of difluoromethylated oxindoles from *N*-arylacrylamides and the difluoromethyl radical, which could be generated from HCF_2SO_2Cl by photoredox catalysis, similarly to Liu's report.[113] They extended in 2015 the method to unactivated alkenes using metal-free conditions.[114]

Several new reports were published after the period covered by the reviews cited above:
For example, the direct difluoromethylation of aryl halides or triflates *via* base metal catalysis was reported in 2016 by Vicic *et al*., using a stable solid [$(DMPU)_2Zn(CF_2H)_2$] complex in addition with catalytic amounts of both nickel catalyst and phosphine ligand at room temperature. This zinc reagent can be stored under inert atmosphere for months (e, top, Figure I.20).[115] The use of nickel is an advantage as this metal is of lower cost, though it is a known carcinogenic metal and it causes allergies.

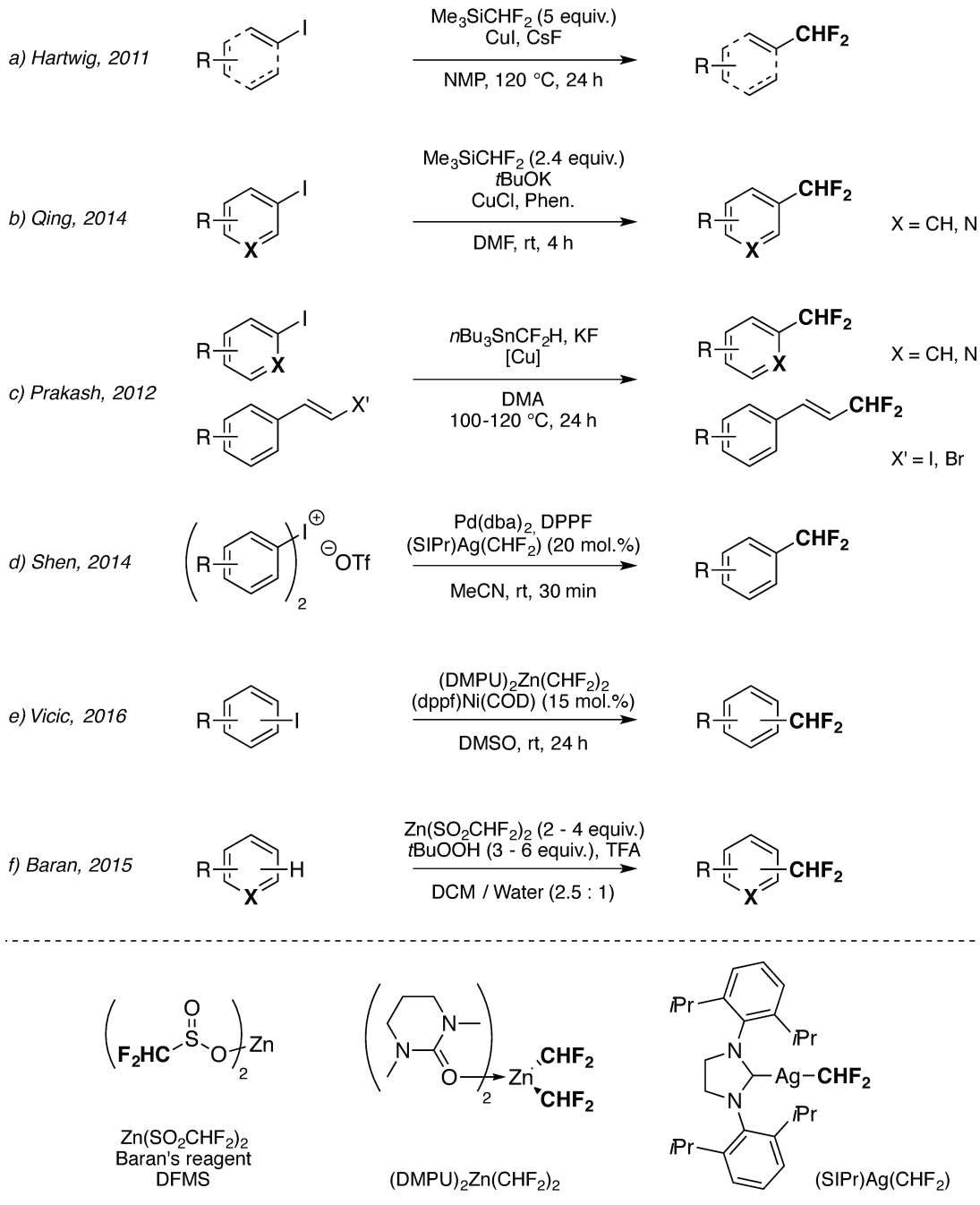


Figure I.20: Direct aromatic difluoromethylation methods recently reported(top) Various difluoromethylating reagents for the direct introduction of CHF_2 (bottom)

iii. Stepwise difluoromethylation:

Using CHF_2-derived reagents (difluoromethyl phenyl sulfone $PhSO_2CHF_2$ and $PhSO_2CF_2Br$, diethyl difluoromethylphosphonate $HF_2C\text{-}PO(OEt)_2$) or functionalized CHF_2-silanes ($SiMe_3CF_2SiMe_3$, CHF_2SiMe_2SPh, $SiMe_3CF_2SO_2Ph$ and $SiMe_3CF_2SePh$) in stepwise approaches extended remarkably the scope of difluoromethylation (and also difluoroacylation). After the introduction of difluoromethylation synthons into the target molecule, their further transformation into the desired $-CHF_2$ is achieved using sometimes energy-costly steps.

Between 2009 and 2015

XCF_2COOEt (X = Br, I)

Yamakawa *et al*. developed in 2011 a direct regioselective ethoxycarbonyldifluoromethylation of aromatic compounds by $BrCF_2CO_2Et$ using Fenton's reagent (ferrocene and hydrogen peroxide) (a, Figure I.21).[116] Shen *et al.* reported in 2012 a Cu-mediated ligandless aerobic difluoroalkylation of arylboronic acids with ICF_2COOEt under mild conditions providing variously fluoroalkylated benzene derivatives in acceptable yields.[117]

Zhang *et al*. explored in 2014 a similar chemistry using Pd-catalysed difluoroalkylation of aryl boronic acids, to access efficiently various aryldifluoromethylated phosphonates and carboxylic acid derivatives.[118] The same group developed a Ni-catalysed similar work, with few improvements, as high generality, excellent functional-group compatibility, low-cost Ni-catalyst, and gram-scale production (b, Figure I.21).[119] Inoue *et al*. developed in 2013 a Co-catalysed version using aryl zinc reagents (c, Figure I.21).[120]

Alternatively, Pannecoucke *et al.*, developed a Cu-catalyzed innate ethoxycarbonyldifluoromethylation of electron-rich arenes,[121] and Zhang *et al*. reported a Pd-catalyzed Heck-type reaction of fluoroalkyl bromides to access ethoxycarbonyldifluoromethylated alkenes.[122] Many aromatics, alkene and several heterocycles bearing the $-CF_2COOEt$ moiety were prepared with moderate to very good yields, but CHF_2-derivatives were not accessed. In all cases, starting substrates can be difficult to prepare, and the decarboxylation steps are energy consuming.

Several groups reported on the use of visible-light photocatalysis for the introduction of ethoxycarbonyldifluoromethyl ($-CF_2COOEt$) or difluoromethyl ($-CHF_2$) groups from ethyl halodifluoroacetates ($XF_2C\text{-}COOEt$) or difluoromethyl sulfonyl chloride ($HF_2C\text{-}SO_2Cl$). Qing *et al*. reported a photoredox Ru-catalysed approach for the direct ethoxycarbonyldifluoromethylation of various heteroarenes (a, Figure I.22).[123] Cho *et al*. developed a similar Ir-catalysed ethoxycarbonyldifluoromethylation of arenes and heteroarenes (b, Figure I.22).[124]

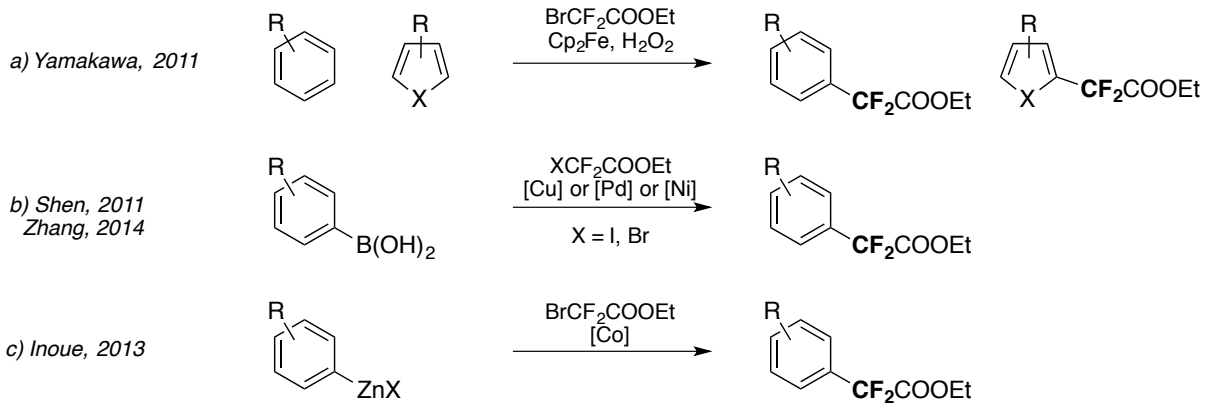


Figure I.21: Stepwise approaches using halodifluoroacetates

Fu *et al*. reported the synthesis of ethoxycarbonyldifluoromethyl oxindoles.[125] Yu *et al*. reported a visible-light-promoted stepwise or one-pot alkylation/decarboxylation sequence from biphenyl isocyanides with $BrCF_2COOEt$, providing difluoromethylated phenanthridines.[126]

Uncovered by Chen's most recent review, a few more examples of photoredox fluoroalkylations were recently reported.
Dolbier *et al*. reported in 2015 an optimized photoredox Ir-catalysed preparation of difluoromethylated phenanthridines using biphenyl isocyanides and CHF_2SO_2Cl in a one-pot process at room temperature.[127]
Fu *et al*. reported in 2015 the Ir-catalysed preparation of ethoxycarbonyldifluoromethyl coumarins *via* mild and efficient visible-light-promoted aryldifluoroacetylation of alkynes with $BrCF_2CO_2Et$.[128]
Gu *et al*. described in 2015 the difunctionalization of *N*-phenylcinnamamides using similar conditions to access ethocarbonyldifluoromethylated quinoline-2-one derivatives.[129] Liu et al. recently reported the direct C–H difluoromethylenephosphonation of arenes and heteroarenes (including pyridine and pyrimidine) with $BrF_2CPO(OEt)_2$ *via* visible-light photocatalysis,[130] this group being present in several bioactive molecules.
However, for all these recent reports, limitations can be given. The methods are not general and several heterocycles only are prepared, often substituted with a CF_2-surrogate ($-CF_2COOEt$) but not the CHF_2 motif. Furthermore, it is so far not applicable to the introduction of CHF_2 onto classical *N*-based heterocycles.

R_3SiCF_2COOEt
In 2011 was reported by Amii *et al*. the Cu-catalysed ethoxycarbonyldifluoromethylation of aryl-iodides using $TESCF_2COOEt$, followed by subsequent hydrolysis and KF-promoted decarboxylation providing moderate to good yields of CHF_2-aryl products. Again, the decarboxylation requires harsh conditions.[131]
Other groups reported nice results, as the Ag-mediated efficient *ortho*-ethoxycarbonyldifluoromethylation of aromatic triazenes (Bräse's group in 2013) with $TMSCF_2COOEt$,[132] or the regioselective hydrodifluoromethylation of unactivated alkenes for an easy access to various vicinal difluoroacetate-containing alkanes (Hao's group in 2014).[133]
Another report from Amii *et al*. showed better potential with the development of a convenient route to CHF_2-pyridines involving Cu-promoted cross-coupling of halopyridines with ethyl difluoro(trimethylsilyl)acetate ($TMSCF_2COOEt$) and subsequent decarboxylation. This strategy provided efficiently difluoromethyl-pyridines, but the use of stoichiometric amounts of copper iodide and $TMSCF_2COOEt$, prior to a subsequent energy-costly decarboxylation, render this approach not optimum for industrial production of such building blocks, in addition to an access to pyridine cores only.[134]

Ando *et al*. reported in 2016 an efficient Ni-catalysed Negishi coupling of bromodifluoroacetamides ($BrCF_2CONR_2$) with arylzinc reagents. This allows access to aromatics bearing α,α-difluoro-α-aryl amide ($-CF_2C(O)NR_2$) motifs. However, only the efficient microwave-assisted amide reduction was reported.[135]
Hartwig's group reported the same year a Cu-catalysed coupling of aryl/vinyl iodides and heteroaryl bromides with α-silyldifluoroamides ($R_3SiCF_2CONR_2$), providing α,α-difluoro-α-(Het-)aryl amides in high yields and functional group tolerance. Moreover, further transformations were included, giving access to a diverse array of difluoroalkylarenes.[136]

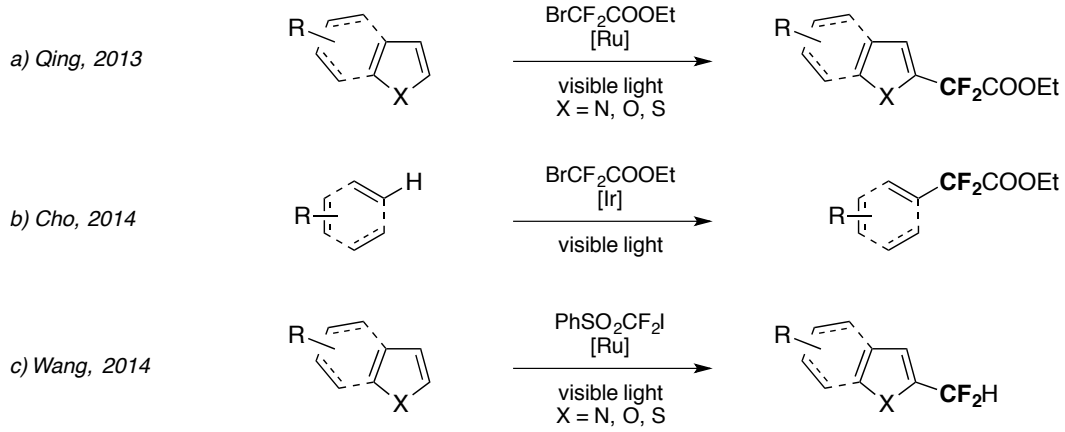


Figure I.22: Alternative photocatalytic stepwise approaches involving radical processes recently reported

$PhSO_2CF_2I$

Wang *et al*. reported in 2014 the use of this well-known difluoromethylation reagent[137] in a novel visible-light photoredox Ru-catalyzed stepwise *C*-difluoromethylation of various electron-rich heteroarenes after efficient and mild reductive desulfonylation (c, Figure I.22).[138] This stepwise method possesses a great potential even though the regioselectivity is sometimes low or different than desired.

It represents a complementary approach to Baran's report (the direct difluoromethylation of electron-poor heteroarenes[108]). Later, they developed a Pd- and Fe-catalysed intramolecular radical aryldifluoromethylation of activated alkenes, giving access to a variety of phenylsulfonyldifluoromethylated oxindoles.[139, 140]

$PhCOCF_2H$

Hartwig *et al*. reported in 2014 the synthesis of a wide range of difluoromethylated arenes using a one-pot, two-step procedure *via* Pd-catalysed arylation of (het)aryl halides and subsequent Haller-Bauer debenzoylation. This method requires a very low Pd-catalyst complex loading. The one-pot sequence could be applied to arenes, and unfortunately not to heteroarenes. Still, several examples of CHF_2-pyridine and -quinolines were prepared in two steps.[141]

These stepwise strategies involve a second step (reductive desulfonylation, dephosphonylation, desulfuration, deselenation) using reducing (*e.g.* alkali metals) or free radical conditions often with low yields. Furthermore, the substrate scope remains limited.

In Hu's review are found other methods for the difluoromethylation of various types of substrates, but cannot be considered for potential industrial applications, especially in the context of fluoroalkyl-heterocycles such as pyrazoles, pyridines, pyrimidines, etc.

Another approach relies on the use of difluorocarbene (a moderately electrophilic species), reacting more easily with electron-rich substrates. For example, heteroatom nucleophiles react nicely with difluorocarbene to provide *O*-, *S*-, *N*-, and more difficultly *C*-difluoromethylation products. This carbene approach will be discussed in the Chapter IV.

3. Introduction of other EFSs

Beside the difluoromethyl group, other emergent fluorinated groups can help the development of novel fluorinated building blocks.
The bibliographic summary will mostly deal with the direct introduction of EFSs onto aromatics. The objective of this PhD project is however to enable their facile introduction into heterocycles, but the reports concerning the introduction of EFSs are very scarce.

C_2F_5
A review disclosed in 2015 summarizes the few methods for the pentafluoroethylation of functionalized arenes.[142] Other types of pentafluoroethylation were reported (several recently, not exclusively on aromatics), with various applications[143-148] (*e.g.*: the synthesis of C_2F_5-indazoles was also recently described[149]). The facile introduction of the C_2F_5-group into heteroaromatics remains challenging.
Even though this group can seem a bit large, it has already proven great effect in a series of bioactive molecules, such as antiprogestin compound ZK-230211.[150] This highly lipophilic group has already demonstrated superior effects to CF_3 analogues in specific examples (antiprotozoal and anticancer activity),[151] but also a similar inhibitory potency (as pentafluoroethyl ketone) for C_2F_5-analogues in comparison with reference protease inhibitors of the hepatitis C virus (HCV).[152] This group has also demonstrated a great potential in anaesthetics (pentafluoroethyl analogue as first potassium channel activator with *in-vivo* airways selectivity)[153].

$CF(CF_3)_2$
This group recently showed potential in interacting with biological systems [*e.g.*: insecticide Flubendiamide (Figure I.17)], or the suppression of photochemical activity of the plants photosystem II by perfluoroisopropyl-dinitrobenzene derivatives.[154]
A perfluoroisopropylation of aryl boronic acids was reported in 2016 in an article describing the potential of this group either in bioactive molecules or modern design of organocatalysts.[155] This group will not be discussed in this manuscript but deserved some attention.

CHFCl
The introduction of this group in aromatic substrates is achieved *via* fluorodechlorination or chlorination of fluorinated substituents. It is generally difficult to achieve and provides low yields. For other substrates, except the historical method (discussed in the Chapter III) using the Yarovenko's reagent,[156] one article reports the beneficial effect of the introduction of such group into amino-acids.[157] Recently, few reports were discussing this EFS (and many others, discussed below)[158] or its direct introduction *via* new electrophilic fluorinating reagents.[159]

$CHFCF_3$
This group is easily prepared by displacement of a leaving group (deoxofluorination of alcohol, etc.) in alpha of a terminal CF_3 moiety. Many references describe its introduction in aromatic substrates using this strategy. Its introduction into heterocycles was also reported, *e.g.* in pyridines,[160] benzimidazoles,[161] tetrazoles,[162] imidazoles,[163] pyridazinones,[164] and several other types of heterocycles. However, no general method was described, and multi-step synthesis is usually achieved.

CF_2Br
Only a few biological applications are reported for compounds bearing this group, even though it is broadly described onto aromatics, and very present in agrochemistry patents. It is often formed by radical bromination of CHF_2 groups, defluorobromination of CF_3 groups, fluorination of CBr_3 groups, building-block approach[158] or even by alkylation of carbanions with difluorodibromomethane (CF_2Br_2). Its introduction into heterocycles can be achieved *via* multi-step synthesis or from fluorinated synthons. The

synthesis of CF_2Br-quinolines[165] and CF_2Br-imidazoles[166] was recently reported, as well as the direct bromodifluoromethylation of benzofurans and analogues,[167] and this list is not exhaustive.
This group is also used to prepare ^{18}F-labelled CF_3-tracers for PET imaging. The introduction of this group is not described in this manuscript.

CF_2Cl
The chlorodifluoromethyl group (CF_2Cl) has shown beneficial effect in biological applications, *e.g.* Mycra3, a potential chemo-therapeutic agent for the treatment of pancreatic cancer.[168] This group is introduced onto aromatics using similar strategies than its bromo-analogue, and many references are available. Its introduction onto heterocycles is also broadly described. A few examples will be included in this manuscript.

$CFCl_2$, $CFBr_2$, CHFOR, CF_2OR, CHFSR, CF_2SR
All these groups can potentially bring beneficial effects to bioactive molecules, but will not be described in this manuscript.

Conclusion

After discussing the various properties of fluorine and the effects of its introduction (as fluorine atom or fluoroalkyl group) into a bioactive molecule, the recent impact of organofluorine chemistry into agrochemical research & development has been demonstrated and illustrated by many examples of marketed agrochemicals containing fluorine under various forms. All actors of agrochemical industry and fields of research (including fungicides, insecticides, herbicides, etc.) are nowadays involved in important research programs dealing with the introduction of fluorinated groups into bioactive compounds.
The interest for this area is not limited to agrochemistry, but also to pharmaceutical research, with several examples given of marketed drugs.
One specific area of research – the SDHI fungicide research, is more specifically interested in the development of new fluorinated structures based on the fluoroalkyl pyrazole core, as several marketed SDHIs have been developed around this motif.

The state-of-the-art of the introduction of the CHF_2 group into heteroaromatics was discussed in details, in addition with other EFS.

The synthetic methods concerning the introduction of the CHF_2 group are numerous, but not as well established as the state-of-the-art introduction of fluorine atom(s) or the trifluoromethyl group. Many innovative strategies were reported, but possess either limitations in the development of new structures (highly expected from agrochemical and pharmaceutical companies) or drawbacks from a synthetic point of view, which prevent their use for industrial applications.

In the next chapter, the specific context of SDHI research will be described in detail, showing the interest of agrochemical companies for the development of novel fluorinated structures (especially *N*-based heterocycles). A new synthetic strategy involving an under-exploited type of fluorinated reagents will be described, followed by new applications providing innovative fluorinated structures.

D. Objectives of the PhD project

The objective of this PhD project was to develop new strategies for the introduction of EFSs into 5-or 6-membered *N*-based heterocycles (pyrazoles, isoxazoles, pyridines, pyrimidines, etc.), providing novel fluorinated synthons for agrochemical research, and by extension for medicinal research (Figure I.23).

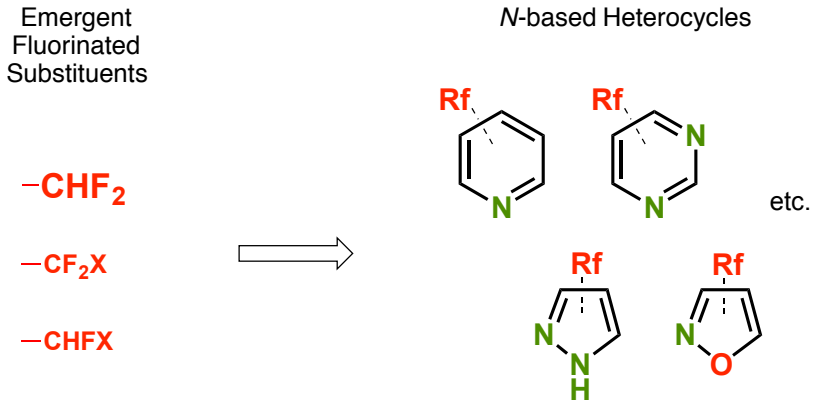


Figure I.23: Objectives of the PhD project represented schematically

The development of cheap, scalable and low waste processes is required to meet the social expectations concerning the modern practice of chemistry at an industrial scale. The atom-economical introduction of the CHF_2 group (and other EFSs) into *N*-based heterocycles remains a challenge.

The use of fluorinated iminium salts was very scarcely described for the synthesis of heterocycles. Consequently, we decided to study the versatility of such electrophilic reagents and to extend their scope of application. TFEDMA was defined as a convenient Fluoroalkyl Amino Reagent (or FAR) for such study due to its high purity and easy storage.

The development of an efficient and scalable access to unprecedented bis(fluoroalkyl)-NH-pyrazoles was highly desired. By extension an access to mono- and bis-fluoroalkyl poly-substituted pyrazoles was targeted. The use of other FARs, and even the development of new FARs were included in the objectives of the PhD project.

The development of mono- and bis-(fluoroalkyl) 6-membered heterocycles (pyridines, pyrimidines, pyridazines, pyrazines, etc.) was also a challenging objective.

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Chapter II

Fluoroalkyl Amino Reagents as New Tools for the Synthesis of Pyrazoles and Analogues Bearing Emergent Fluorinated Substituents

Table of contents

Pyrazoles are a class of nitrogen-based heterocycles of great importance in medicinal and agrochemical research. Several reviews were reported concerning the various physico-chemical properties and methods of synthesis of diversely functionalized pyrazoles over the past few years.[2-4]

Pyrazoles have demonstrated activity as antimicrobials, analgesics, antitumor agents, antimalarials, protein kinase inhibitors, food colourings, UV stabilizers, as components in liquid crystals, but also in agrochemistry as herbicides and fungicides.[5]

An example of pyrazole-based modern drug is Celecoxib (Figure I.12), a nonsteroidal anti-inflammatory drug (NSAID) acting as highly selective COX-2 inhibitor (cyclooxygenase-2, enzyme responsible for inflammation and pain) (Figure I.12), but also the less related anabolic steroid Stanozolol. The pyrazole motif is up-to-now rather absent in marketed pharmaceuticals, unlike other nitrogen-based rings.

In agrochemistry, the pyrazole core is much more represented, with the example of the herbicides Pyraflufen-ethyl (Figure I.14) and Pyroxasulfone (Figure I.18), but more importantly the new generation of SDHI pyrazole-carboxamide fungicides (Figure I.15).

SDHI fungicides, originally called carboxamide fungicides, were discovered more than 40 years ago. The first, narrow-spectrum compound of this class (Carboxin) was first marketed in 1966, mainly as a seed treatment. Between 1971 and 1997, a series of SDHIs was developed [Benodanil, Fenfuram, Mepronil, Flutolanil (a CF_3-benzene carboxamide), Furametpyr, and Thifluzamide, Figure II.1], and gave only slightly broader-spectrum control compared with Carboxin. These "first generation" carboxamides were limited to a few diseases (basidiomycetes) and crops, *e.g*. *Puccinia horiana*, chrysanthemum rust, or *Ustilago nuda*, loose smut in barley, due to resistance issues.[6]
The first carboxamide with truly broad-spectrum foliar activity was Boscalid (a chloropyridine carboxamide), launched in 2003. The further development of this fungicide class produced "new generation" SDHIs, *e.g.* Penthiopyrad (2012, Dupont), a CF_3-pyrazole carboxamide, or Isopyrazam (2010, Syngenta), Sedaxane (2011, Syngenta), Bixafen (2011, Bayer CropScience) and Fluxapyroxad (2012, BASF), SDHIs sharing a CHF_2-pyrazole carboxamide core (Figure I.13). Nowadays, 18 SDHI fungicides are currently listed, and their "overall" spectrum is extremely broad, being comparable with the quinone-outside inhibitors (Q_oIs, affecting the fungal cell respiration chain) (except for oomycete activity, still lacking).

In this chapter will be discussed the context of SDHI fungicides – an important class of "new generation" carboxamide agrochemicals, and more specifically the class of pyrazole-carboxamide SDHIs with their mode of action (MoA); the phenomenon of pathogens resistance will be briefly introduced.

Then, the development of new synthetic strategies for the facile and innovative synthesis of never described mono- and bis-fluoroalkyl pyrazoles bearing emergent fluorinated substituents (EFSs) will be detailed, for potential applications in agrochemical and pharmaceutical research. Indeed, these EFSs have not proven yet their potential in the discovery of new bioactive entities. A part of this chapter will be dedicated to these new synthetic strategies.
The development of new fluorinated building blocks (especially fluoroalkyl-pyrazoles) is important in order to discover new active fungicides with new MoA, overcoming the problem of cross-resistance that could dramatically lower the efficacy of already employed SDHIs.

A. Pyrazole-carboxamides as modern succinate dehydrogenase inhibitor (SDHI) fungicides

Among 55 classes of fungicides reported (list from the Fungicide Resistance Action Committee, or FRAC), several were shown in the introduction of this manuscript (Figure I.15). Notably, sterol biosynthesis inhibitors [or demethylation inhibitors (DMIs), affecting fungi cell membranes stability] and quinone-outside inhibitors (Q_oIs) are the most prevalent tools in agricultural disease control strategies. However, the succinate dehydrogenase inhibitor (SDHI) class shows a remarkably fast development; they show a non-comparable growth in terms of new compounds recently launched into the market. The rapid penetration of this new technology into such a complex market results from the high level of activity of « new generation » SDHIs, and a lack of effective alternative disease control options.

The development of innovative treatments represents a great chance for farmers to efficiently control diseases and maintain/increase crop yields and quality. As a consequence, it has been recorded in 2012 that 60% of UK's cereal farmers used at least one SDHI-containing product per season only two seasons after first introduction. Similarly in Germany, SDHI treatments in cereals grew from 15 to 25% of the market in 2012.[1]

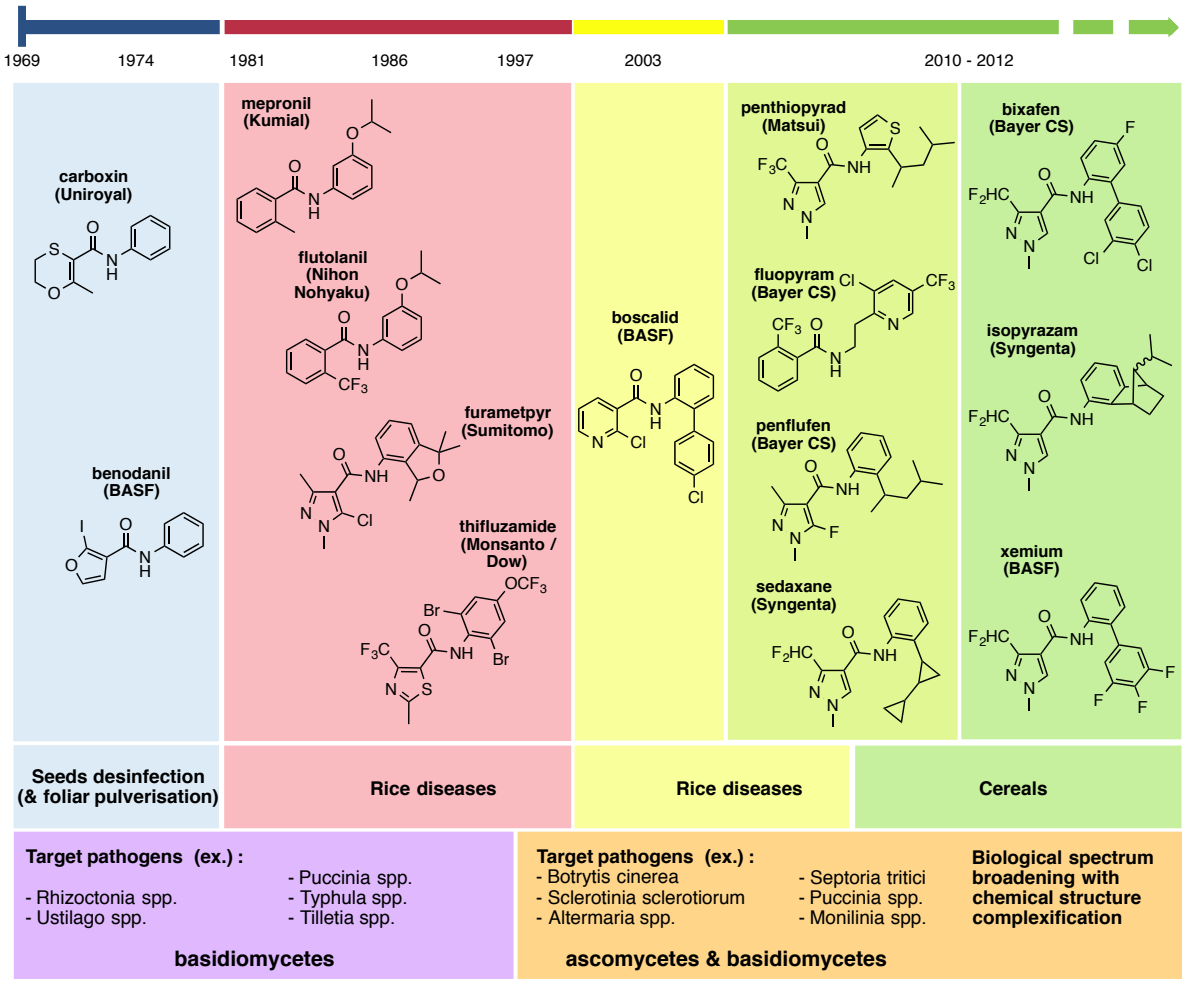


Figure II.1: SDHIs chronology; Source: BASF©

Succinate dehydrogenase (or succinate-coenzyme Q reductase (SQR) or respiratory Complex II) is a membrane-anchored protein considered as an essential component of the respiratory chain. It consists of four subunits:

- flavoprotein subunit (SDH A) catalysing the oxidation of succinate to fumarate
- iron-sulfur protein (SDH B) containing three iron-sulfur clusters
- two membrane anchor subunits (SDH C and SDH D)

The role of SDH is essential as it is the only enzyme participating in both citric acid cycle and electron transport chain.[7]

SDH simultaneously catalyse both oxidation of succinate to fumarate and reduction of ubiquinone to ubiquinol in the inner mitochondrial membrane. In contrast to other dehydrogenases of the Krebs cycle, SDH transfers succinate-derived electrons directly to the ubiquinone site (*via* three Fe-S clusters: [2Fe-2S], [4Fe-4S], and [3Fe-4S]) and not to soluble NAD^+ intermediates. Thus it is considered as an essential component of the respiratory chain (Figure II.2).

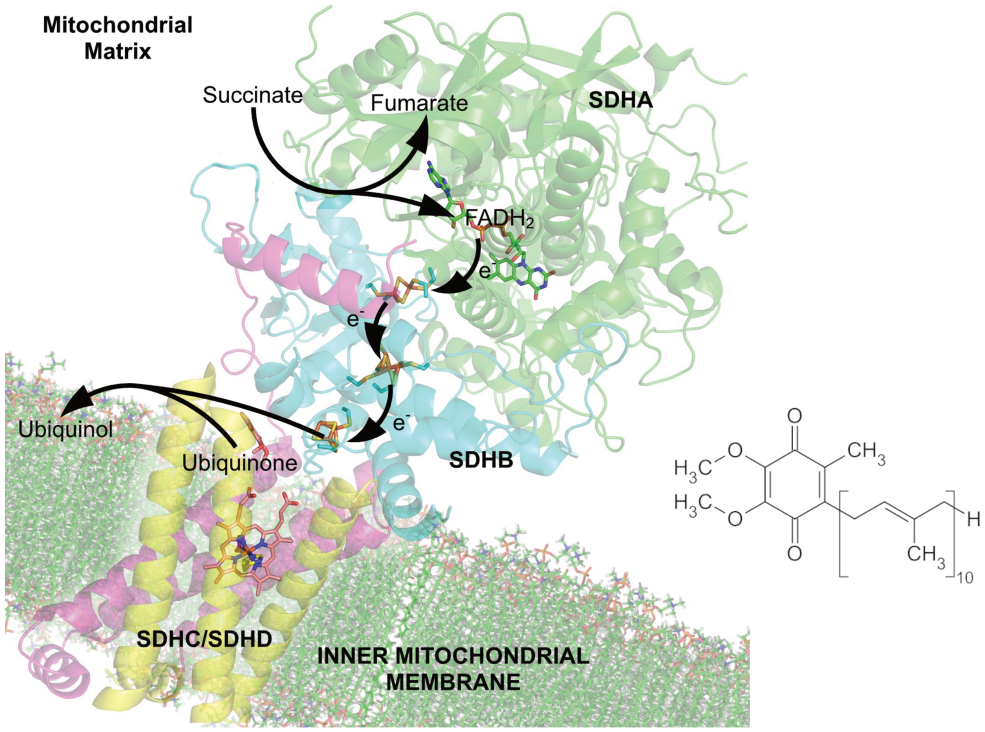


Figure II.2: SDH catalyses the electron transfer from succinate to ubiquinone (shown on the right) *via* flavoprotein subunit, iron-sulfur clusters and heme b. Fumarate and Ubiquinol are produced

Carboxamide-type SDHIs bind strongly to the ubiquinone-binding pocket (or Q_p site) and consequently block physically the access to the substrate. This prevents further enzymatic cycling of succinate oxidation, and correct proceeding of the respiratory cycle (or Krebs cycle), causing death of the fungal cell. The ubiquinone-binding pocket (or Q_p site) is structurally defined by the interface between the SDHB, -C, and -D subunits. The large diversity in chemical structures and diversity of biological spectrum displayed across SDHIs is caused by a high degree of variation for SDHC and SDHD sub-units across species.

The common feature of all SDHIs displaying large structural diversity is a central amide bond, essential for H-bond interactions in the ubiquinone binding-site of SDH (Figure II.3, bottom: "Polar cavity").

The "core" of the molecule attached to the carbonyl of amide bond, is used for classification. Hence, six main chemical types exist, depending on the core. The core moiety is essential for binding and *in vivo* potency, as it enters deeply into the active site of SDH. *N*-containing heterocycles (pyrimidine or pyrazole) supposedly increase the binding affinity *via* π-π interactions and additional H-bonding (through the

aromatic nitrogen) to the binding site. The pyrazole ring is the most represented core in marketed SDHIs, and a special emphasis will be put on this class of SDHIs in this chapter. (Figure II.3, top, red-dashed left panel; bottom, red circle). A linker is attached to the opposite amine side of the amide bond, and can be substituted or not.

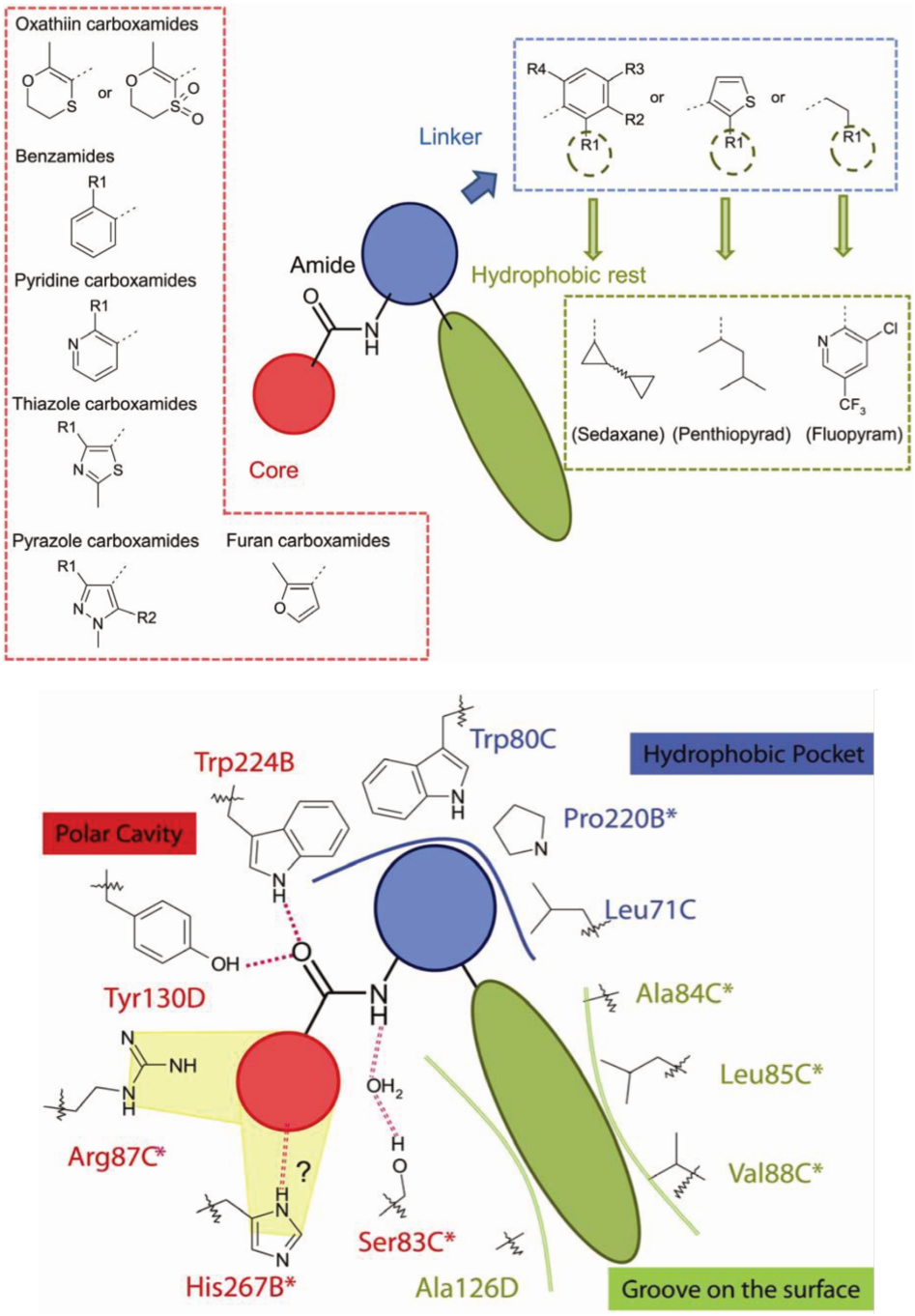


Figure II.3: Schematic representation of SDHIs fungicides (top); binding interactions of carboxamides inside *Mycosphaerella graminicola* ubiquinone-binding site (bottom).[1]

Most frequent linkers found in SDHIs are phenyl, thiophene or ethyl linkers. They ensure optimal hydrophobic contacts or π-π interactions to the binding site (Figure II.3, top: blue-dashed top-right panel; bottom: "hydrophobic pocket").
A hydrophobic rest usually substitutes the linker in *ortho*, forming with the amide an angle being crucial for the activity. When a thiophene ring replaces the phenyl linker, a close angle is maintained; in the case of an ethyl linker, a gauche conformation seems to help maintaining a similar angle. The hydrophobic rest has an important influence on the biological spectrum and potency of the compound, being partly exposed at the surface of the enzyme due to hydrophobic interactions with residues of SDHC and SDHD sub-units (Figure II.3, top: green-dashed right panel; bottom: "groove on the surface").[1]

The most recently marketed SDHIs (Figure I.15) cover all major relevant fungal classes in both foliar and seeds treatments, except the oomycetes (fungus-like eukaryotic microorganisms), especially *Pytophthora infestans* (late blight) and *Plasmopara viticola* (downy mildew). No SDHI treating efficiently these types of pathogens has been discovered up-to-now. Hence, there is still wide space open for the discovery of such key crop control ingredients, and new chemical structures could be a tool for reaching this objective. However, all new generation SDHIs share a common 3-CHF_2-pyrazole-carboxamide motif, and this feature seems the most active for now. The pyrazole part seems to be well optimized especially for the cereal pathogens treatment (foliar or seeds). Interestingly, CF_2H located in position 3 shows higher effect than CF_3.[8]
The variation of lipophilic rests in the recently marketed pyrazole carboxamide fungicides is obviously due to SAR studies and structure optimization, but also a way to overcome the intellectual property issue for a company trying to share the market with another installed competitor.

Resistance aspects

The spectrum of current SDHIs is very broad; 8 plant pathogens for monocotyledonous and 11 for dicotyledonous crop plants are monitored and reported by the FRAC [(fungicide resistance action committee), Crop Life, www.frac.info]. This may lead to an intensive use of SDHIs and high selection pressure for certain pathogens populations in certain areas. These populations receive several applications of SDHIs during the same cropping season, and the selection pressure exerted remains very high.[1]
The more recent fungicides are now intensively applied in various crops and deliver a broader spectrum of activity; consequently, several pathogens have already developed almost complete resistance or reduced sensitivity to the major fungicide classes used to control them; many cereal pathogens developed resistance to the Q_oIs, and reduced sensitivity to the demethylation inhibitor (DMI) fungicides, with dramatic effects in crops.[9] Pyrazole-carboxamides SDHIs also faced – in a smaller extent, resistance at an early stage,[10] but Complex II inhibitors resistance is rather limited so far.
However, this is a very critical concern in modern crop protection, and it is important to protect SDHI fungicides longevity and delaying resistance development, by using modern resistance-management strategies, suitable use recommendations, intelligent mixing concepts, etc. The resistance for SDHIs should be consequently reduced. The FRAC reports annually concerning the current resistance situation for SDHIs.
In parallel, new pyrazole carboxamide SDHIs are still being developed, as this class of fungicides presents a great potential, and resistance aspects require developing new products with new mode of actions (MoA), to which mutated pathogens will not survive.[11, 12]
The presence of bis-fluoroalkyl substituted agrophores on the market (Figure I.18) and the dynamics of the SDHI research field inspired the development of new synthetic strategies for the preparation of new bis(fluoroalkyl)pyrazole carboxamide structures. This is the main topic discussed in the following part of this chapter.

B. Introduction of EFSs into Pyrazoles – State-of-the-art

The high potential of pyrazole structures has been described in the introduction of this chapter, and represents an important research field, especially for agrochemical companies (*e.g.*: Bayer CropScience). In this part will be described the previous methods for the preparation of fluorinated pyrazoles, in order to understand the necessity to develop new scalable, cheap and efficient methods for the introduction of EFSs in pyrazoles and other heterocycles.

The synthetic approaches towards pyrazoles bearing "classical" fluorinated substituents (F or CF_3) are rather documented. For monofluorination strategies of various organic substrates, an excellent review was recently published and described the most recent innovations and latest fluorination reagents developed.[13] Late-stage aliphatic and aromatic monofluorination was also shortly reviewed.[14] The preparation of a diversity of monofluorinated pyrazoles has also been reviewed by Fustero *et al*.[15]
For trifluoromethylation of various organic substrates, excellent reviews have been published and cover many aspects of this chemistry.[16] Additional reports were recently published concerning new strategies or reagents for trifluoromethylation.[17-20]
The preparation of CF_3-pyrazoles usually relies on the use of CF_3-building-blocks,[21] and is performed *via* Michael-type additions (from α,β-unsaturated species), acid-catalysed or base-mediated condensations (from 1,3-dicarbonyls and hydrazines), multiple-component processes, metal-mediated cyclization and coupling reactions, 1,3-dipolar addition (from alkynyl functional groups), cycloaddition of alkynes with CF_3-sydnones, etc. Sequential trifluoromethylation/cyclization reactions are also known.[22]
Aromatic direct trifluoromethylation has been broadly studied and reviewed.[23] However, direct pyrazole trifluoromethylation is scarcely described (dechlorination-fluorination, deoxydifluorination, Cu-catalysed trifluoromethylations, etc.).[5] Direct *N*-trifluoromethylation of azoles (including pyrazoles) was reported using Togni's reagent.[24] Recently, an additional one-pot method has been reported for the preparation of CF_3-containing pyrazoles, pyrazolines and isoxazolines substituted with hydrazone or oxime groups. 5-(CF_3)-furan-3-ones were reacted with two equivalents of the corresponding hydrazines or hydroxylamine under acidic assistance.[25] The use of hydrazine dianions was also recently proven efficient for this purpose.[26] These building blocks remain of high interest as a few examples of modern SDHIs are built around this motif, *e.g.* Penthiopyrad (3-CF_3-pyrazole carboxamide SDHI, Figure I.15). More results should probably be reported in a near future.
In 2015, Sloop *et al*. published a review which summarizes the preparation of pyrazoles bearing fluorinated substituents (mostly F and CF_3, with several examples of CHF_2-pyrazoles) in C-3, C-4, C-5 or 1-*N*, by means of all these strategies and others.[5] The synthesis of pyrazoles bearing emergent fluorinated substituents such as CHF_2 and others will be discussed in more details.

1. Mono-Fluoroalkyl Pyrazoles

The preparation of difluoromethyl pyrazoles was studied by many research groups and a large amount of patents include such structures, especially for agrochemical applications.[27, 28] Even though the results published by Baran's group described the efficient difluoromethylation of various heteroarenes[29], this method was not applied to pyrazoles, and requires large quantities of reagents, which makes it non-suitable for industrial process. We have also seen that many difluoromethylation techniques were so far not suitable for industrial scale approaches. When looking more deeply in the literature, more relevant results concerning the preparation of difluoromethylated *N*-based heterocycles can be found. The use of difluoromethyl synthons showed more promising potential in this objective.
The 3-CHF_2-pyrazole carboxamide motif showed high activity against a variety of crops diseases, and the new-generation top-selling fungicide Bixafen® (Bayer CropScience) is prepared from the key intermediate ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate (DFMMP).

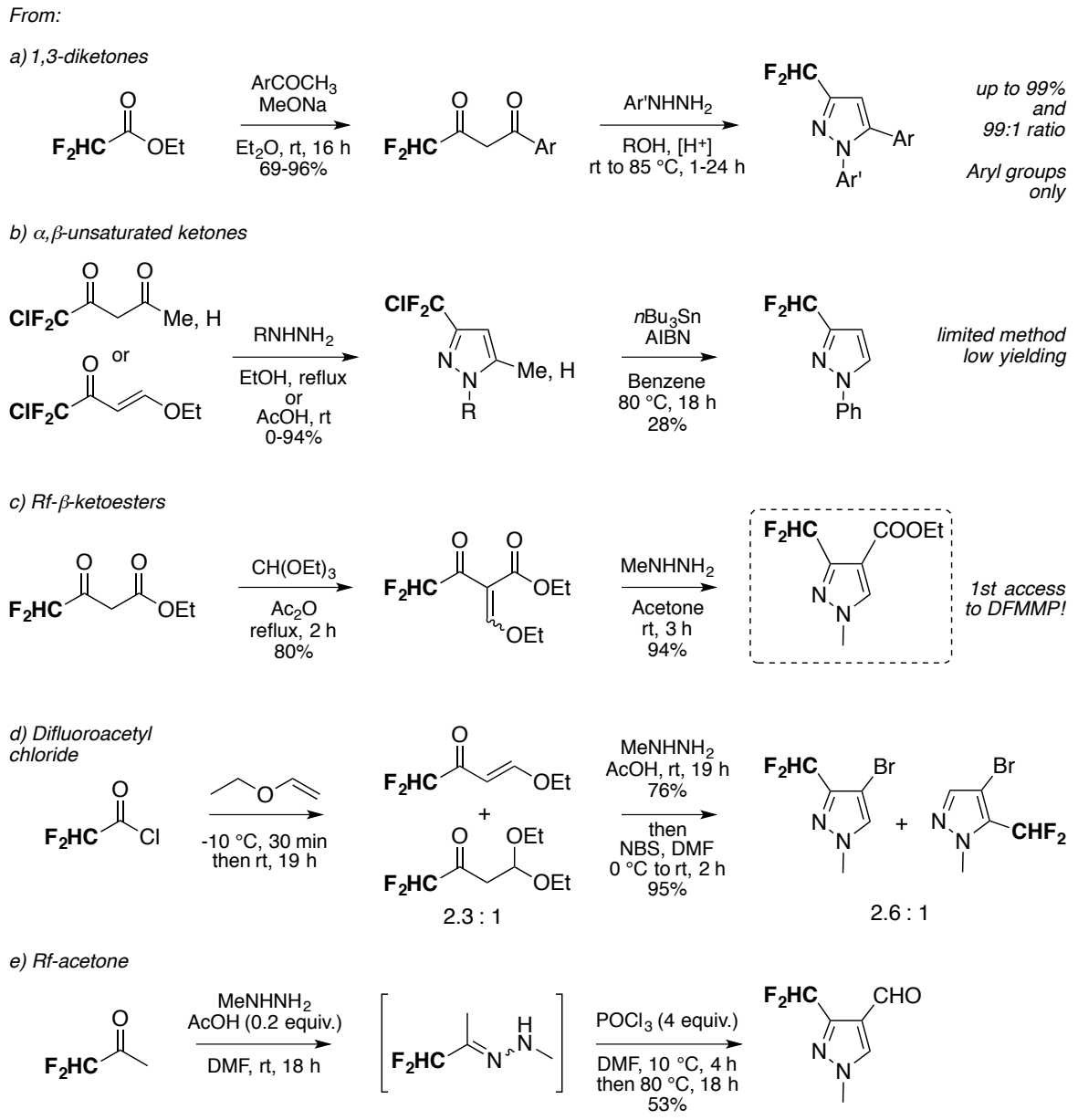
In 2003, Martins *et al*. already reported on the preparation of 3-CHF_2-pyrazoles using synthons approach from a Rf-diethoxypentenone, but the scope and efficiency of the method was rather limited.[30] Various strategies can be envisaged to access this intermediate, needed by several agrochemical leading companies, which all possess SDHI top-selling fungicides built around this core. Each company must develop its own production strategy to overcome concurrential intellectual property issues.

For economical considerations, it has to be prepared according to the most efficient, high yielding, atom-economical, low wasting and regioselective approach. Different strategies are available in the literature, and alternative strategies are frequently proposed[31] and patented. Our group published a review in 2013 covering the various approaches reported for the preparation of CHF_2-pyrazole building blocks from fluorinated synthons (Scheme II.1).[6] Amongst many interesting results, only one allowed the preparation of the desired DFMMP intermediate from CHF_2-acetoacetate (c, Scheme II.1). Further efforts were placed in the optimization of this approach avoiding the use of fluorinated acetoacetates, difficult to access at the corresponding period.
Various strategies were attempted to access fully regioselectively and quantitatively to DFMMP (Scheme II.2), as:

- Reductive defluorination and cyclisation (a)
- Radical reduction of $-CF_2Cl$ into $-CF_2H$ directly on the pyrazole ring (b)
- Preparation of enaminoketones from acylfluorides and aminoacrylates, and further cyclization (c)
- Intramolecular cyclization of hydrazines (after benzilidene deprotection, BASF)(d)
- Intramolecular cyclization of hydrazines (after dibenzaldazine deprotection) (e)
- Introduction of CHF_2 *via* the hydrazine (f)
- Dichloroacylation of aminoacrylate and fluorination of the 3-$CHCl_2$-pyrazole with TREAT-HF (g)
- Cyclisation of $CHCl_2$-ethoxyenone and late fluorination of the pyrazoles with TREAT-HF (h)

The objective was to optimize the preparation cost while maintaining the regioselectivity and high yield of the reaction. However, It seems difficult to combine quantitative yield and full regioselectivity for this key intermediate.
It has to be noted that ethyl difluoroacetoacetate became commercially available at a reasonable price only recently (similarly to ethyl difluoroacetate), explaining why the strategies to access efficiently DFMMP were not always based on the use of this reagent. Its CF_3-analogue was much more easily available from commercial sources.

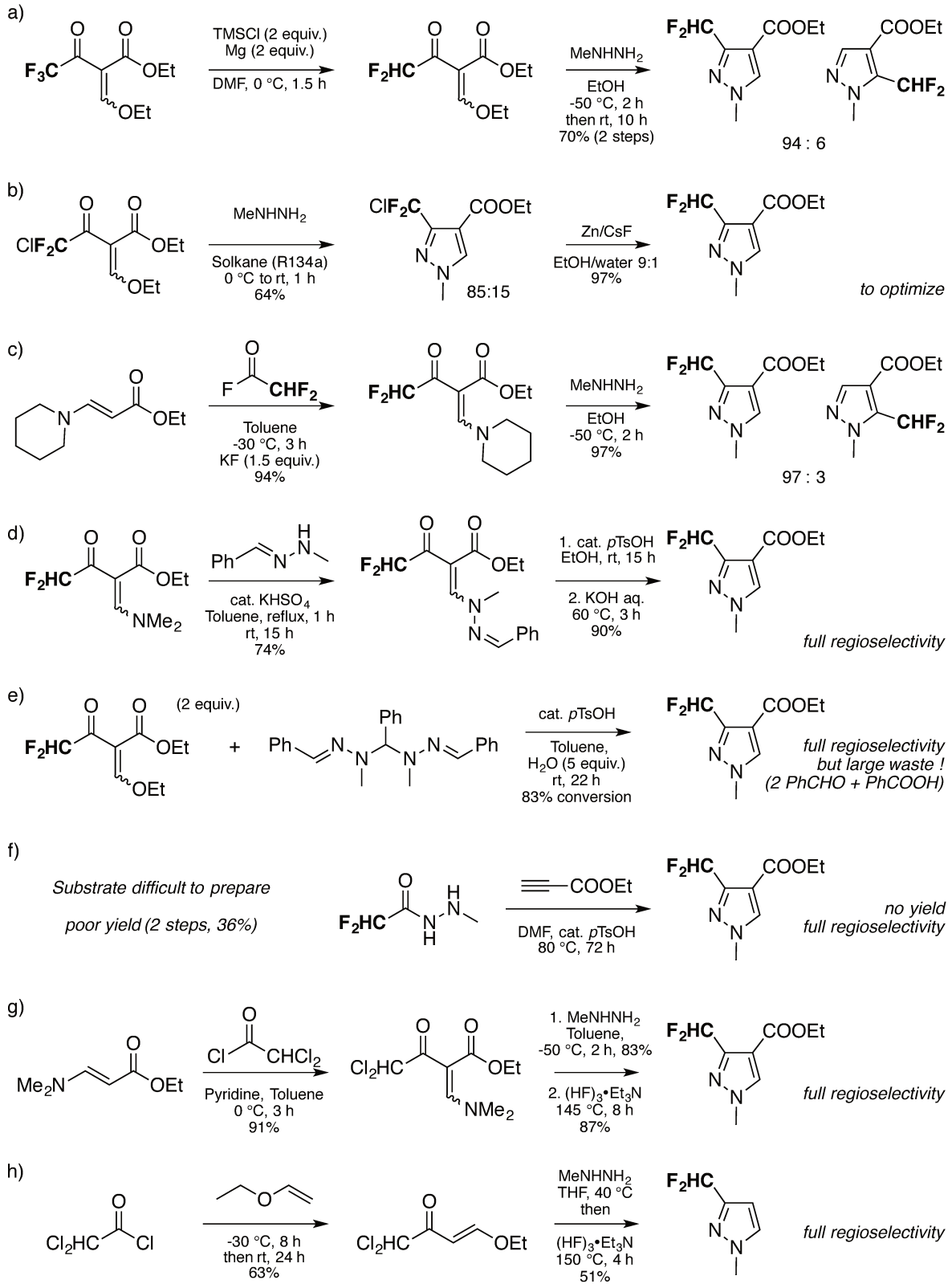
The preparation of CHF_2-pyrazoles from functionalized or difluoroacylated chromones (providing respectively 3-(2'-hydroxyphenyl)-5-CHF_2-*N*-methylpyrazoles and 3-CHF_2-4-(2'-hydroxyphenyl)carbonyl-*N*-methylpyrazole) and the late-stage deoxofluorination of functionalized pyrazoles carboxaldehydes were also reported in our review. The resulting CHF_2-pyrazoles were prepared in moderate to good yields (Scheme II.3).



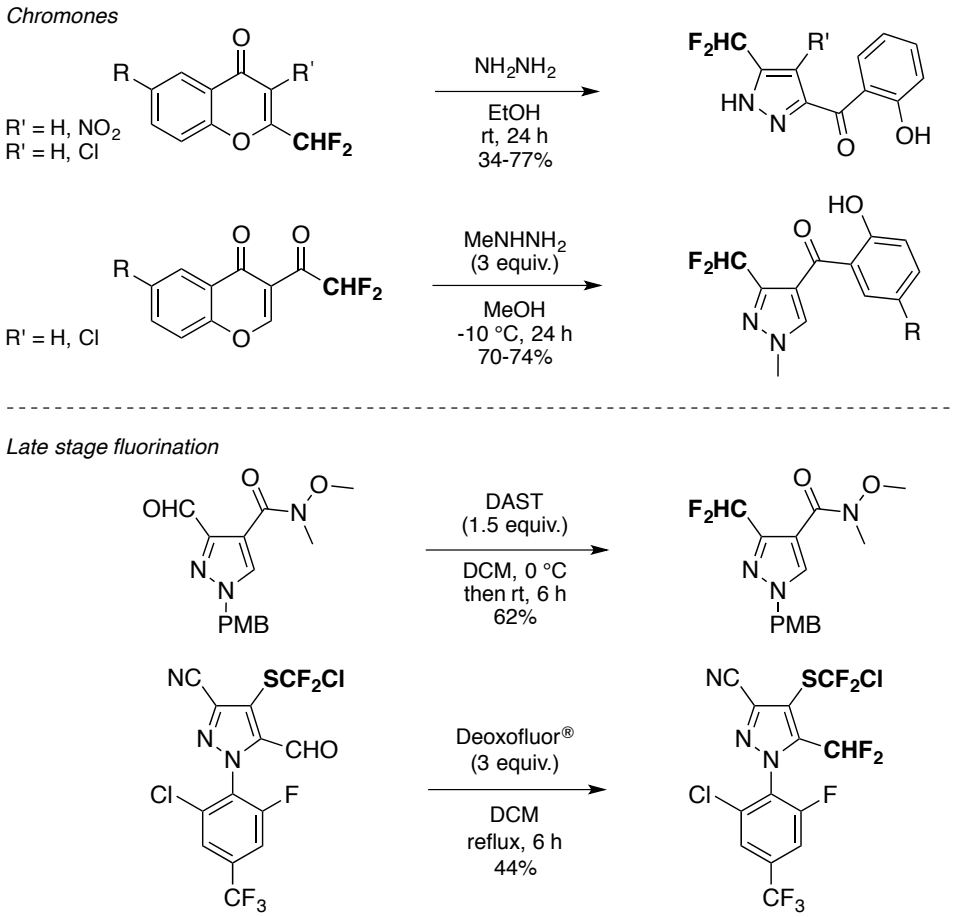
Scheme II.1: Various methods reported in Giornal's review for the preparation of 3-CHF_2-pyrazole building blocks

A few more examples of 3-CHF_2-5-hydroxypyrazoles and 3-CHF_2-5-alkyl/aryl pyrazoles were described using ethyl difluoroacetoacetate, difluoromethylated butynoates or CHF_2-alkynyl ketones (Scheme II.4).

In 2015, another approach based on CHF_2-synthons was reported by Mykhailiuk *et al.* for the preparation of important 3-CHF_2-5-pyrazole carboxylate building blocks, based on the [3+2] cycloaddition of alkynes with 2-diazo-1,1-difluoroethane (CHF_2CH-N_2, generated *in situ* from difluoro-ethylamine hydrochloride and sodium nitrite). This potentially toxic and explosive gaseous intermediate seems not suitable for ton-scale production (Scheme II.5).[32]



Scheme II.2: Various optimization strategies reported in our review for the preparation of DFMMP.

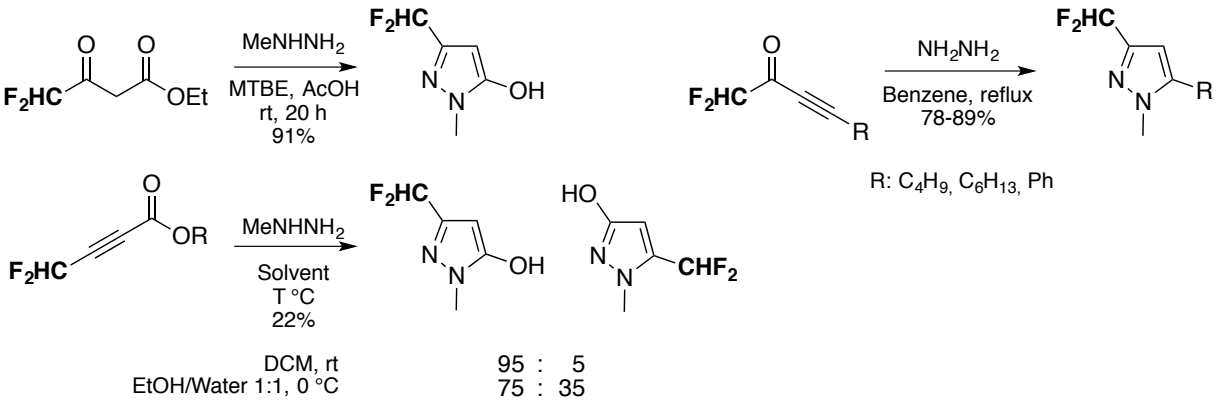


Scheme II.3: Preparation of (hydroxyphenyl)-carbonyl pyrazoles using chromones (left); late-stage deoxofluorination of pyrazole carboxaldehydes

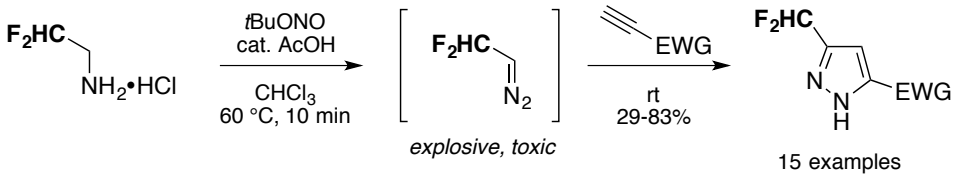
The strategy used by Bayer CropScience[33] relies on a new approach, based on the use of a specific Fluoroalkyl Amino Reagent (or FAR), 1,1,2,2-tetrafluoro-*N*,*N*-dimethylethan-1-amine (or TFEDMA, or Petrov reagent).[34]

FARs have recently become very promising reagents for the introduction of challenging EFSs such as CHF_2 and related. Their reactivity (after prior activation) will be discussed in details later in the chapter. The initial strategy involved the nucleophilic attack of ethyl 3-methoxyacrylate on the activated FAR. The resulting iminium intermediate was further cyclized by treatment with methyl hydrazine, and afforded the desired DFMMP with a 87:13 ratio of isomers. This is explained by the presence of two electrophilic centres resulting from a delocalization of the positive charge along the conjugated system. The hydrazine attack is not fully controlled in this case. This ratio was improved by replacing the methoxyacrylate by ethyl dimethylaminoacrylate, providing a ratio of 92:8.

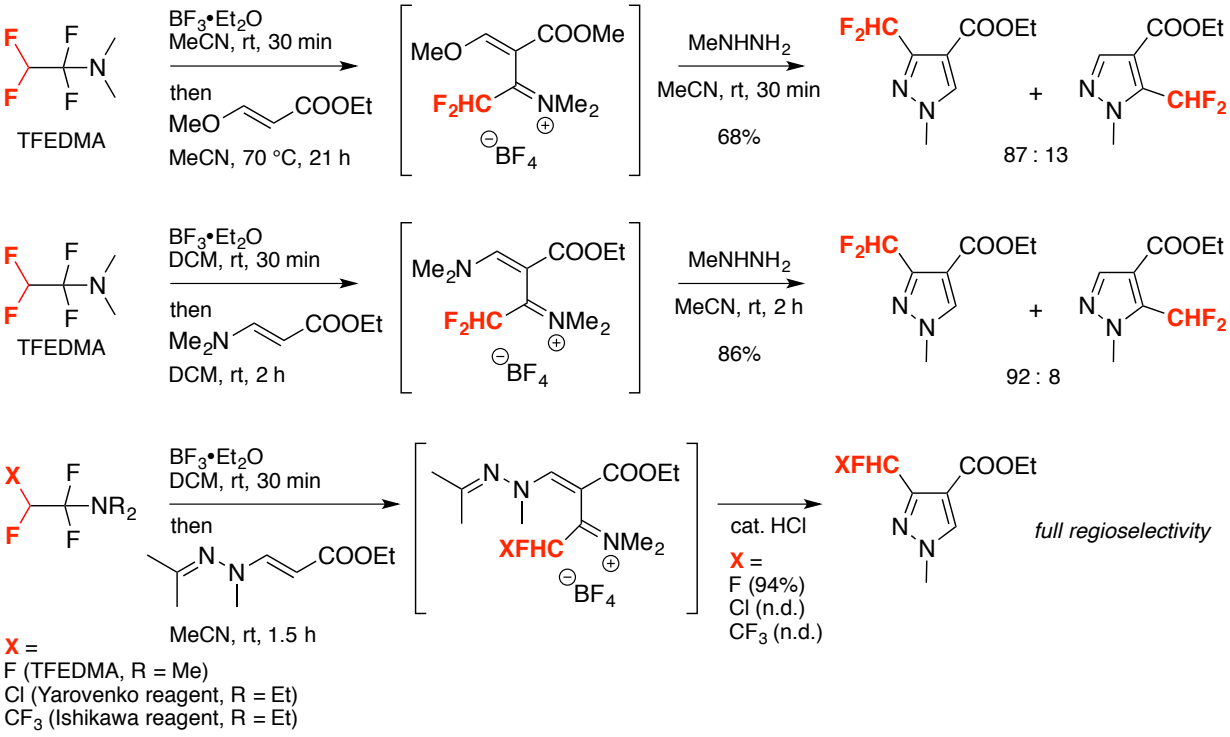
Finally, a strategy similar to examples d) and e) of the Scheme II.2 provided a full regioselectivity, by protecting an amino group from the condensed hydrazine as an acido-labile imine (Scheme II.6). The two other FARs were successfully employed in this strategy (yields were not reported).



Scheme II.4: Reported preparation of 3-CHF_2-5-hydroxypyrazoles and 3-CHF_2-5-alkyl/aryl pyrazoles



Scheme II.5: [3+2] Cycloaddition approach for 3-CHF_2-pyrazole building blocks.



Scheme II.6: New approach in the preparation of fluoalkyl pyrazole building blocks;
Use of Fluoroalkyl Amino Reagents and acrylates for the optimized preparation of DFMMP

2. Bis-Fluoroalkyl Pyrazoles

After promising results in the regioselective preparation of DFMMP, our group decided to study their potential of FARs for the preparation of other types of fluorinated building blocks. For example, the development of an efficient method to access bis(fluoroalkyl)pyrazoles was an important topic, in the context of a scientific collaboration between Bayer CropScience and our group (LCR C2OF, Bayer CropScience, CNRS), in the perspective of the discovery of new bioactive ingredients (Figure II.4).

The synthesis of novel fluorinated building blocks was deeply studied in our group, and an article was reported in 2013 on the preparation of unsymmetrical 3,5-bis(fluoroalkyl)-pyrazoles from fluorinated acetoacetates.[35, 36] This one-pot procedure afforded highly substituted pyrazole carboxylates **II.8-11** in good yields and excellent regioselectivity (>97:3), and the subsequent saponification provided the corresponding pyrazolic acids **II.12-14** representing valuable building blocks (top, Scheme II.7).

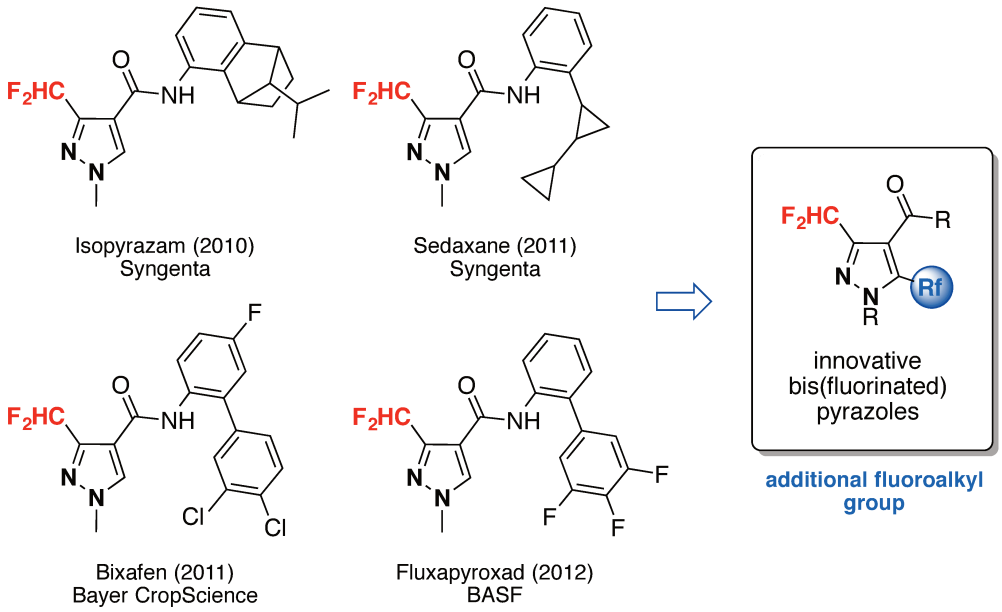
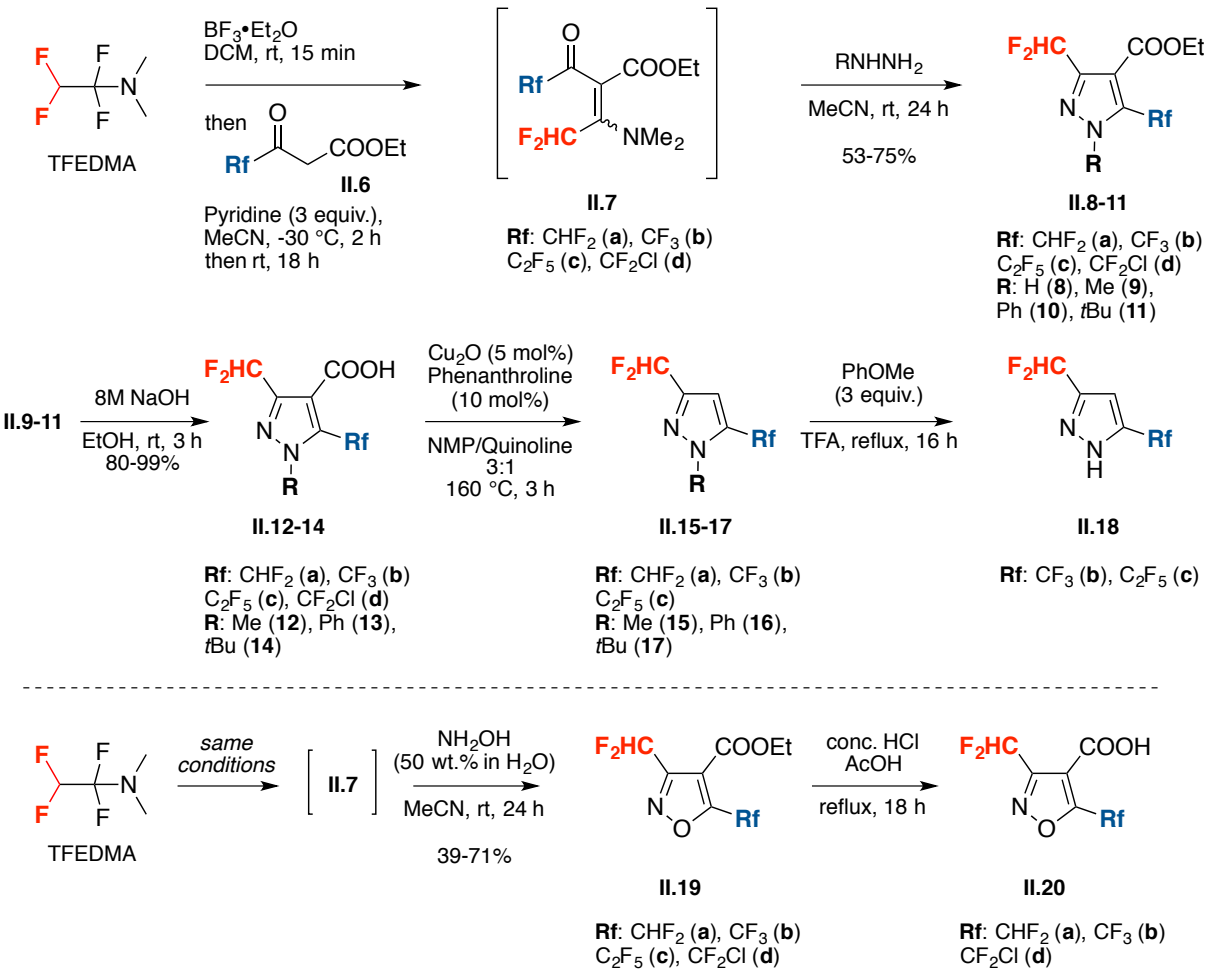


Figure II.4: Recent high interest from companies (*e.g.*: Bayer CropScience) in bis(fluoroalkyl)pyrazole building blocks[36]

A year later, our group reported the work of a PhD student (F. Giornal) in collaboration with Bayer CropScience on the development of a scalable process for the preparation of such compounds. An additional decarboxylation step allowed the access to unprecedented 3,5-bis(fluoroalkyl)pyrazoles **II.15-17**. It has to be noted that the saponification could not occur in the case of *N*H-pyrazoles, and an alternative method was applied to access two examples of 3,5-bis(fluoroalkyl)-*N*H-pyrazoles **II.18** *via* cleavage of the *N*-*tert*-butyl moiety of **II.17b-c** under harsh acidic conditions (Scheme II.7, top).[35-37] A similar strategy was applied by a postdoctoral fellow of our group (G. Landelle) for the preparation of 3,5-bis(fluoroalkyl)-isoxazoles **II.19** by using hydroxylamine instead of hydrazines, but was not published. The corresponding isoxazolic acids **II.20** were also accessed (Scheme II.7, bottom). Following these results, the key objective was to prepare more efficiently 3,5-bis(fluoroalkyl)-pyrazoles with a broader substitution pattern by means of efficient techniques.



Scheme II.7: First preparation of 3,5-bis(Rf)-4-pyrazole carboxylates, saponification, decarboxylation and first access to 3,5-bis(Rf)-*N*H-pyrazoles reported in our group (top); First preparation of 3,5-bis(Rf)-4-isoxazole carboxylates (unpublished, bottom)

3. EFS-substituted Pyrazoles

Concerning the preparation of pyrazoles substituted with other EFSs than CHF_2, several examples were found in the literature, and are summarized below.

C_2F_5

Several patents describing the synthesis of C_2F_5-pyrazoles from C_2F_5-acetic anhydride, 1,3-diketones, etc. (using multi-component synthesis) are available online.[27, 28] An early example was described in 1985, concerning the synthesis of a highly fluorinated pyrazole compound starting from a C_2F_5-based perfluorinated alkene [perfluoro(2-methyl-2-pentene)] and *via* a perfluorinated azine.[38]

In 1990, the synthesis of 3-C_2F_5-4-acylpyrazoles was described from acylation of acetylacetone or malonic ester using perfluoropropionic acyl fluoride, and subsequent cyclization of the tricarbonyl intermediate with hydrazines.[39] This route was hard to employ and is too limited. Furin *et al.* reported in 2001 the preparation of a perfluorinated 3-ethyl-4-methyl-*N*-phenylpyrazole and its *N*H-analogue by condensation of perfluoro(2-methyl-2-pentene) with pentafluorophenyl- or propionylhydrazine. Only two examples or hardly exploitable compounds were accessible *via* this approach.[40] Martins *et al.* reported in 2003 (in the same report previously cited) the preparation of two 3-C_2F_5-5-ethoxy-pyrazoles (*N*-substituted with H or CH_3) from C_2F_5-diethoxypentenone, but again this approach was very limited.[30]

After their first report on the preparation of CHF_2-pyrazoles using *in situ* generated CHF_2-diazomethane (Scheme II.5), Mykhailiuk *et al*. reported the preparation of 3-C_2F_5-pyrazoles using a similar strategy from C_2F_5-diazomethane.[41] Identical advantages and drawbacks can be listed when compared to their previous reports.
Dang, Langer *et al*. reported an innovative and selective method for the efficient one-pot synthesis of 5-C_2F_5-*N*H- or -*N*Me-pyrazoles, by cyclization of hydrazone dianions with ethyl C_2F_5-carboxylate. CF_3 and C_3F_7 substituents were also included. This approach uses mostly cheap and easily accessible material, except the required *n*-butyllithium, which is not suitable for industrial application.[26]

CHFCl
Pyrazoles bearing this EFS are very scarcely reported, and only one patent example describes such compound.[42]

$CHFCF_3$
Pyrazoles bearing this substituent are also scarcely reported. Fustero *et al*. published the preparation of 3-($CHFCF_3$)-pyrazole by late fluorination of its 1-hydroxy-2,2,2-trifluoroethyl analogue using Deoxofluor®.[43] Otherwise no examples of such pyrazoles are reported.

CF_2Br
Yongming *et al*. described the Au(I)-catalysed regioselective synthesis of 5-CF_2Br-alkyl/aryl-pyrazoles from CF_2Br-alkynyl ketones and hydrazines in presence of a catalytic amount of silver hexafluoroantimonate ($AgSbF_6$). In the absence of this additive, an opposite ratio of isomers up to 80/20 was observed, proving the potential of this method. A recent report concerning new examples of similar pyrazole was reported, but was published into a Chinese journal with difficult access to the article.[44]

CF_2Cl
One example of CF_2Cl-pyrazole was reported in an article from 1993, describing the 1,3-dipolar cycloaddition of ethyl diazoacetate with CF_2Cl-acetylenes and analogues.[45] More recently, a published review from our group reported the cyclization of chlorodifluoromethyl-1,3-diketones and enones to obtain the corresponding CF_2Cl-pyrazoles, which were further transformed into CHF_2-analogues (Scheme II.1).[46]

In the previous sections of this Chapter, the fast expansion of the SDHI fungicides area has been detailed as well as their mode of action. In this context, the 3-CHF_2-pyrazole carboxamides are considered as very efficient and several compounds are currently on the market. The key intermediate DFMMP is crucial in the production of a marketed SDHI fungicide (Bixafen, Bayer CropScience), and the various innovative methods for its preparation have been summarized. Recently, an industrial process using TFEDMA (a Fluoroalkyl Amino Reagent, or FAR) for the efficient and highly regioselective preparation of DFMMP has been developed. In the next part, a large focus will be placed on the description of the FARs, from the very early reports of their preparation in the 1950's to the most recent synthetic strategies developed. Afterwards, the results obtained during this PhD will be disclosed in full details.

C. Fluoroalkyl Amino Reagents – A new tool

FARs are a class of chemicals that was slightly forgotten over the last decades, as the organofluorine chemistry started to encounter a real "boom" in various research fields. As demonstrated in the Chapter I, many bioactive compounds bearing classical but also emergent fluorinated substituents were commercialized over the last decades. Nowadays the agrochemistry faces a real need for the discovery of new bioactive ingredients (with new modes of action), which will be able to overcome the resistance observed with some agrochemicals (*e.g.*: strobilurins Q_OIs, site-selective fungicides, facing large resistance phenomenon). For this purpose, the development of new building blocks is crucial, and the introduction of EFSs can be a possibility of accessing new candidates. FARs are definitely a new alternative for preparation of valuable fluorinated compounds. This will be discussed along this chapter.

1. History and development

Early reports concerning the synthesis of the preparation of α,α-difluoro-dialkylamines from fluorinated alkenes were reported right after the WWII. It correlates with the discovery of PTFE in 1938 (and a period of war coming after). During the following decades, several articles from American, Russian or Japanese scientists reported on the preparation or uses of such chemicals. After 1950, Pruett *et al*. were the first to report on the reaction of fluorinated alkenes and nucleophiles.[47]

Knunyants *et al*. reported in 1956 the reaction of perfluoropropene with diethylamine with little details, which are also difficult to find. In 1959, Yarovenko *et al*. reported on the preparation of the FAR named after him, the Yarovenko reagent (or 2-chloro-*N*,*N*-diethyl-1,1,2-trifluoroethan-1-amine), but the access to this reference is similarly difficult. This FAR was already described in Pruett's report. At the same period, England *et al*. reported the reaction of 1,1-difluoroolefins with sodium cyanide, and two years later the same team reported on the addition of many nucleophiles on fluoroolefins.[48] The fluorination of steroidal alcohols, hydroxyl-carbohydrates, and other functional groups (carbonyl, esters and amino-groups) was reported using the Yarovenko reagent a few years later, as well as natural products.[49-55]

In 1975, Wakselman *et al*. published the first acylation of electron-rich heterocycles (dimethylamino-benzenes or -naphthalene, indole, thiophene and *N*Me-pyrrole) using three FARs in their activated fluoro iminium salts form.[56]

The highly electrophilic fluoro iminium salt undergoes electrophilic aromatic substitution in presence of electron-rich arenes. The hydrolysis of the resulting aryl-iminium intermediate provided the fluoroacylated compounds in 30-78% (Figure II.5). In 1979, Ishikawa *et al*. reported the use of *N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (resulting from the condensation of perfluoropropene and diethylamine) for the fluorination of alcohols, similarly to the Yarovenko reagent.[57, 58] This FAR is known as the Ishikawa reagent. The same year, this group published the preparation of fluorinated benzoxazole, benzimidazoles, benzothiazole, benzodioxole and quinazolone bearing the –CHFCl motif from the Yarovenko reagent without Lewis acid activation, with yields ranging from 50 to 75% (Figure II.6).[59]

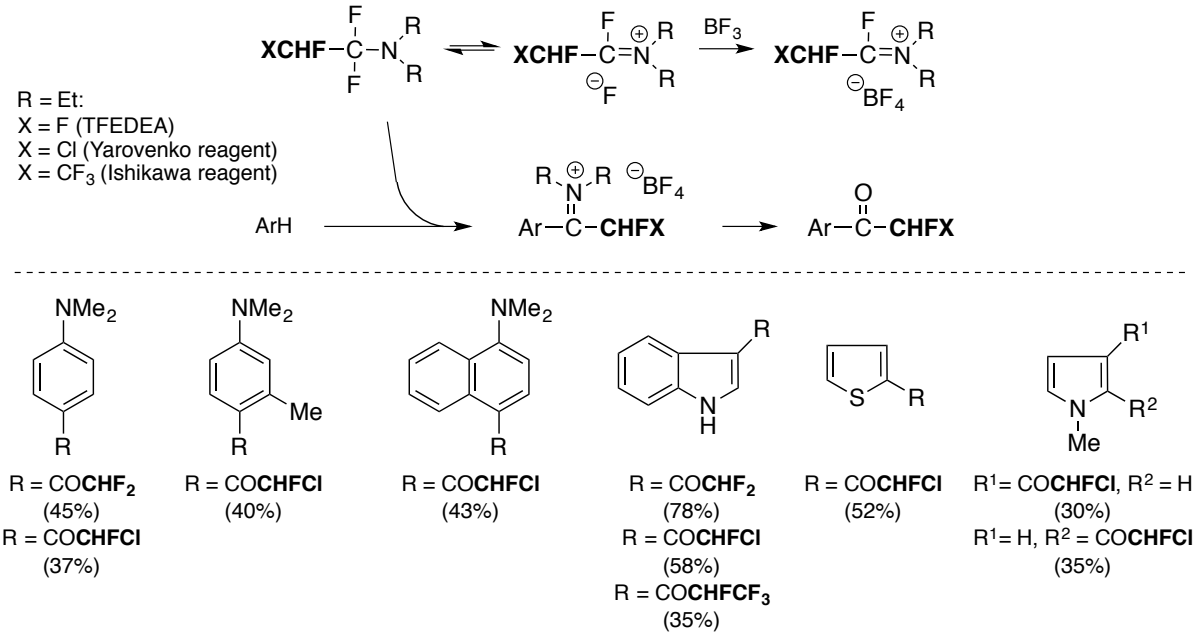


Figure II.5: Historical report from Wakselman (1975) on the Lewis acid activation of FARs and acylation of electron-rich arenes and heteroarenes

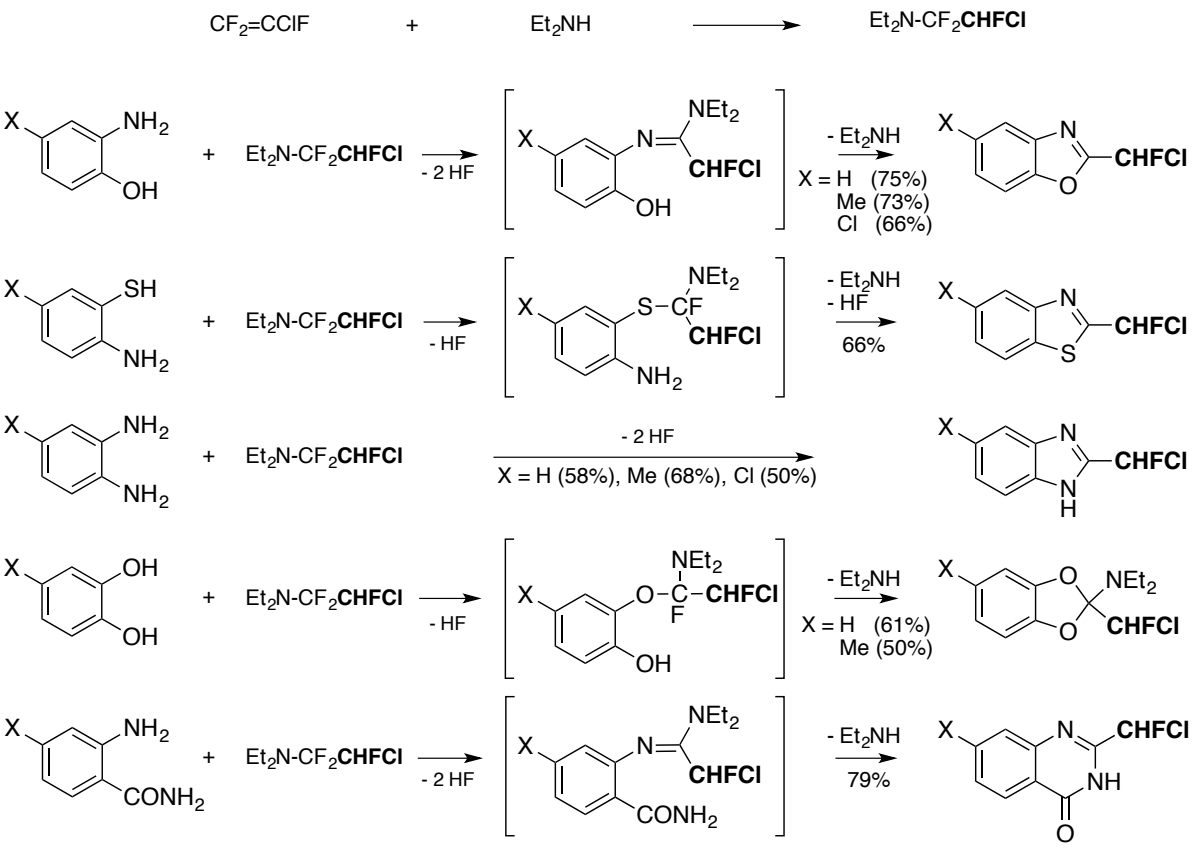


Figure II.6: Report from Ishikawa *et al.* (1979) of the first use of (non-activated) FARs for the synthesis of fluorinated heterocycles

Surprisingly, the synthesis of fluorinated heterocycles by means of FARs was not much reported after these initial findings. In 1980, their use as dehydrating agent to prepare acetylenic ketones from β-diketones was reported.[60] A few years later, they were used without activation as fluorination reagents for the conversion of perfluorinated carboxylic acids into the corresponding acyl fluorides.[61, 62]

In 1985 was reported the use of the gaseous precursor of Ishikawa reagent (perfluoropropene, PFP) or its hydrolysis product (*N*,*N*-diethyl-2,3,3,3-tetrafluoropropanamide) to prepare α-fluoro-β-ketoesters or diesters (top and middle, Figure II.7). These products were further converted into a variety of fluoro-heterocycles, including 4-fluoro-pyrazoles (bottom, Figure II.7).[63]

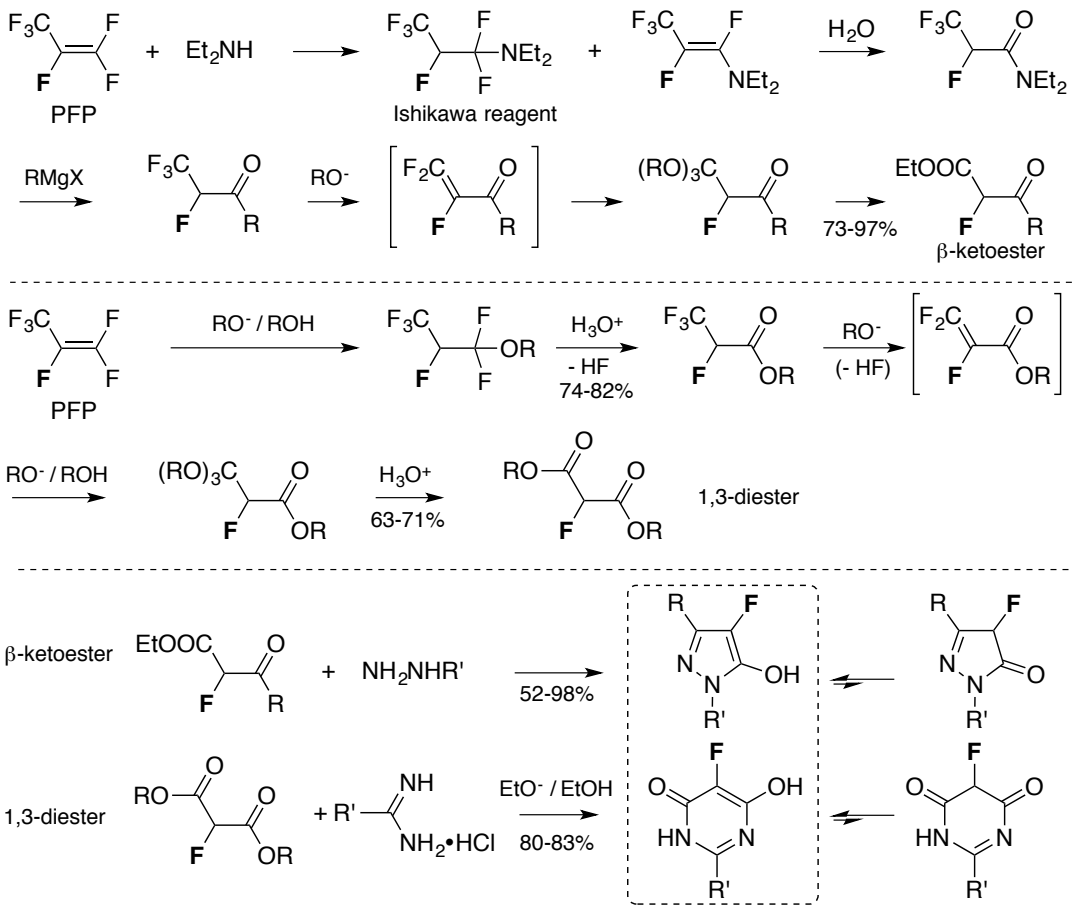


Figure II.7: Historical report of the first fluorinated *N*-based heterocycles prepared using PFP

During the next decades, FARs were used almost restrictively as fluorinating reagent for various alcohols. In 2001, Petrov *et al*. reported a nice review on the use of TFEDMA (1,1,2,2-tetrafluoro-*N*,*N*-dimethylethan-1-amine) as selective fluorinating reagent, with an optimized preparation procedure in sealed system without solvent. This FAR is sometimes called the Petrov reagent.[34]
In 2002, the Ishikawa reagent was used as amide coupling reagent (for its capacity to convert carboxylic acids to acyl fluorides).[64] In 2011, the same group reported on the reaction of non-activated TFEDMA with linear 1,3-diketones (providing deoxofluorination of ketones) and with cyclic 1,3-diketones (providing difluoroacylated compounds). And more recently came different applications for the FARs, as discussed in the next part of this chapter.

2. Preparation and availability

Nowadays, Petrov reagent **1A**, Yarovenko reagent **1B** and Ishikawa reagent **1C** are commercially available from many suppliers, but they are still prepared by hydroamination reaction when reacting the corresponding alkene with a secondary amine. The FARs **1A-C** are prepared from bulk chemicals produced on ton-scale in the plastic industry (Figure II.8). This represents an advantage, as both ingredients for the preparation of FARs are rather cheap.

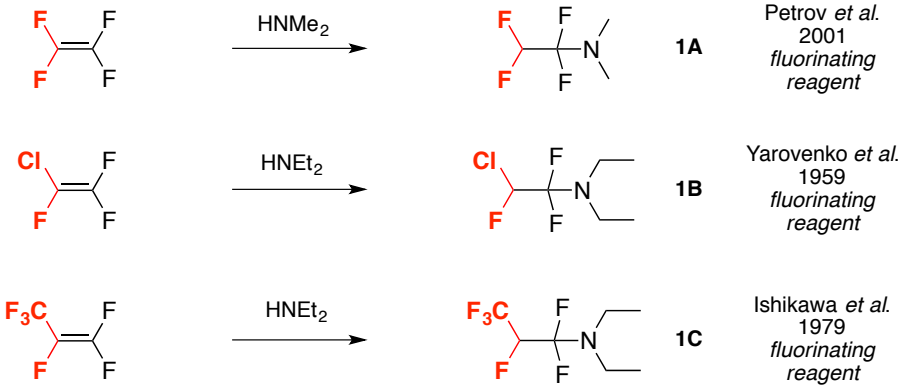


Figure II.8: Commercially available FARs 1A-C

TFEDMA **1A** can be purchased with a relatively high purity (>97%), and the use of this yellow oil is very convenient. The only measure is to sample this FAR (stored in a Teflon bottle) under argon flux, as it is moisture sensitive, and its hydrolysis results in a release of hydrofluoric acid (HF).
Yarovenko reagent **1B** is a dark brown oil (available with 97wt.% purity) whereas Ishikawa reagent **1C** is a pale brown oil of lower initial purity (*ca.* 90wt.%). However, both FARs degrade much more rapidly than TFEDMA, and their purity has to be evaluated prior to use by means of NMR analysis in anhydrous and non-nucleophilic deuterated solvents (*e.g.*: CD_3CN). They need to be similarly sampled under inert atmosphere.

3. Reactivity of FARs

As it has been reported over the last decades, FARs possess a peculiar reactivity due to the presence of highly electron-withdrawing fluorine atoms located on a single branch of a tertiary amine. The negative hyperconjugation phenomenon occurring from the nitrogen non-bonding orbital electron pair towards an empty C-F bond σ* anti-bonding orbital weakens this latter, and an equilibrium between the amino- and the iminium forms occurs. This phenomenon gives to α,α-difluoro-dialkylamines (or FARs) their specific reactivity. The naturally occurring fluoro iminium fluoride salt can be hydrolysed in contact with air, releasing two equivalents of HF while forming the corresponding acetamide. It is also used for fluorination of alcohols (ROH), as previously described. Once activated, the iminium is highly moisture sensitive, and can also release one equivalent of HF after hydrolysis (Figure II.9). By adding a suitable Lewis acid (BF_3•Et_2O, $AlCl_3$, etc.), the difluoro amine/fluoro iminium equilibrium can be fully shifted to the iminium tetrafluoroborate salt.

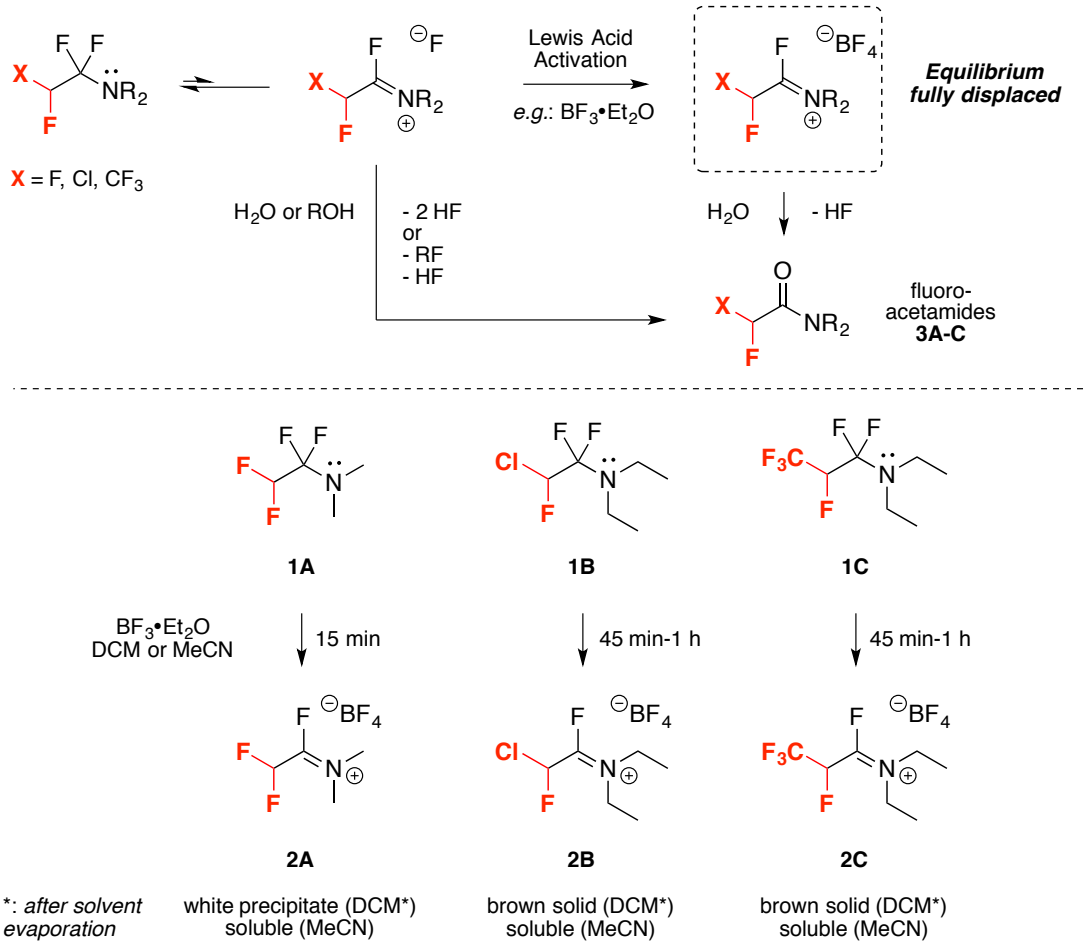
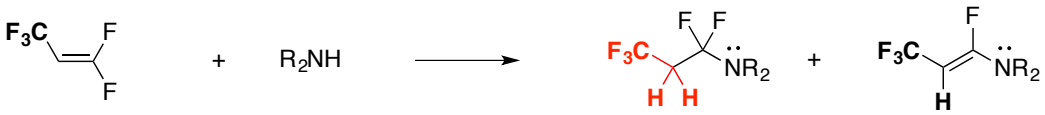


Figure II.9: Specific reactivity of FARs (top), and Lewis acid activation towards highly electrophilic fluoro-iminium salts 2A-C (bottom).

The activation of TFEDMA **1A** is readily occurring in DCM (forming rapidly a precipitate) or MeCN (soluble). The corresponding iminium **2A** can be isolated quantitatively after evaporation of the DCM as a white solid stable for a few hours under inert atmosphere, but only a few minutes under open air. This FAR is sufficiently convenient to use to avoid this step and to be activated in MeCN directly, as this solvent is the solvent of choice for the further reactions.
However, the FARs **1B** and **1C** are of initial lower purity, but also more slowly activated. Typically, the activation of these FARs was achieved over 30min to 1h. A precipitation of their corresponding iminium salts **2B** and **2C** in DCM will be preferred when employing these FARs (Figure II.9).
Concerning the choice of the Lewis acid, boron trifluoride diethyl etherate (BF_3•Et_2O) is a very efficient example, but aluminium(III) chloride ($AlCl_3$) can also be used. The activation of TFEDMA **1A** with $AlCl_3$ is slightly longer, and takes typically one hour in MeCN instead of <15min with BF_3•Et_2O.
The resulting counter-anion is also important in the reactivity of activated FARs. Tetrahedral BF_4^- is less nucleophilic and basic than nitrates and halides, and BF_4^- salts are usually also more soluble in organic solvents. BF_4^- is however slightly sensitive to hydrolysis. One can usually consider that its cation is the reactive specie, whereas the tetrahedral BF_4^- anion is inert.

An issue concerning the preparation of FARs is the possibility of elimination of HF, resulting in the formation of α-fluoroenamine, as reported by Ishikawa *et al*. in 1979, and more recently by Walkowiak *et al*. in 2012.[57, 65] This group reported on the preparation of other potential FARs from 1,1,3,3,3-pentafluoropropene (PFP) and secondary amines, which could be employed for the chemistry which will be described later in the manuscript. (Figure II.10).



$HNMe_2$	8	92
$HNEt_2$	<1	>99
Pyrrolidine	83	17
Piperidine	**>99**	<1
Morpholine	89	11

Figure II.10: Influence of the secondary amine on the elimination process of FARs

To overcome this elimination issue, Yarovenko and Ishikawa reagents are prepared from diethylamine, providing *N*,*N*-diethyl analogues which are less prone to elimination, have a rather good stability upon storage (at the opposite of their *N*,*N*-dimethyl analogues which eliminate rapidly). Each FAR possesses a specific behaviour concerning the elimination, and Petrov reagent is a good example of a *N*,*N*-dimethyl FAR not prone to elimination.

It has to be noticed that the use of such reagents is rather simple on small-scale reactions (up to reasonable gram scale), even though small quantities of HF are released. Simple glassware (usually Schlenk-type) was conveniently used repeatedly over the PhD project without excessive corrosion. Teflon flasks were preferred with reaction between 10 and 50g scale. In the perspective of industrial scale processes, the handling of HF will have to be dealt with similarly to other large-scale fluorinations, with specific care about released hydrofluoric acid. As previously described, Wakselman *et al*. (1975) used the electrophilic character of the iminium tetrafluoroborate salts of TFEDMA, Yarovenko and Ishikawa reagents to acylate electron-rich arenes, but no further results were reported on the use of such activated FARs. In 2008, Pazenok *et al*. reported on the use of activated TFEDMA (after treatment with BF_3•Et_2O) in a patent describing the preparation of DFMMP, the key intermediate of Bixafen® (a modern SDHI fungicide, described in Chapter II).[33] In our group, several articles were published in relation with organofluorine chemistry. F. Giornal's PhD project, and G. Landelle's post-doctoral one-year fellowship were partly dedicated to the FAR chemistry, with the preparation of innovative 3,5-bis(fluoroalkyl)pyrazole and isoxazole building blocks (Scheme II.6). We decided to study the chemistry of FARs in more details.

D. Development of novel fluorinated pyrazole building blocks

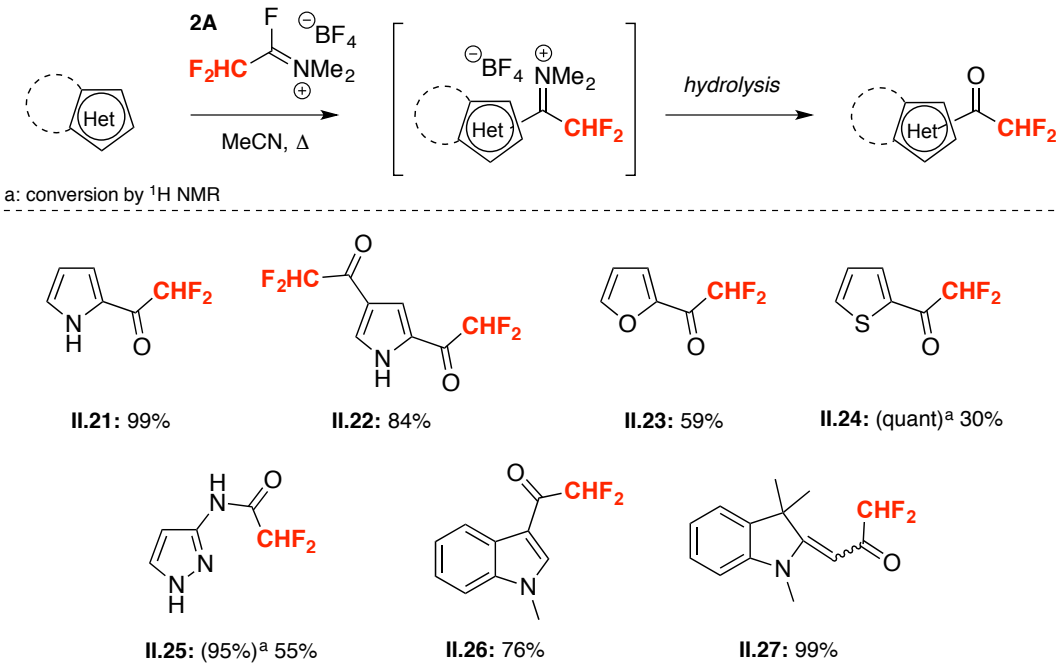
Before considering the synthesis of more complex fluorinated structures, it was necessary to complete the knowledge concerning TFEDMA but also the other FARs (Yarovenko and Ishikawa reagents). A large study was achieved using TFEDMA as a reference FAR, before developing other methods to prepare innovative building blocks using FARs.

1. Reactivity of activated FARs – Example of TFEDMA

The Petrov reagent was chosen to perform a study of the versatility of FARs used in their activated form. In a first approach, the difluoroacylation initially performed by Wakselman *et al*. in 1975 was further studied.

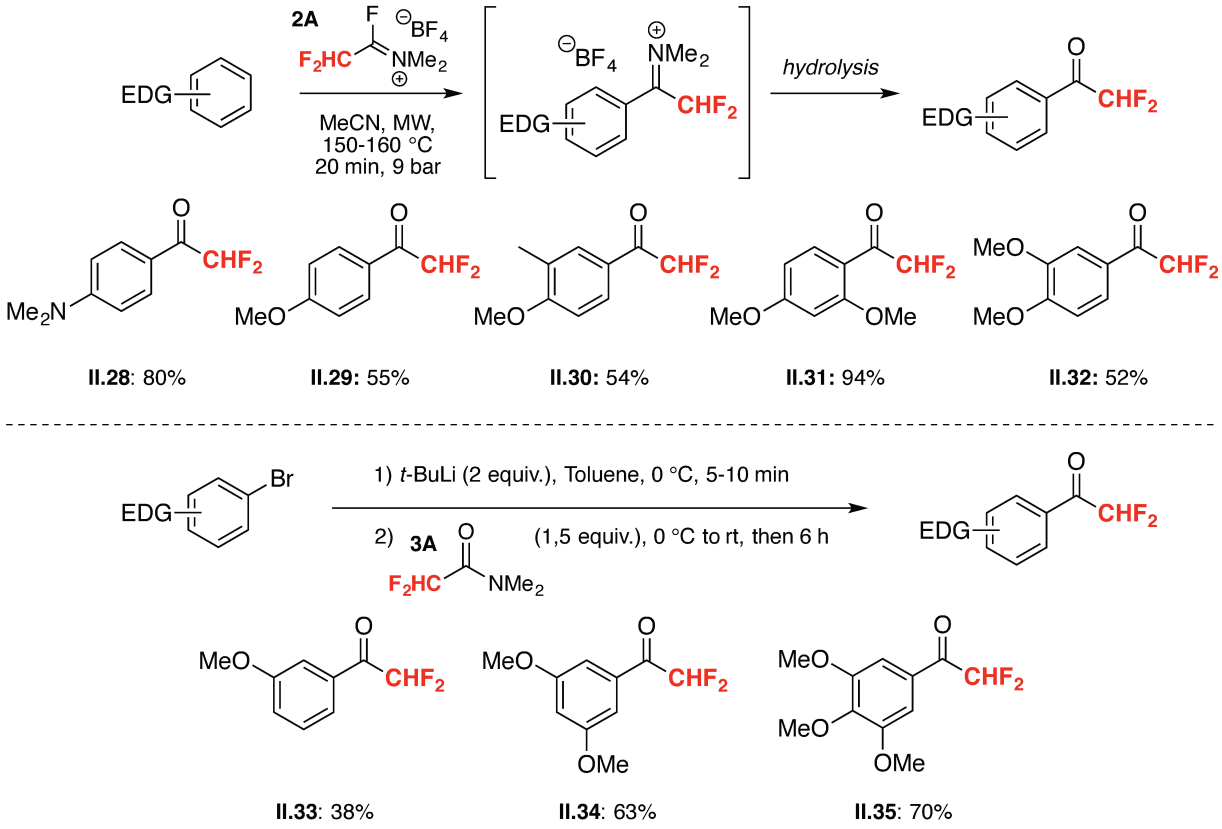
a) Difluoroacylation of electron-rich substrates using TFEDMA

Electron-rich heterocycles were efficiently difluoroacylated under thermal conditions using activated TFEDMA **2A**. Again, the most electron-rich position was selectively acylated. Reaction time was completely substrate-dependant, and is comprised between 1 and 72h for several examples. Pyrrole was efficiently difluoroacylated (**II.21**) and a second difluoroacylation was achieved to provide **II.22** with high yield. Furan and thiophene gave lower yields, due to a high volatility and sensitivity towards hydrolysis or decomposition of **II.23** and **II.24**. 3-Aminopyrazole reacted *via* its most nucleophilic position (the amino group), providing the corresponding amide **II.25** *via* nucleophilic attack. *N*-methyl indole and trimethyl-methyleneindoline were very efficiently converted into products **II.26** (see Figure II.11) and **II.27** in short reaction times. Interestingly, the iminium tetrafluoroborate salt intermediate of the reaction with *N*-methyl indole can be quantitatively isolated. Pyrazole, imidazole, or benzofuran were not compatible with this reaction.



Scheme II.8: Difluoroacylation of electron-rich heterocycles using activated FAR 2A

The difluoroacylation of electron-rich arenes was achieved initially using thermal conditions, but the use of microwave assistance lead to much shorter reaction time and higher yields. The yields were satisfying especially when looking at the literature. Indeed, very few methods for the direct introduction of difluoroacyl group were reported. The regioselectivity of the electrophilic aromatic substitution acylation was governed by the presence of electron-donating substituents and the most electron-rich position was selectively acylated (top, Scheme II.9). To control the position of difluoroacylation, a parallel strategy was developed using the corresponding bromo-arenes. After a Br-Li exchange (using *t*-BuLi) in toluene at 0 °C for 5-10min, the lithiated arenes were canulated onto a solution of the 2,2-difluoro-*N*,*N*-dimethylacetamide **3A** in toluene. After 6h at room temperature, the reaction was complete. This alternative route was slightly less effective depending on the substrate. The use of ethyl difluoroacetate was not providing similar results, probably due to bis-addition of the nucleophile or side-reactions (bottom, Scheme II.9).



Scheme II.9: Difluoroacylation of electron-rich arenes by electrophilic aromatic substitution (top) and Br/Li exchange strategy before trapping with acetamide 3A (bottom)

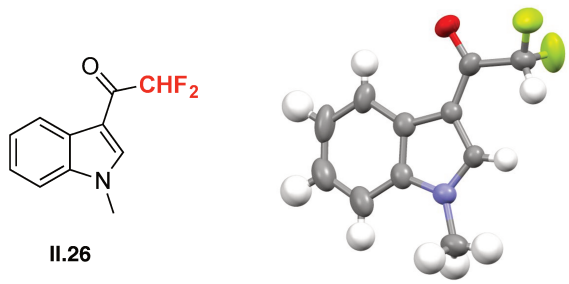
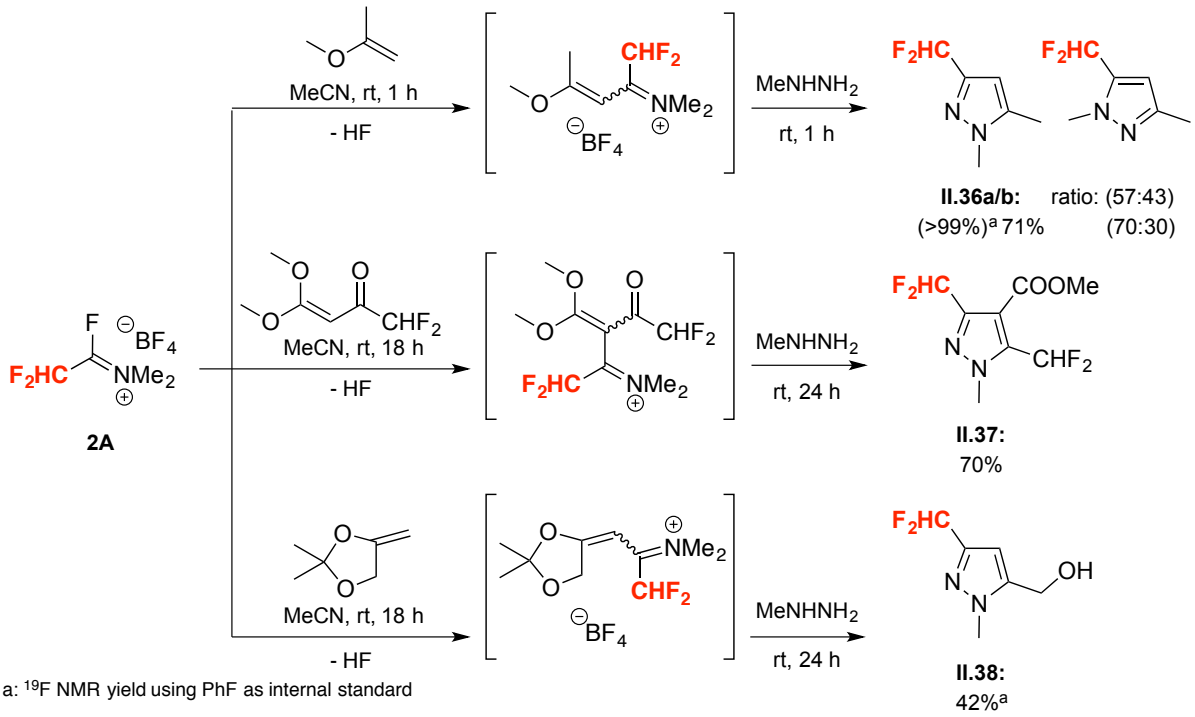


Figure II.11: Crystallographic analysis of a single crystal of compound II.26

b) TFEDMA as CHF_2-transfer reagent

The activated TFEDMA **2A** was further used for the synthesis of CHF_2-heterocycles such as pyrazoles. Different types of nucleophilic substrates (vinyl ethers and analogues, silyl enol ethers, CH-acidic compounds) were considered and efficiently provided the desired products after formation of an iminium intermediate and further treatment with hydrazines or hydroxylamine. All examples providing pyrazoles can potentially be applied to the synthesis of the corresponding isoxazole by replacing hydrazines by hydroxylamine.

The first reactions were attempted with vinyl ethers (2-methoxypropene) and analogues (self-prepared 1,1-difluoro-4,4-dimethoxybut-3-en-2-one, or 2,2-dimethyl-4-methylene-1,3-dioxolane provided by BCS) (Scheme II.10) :

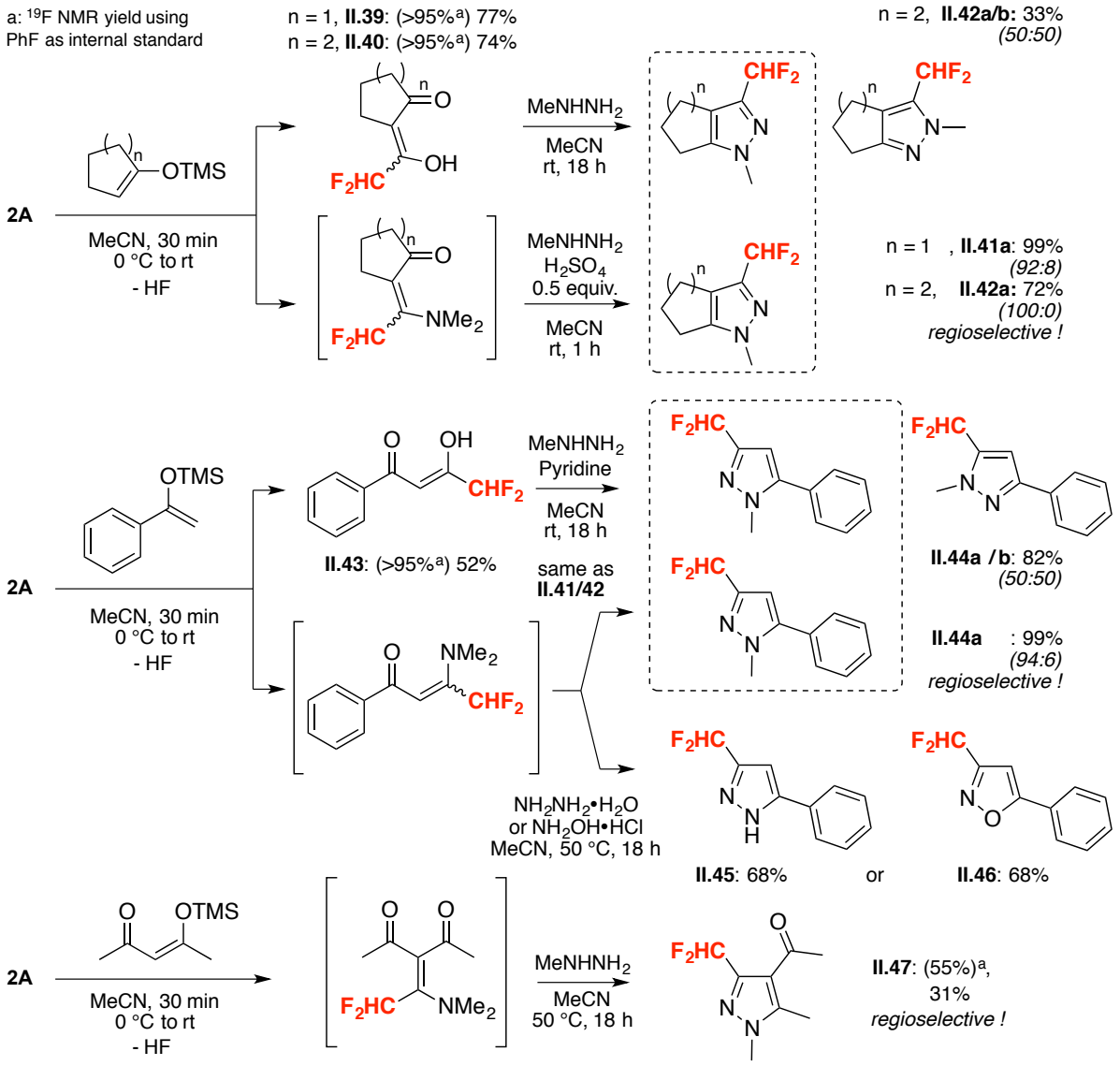


Scheme II.10: Reaction of 2A with vinyl ethers and analogues

The regioselectivity is difficult to comment at this stage, but we suppose a favourable attack of the NH_2 moiety of methyl hydrazine onto fluoro iminium electrophilic centre. Pyrazoles **II.36a/b** were easily purified by distillation under reduced pressure. Bis(fluoroalkyl)pyrazole carboxylate **II.37** was efficiently prepared from the starting ketene acetal; the synthesis of hydroxyl pyrazole **II.38** was difficult to reproduce and the best result was obtained when the $AlCl_3$ was used to activate the FAR **1A**.

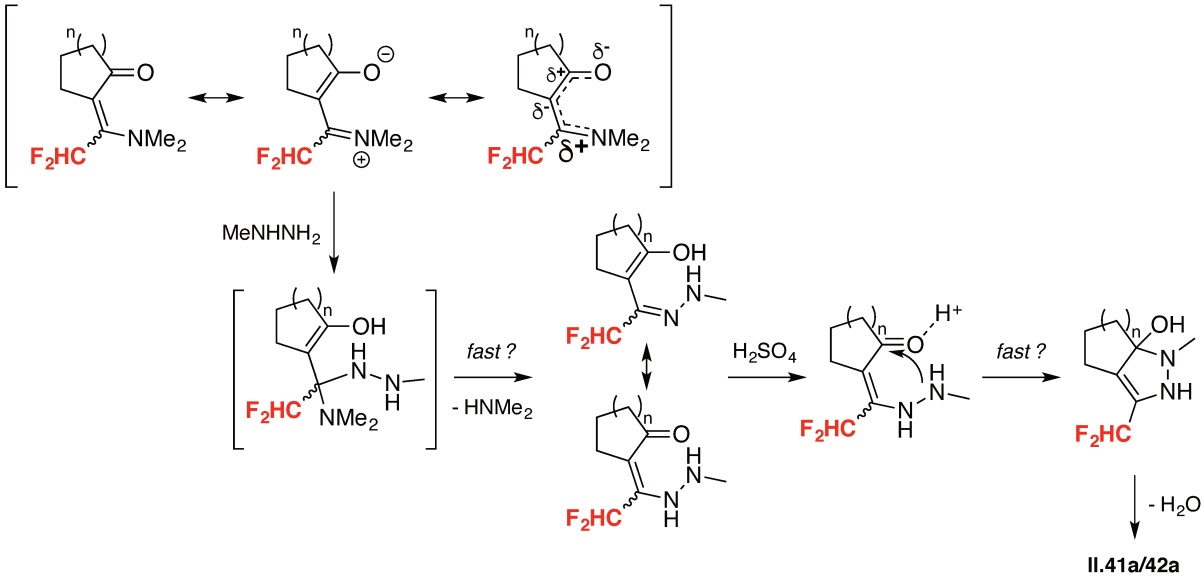
Silyl enol ethers of cyclopentanone, cyclohexanone or acetophenone have been used and proved a great compatibility with such iminium reagents. Indeed, the enolates rapidly formed *in situ* (by Si-O bond cleavage due to the large presence of fluoride sources in the media) reacted very rapidly with **2A** and the resulting intermediates were formed quantitatively. The isolation of hydroxy enones **II.39**, **II.40** and **II.43** was achieved with good yields after hydrolysis of the corresponding iminium intermediates, even though a partial degradation was observed. hydroxy enones **II.40** and **II.43** were cyclized in presence of methyl hydrazine and formed a 50:50 mixtures of regioisomers **II.42a/b** (low yield due to the absence of acidic assistance) and **II.44a/b**. This shows a similar reactivity of both electrophilic centres of β-hydroxy enones towards methyl hydrazine, regardless of the nucleophilicity of both NH_2 and NH of methyl hydrazine. This parameter will be discussed later in the manuscript. However, when the addition of methyl hydrazine was

achieved *in situ*, an apparent discrimination was observed regarding both electrophilic centres, as a good to excellent regioselectivity was observed (92:8 to 100:0) (Scheme II.11).



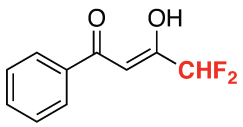
Scheme II.11: Summary of CHF_2-pyrazole synthesis starting from silyl enol ethers.

This led us to consider the fluoro iminium moiety as the most electrophilic centre of such intermediates, and that the NH_2 moiety of methyl hydrazine attacked at this position for steric reasons. The further ring closure could occur *via* nucleophilic attack of the NH part onto the protonated carbonyl group of the enone under acidic assistance. Cycloalkyl-fused pyrazole **II.41a** and **II.42a** and pyrazoles **II.44a** and **II.47** could be regioselectively prepared (Scheme II.11).



Scheme II.12: Mechanistic proposal for regioselective addition of methyl hydrazine

Notably, the reaction providing **II.47** was difficult to reproduce, and even not working when using the TBDMS analogue of the starting substrate. Moreover, the 4-acyl pyrazole **II.47** was also volatile and easily degradable upon storage. The procedure has also been applied to Danishevsky's diene without success. Ethyl CF_3-acetoacetate was converted into a TMS-silyl enol ether, and the same procedure provided the bis(Rf)pyrazole carboxylate **II.9b** with 28% yield only.



II.43

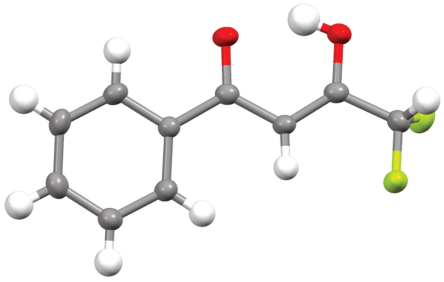
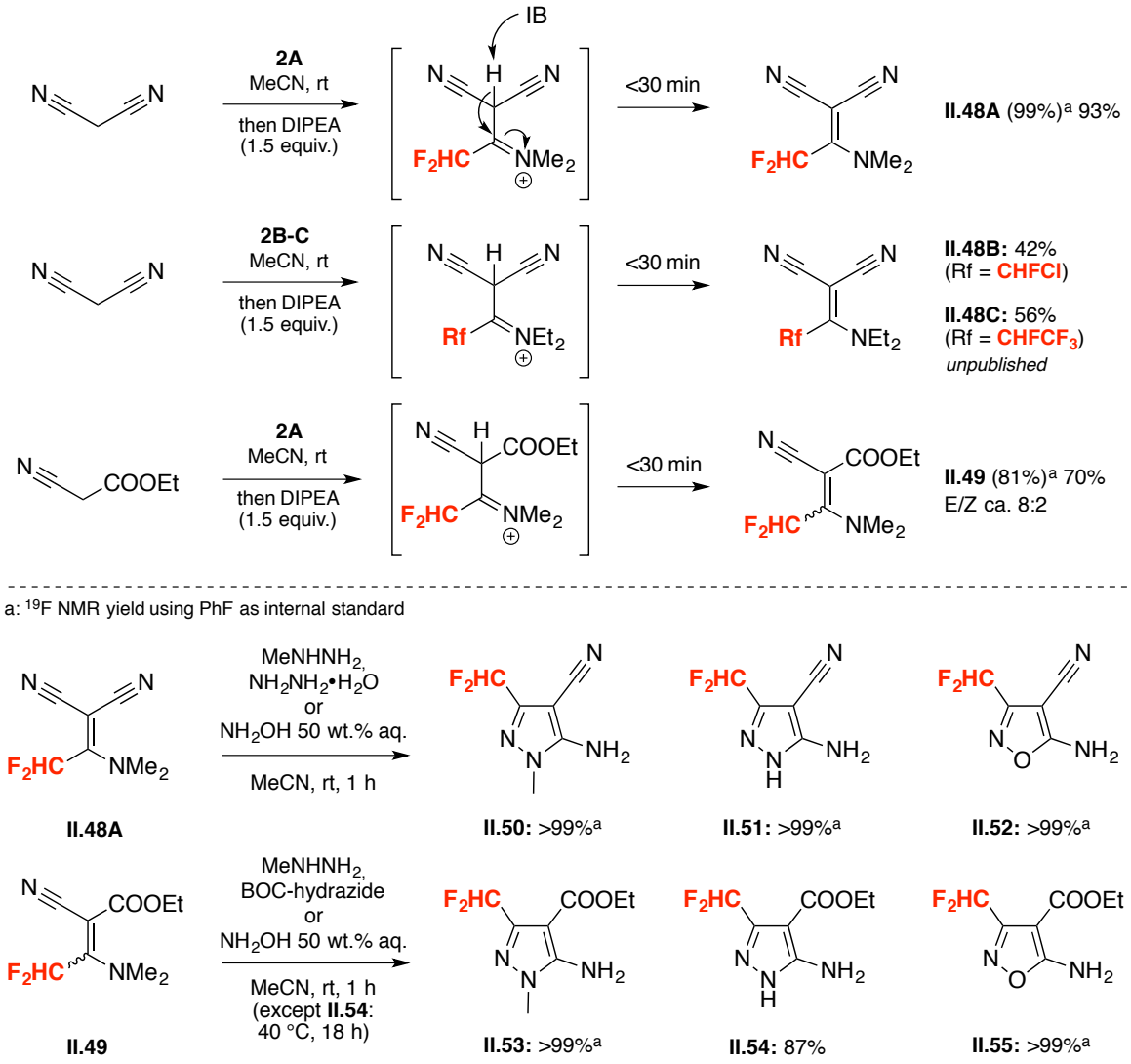


Figure II.12: Crystallographic analysis of a single crystal of compound II.43

Finally, we considered two CH-acidic substrates (malonitrile and ethyl cyanoacetate) for the reaction with activated TFEDMA **2A**. The malonitrile was initially deprotonated using either sodium hydride or LDA, and the subsequent addition of a solution of **2A** in MeCN was followed by the addition of hydrazines or hydroxylamines to access the heterocyclic products **II.50-55** in one-pot. Poor results were obtained at this stage, with yields ranging from 7 to 31%. The strategy evolved and the optimization of the CHF_2-alkylidene adducts **II.48-49** was attempted. Rapidly, the use of tertiary amines (DIPEA, Et_3N) was found to be very efficient, and the conversion was complete in a short reaction time (Scheme II.13).

The isolation of adducts **II.48-49** was more difficult, and several strategies were attempted (aqueous work up, silica gel chromatography, flash chromatography with SiO_2 and later with Al_2O_3). Finally, the preparation of an alumina cake of the reaction mixture, followed by a rinse with cyclohexane (and additional Et_2O up to 30% if needed) was the best compromise. The desired adducts were isolated with high yield and purity. Adducts **II.48A** and **II.48C** and formed a single crystal suitable for crystallographic analysis (Figure II.13).



Scheme II.13: Preparation of key adducts II.48 and II.49 (top); Synthesis of 3-CHF_2-5-amino-4-pyrazole or isoxazole carbonitriles or carboxylates II.50-55 (bottom)

Once adducts **II.48-49** were easily accessible, the corresponding 3-CHF_2-5-amino-4-pyrazole and isoxazole carbonitriles and carboxylates **II.50-55** were prepared. The addition of hydrazines or hydroxylamine afforded in less than one hour all desired products, except **II.54**, which was prepared using BOC-protected hydrazine, the protecting group being cleaved during silica gel purification. The use of hydrazine hydrate gave a yield twice inferior for this example. The 5-amino isoxazole **II.55** provided a single crystal suitable for crystallographic analysis (Figure II.13).

As described in the Chapter I, bioactive agrochemicals bearing a 5-aminopyrazole core have shown activity as herbicides or insecticides, especially with EFSs in position 4 (*e.g.*: Fipronil, Figure I.10).

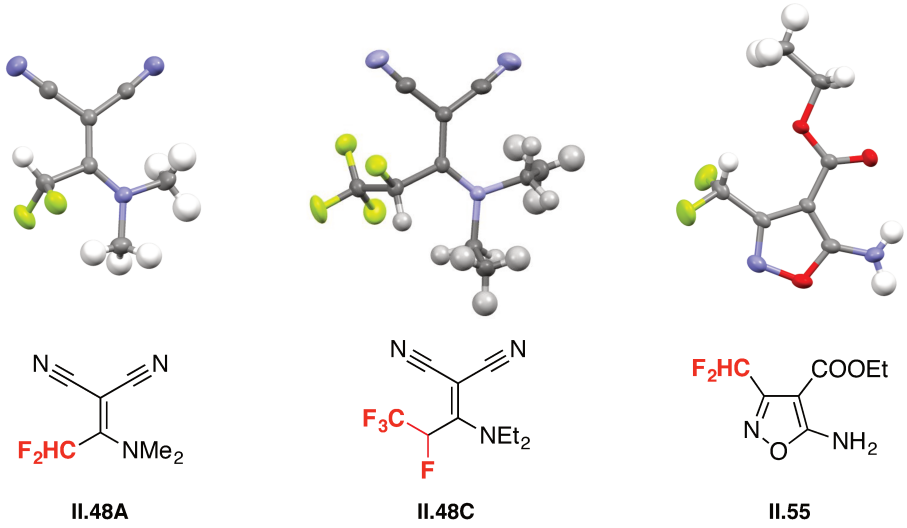


Figure II.13: Crystallographic analysis of a single crystal of compound II.48 (left), II.48C (centre) and II.55 (right)

This study demonstrated how efficiently the use of activated FARs could be for the introduction of CHF_2 motif into a variety of heteroaromatic substrates, but also for the difluoroacylation of electron-rich arenes. With these results, an article was published in 2015 summarizing this study concerning the reactivity of activated FARs, with the example of TFEDMA:
« *in situ* generated fluorinated iminium salts for difluoromethylation and difluoroacetylation », E. Schmitt, B. Rugeri, A. Panossian, J. P. Vors, S. Pazenok, F. R. Leroux, *Org. Lett.* **2015**, *17*, 4510-4513.

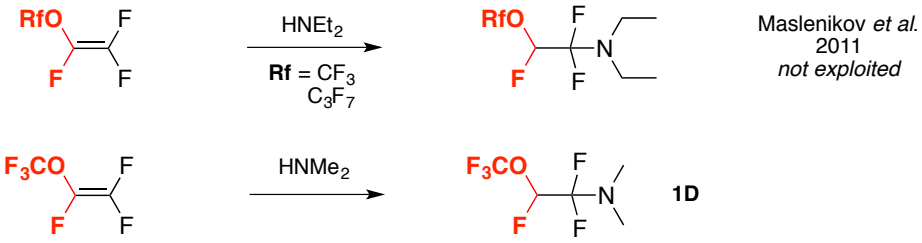
This project was thought to provide expertise in the use of FARs, especially in their activated iminium tetrafluoroborate salt forms. Another objective was to introduce novel EFSs into heteroaromatics; it was decided to develop a new FAR starting from another commercially available precursor. This topic will be discussed in the next part of this chapter.

2. Development of a new FAR

As the use of TFEDMA showed great potential, we decided that the use of other FARs was also a key aspect of this PhD; the development of a new FAR was defined as an objective, in addition to the use of commercially available FARs (Yarovenko and Ishikawa reagents **1B-C**).

Interestingly, after an earlier report for the addition of amines onto perfluoropropoxyethylene in 1999, opening the way to the preparation of other FARs,[66] an article from Maslenikov *et al.* described in 2011 the reaction of secondary amines with perfluorinated vinyl ethers, and one example of condensation of such new FARs with aniline. Little experimental details were given for the preparation of these potential new FAR.[67]

As this group reported on the preparation of *N*,*N*-diethyl FARs (usually less reactive), with very few applications, it was defined that the *N*,*N*-dimethyl analogue will be attempted, in order to obtain a similar reactivity than previously observed with activated TFEDMA. The commercially available perfluorinated gaseous 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (or perfluoromethyl perfluorovinyl ether) was purchased from Apollo Sc. Ltd. and directly employed. This cheap and bulk chemical seemed suitable for such a project. Moreover, it would allow for the introduction of a novel EFS, the fluoro-trifluoromethoxy-methyl group ($CHFOCF_3$). We decided to apply a similar procedure for its preparation (Scheme II.14):



Scheme II.14: Potential unexploited FARs shortly described in 2011, and strategy defined to prepare our new FAR

The initial strategy was to bubble the perfluoromethyl perfluorovinyl ether (b.p.: -23 °C) through a commercially available solution of dimethylamine in THF (from Aldrich®), but after several poorly successful attempts, a large amount of the available gas was wasted. Another method was to liquefy the gas at -78 °C under inert atmosphere and to add the secondary amine at this temperature. After a first conclusive attempt, the method was optimized along the whole PhD project.
The current procedure is now the following: the required amount of gas is liquefied at -78 °C and one equivalent of dimethylamine solution in THF is added at this temperature. After 5-10min, the cold bath is removed and the temperature is left to rise slowly to room temperature. A water bath is placed after 5-10min, in order to increase thermic exchanges during the Lewis acid activation. The activation using BF_3•Et_2O is achieved *in situ* under vigorous stirring to avoid any undesired side-reaction or degradation of the *in situ* generated FAR. After 15min at room temperature, an excess of DCM is added to allow the precipitation of the fluoro iminium salt. After decantation the supernatant DCM is removed using a cannula and the resulting wet solid is dried under vacuum, to yield a white precipitate **2D** (similarly to **2A**). The overall yield is *ca.* 85% (Figure II.14). Most of the results of the following parts of the manuscript have been achieved without precipitation of the iminium, and in many cases yields were good to excellent. This procedure was included in a patent filed recently:

F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing substituted pyrazoles containing haloalkoxy-haloalkyl- and haloalkylthio-haloalkyl groups from from α,α-dihaloalkylamines and ketimines, *BCS153048* (Bayer CropScience AG / CNRS / Université de Strasbourg; filed 24/06/2015).

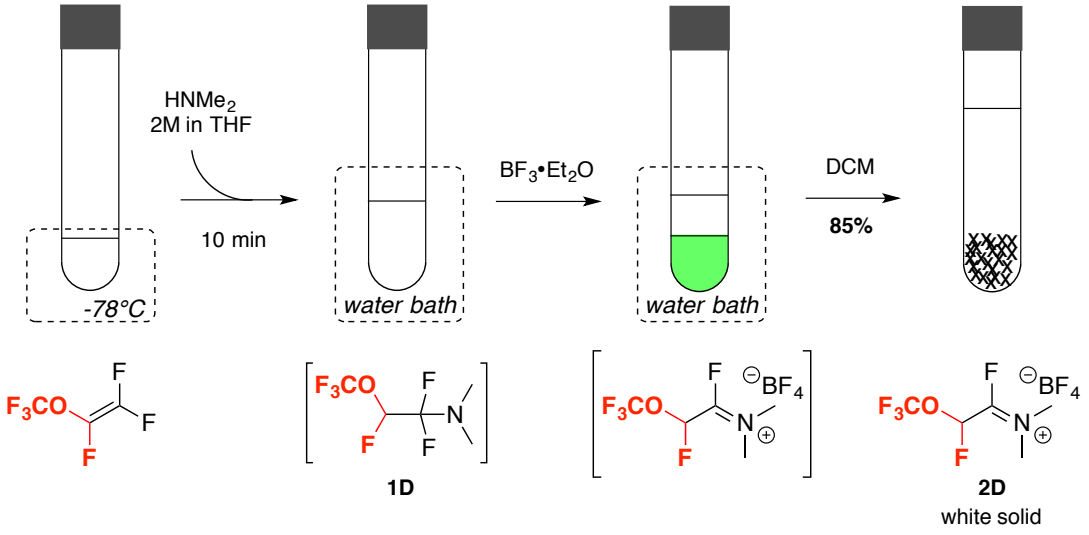


Figure II.14: Optimized procedure for the preparation of the new FAR from perfluoromethyl perfluorovinyl ether

This procedure can potentially be applied to other gaseous perfluorinated alkenes, provided that the resulting FAR does not spontaneously eliminate to give the fluoroenamine. This could lead to several other valuable fluoroalkyl transfer reagents (Figure II.15).

Another perspective of the development of new FARs could be the use of trifluorovinyl arenes or heteroarenes, or of aliphatic 1,1,2-trifluoroalkenes, enabling the efficient introduction of aromatic groups prone to further functionalization (Figure II.16). After the development of a new FAR and the opening of perspectives in this field of research, the next objective was to develop new methods for the efficient preparation of bis(fluoroalkyl)pyrazole building blocks using the FARs previously available or freshly developed.

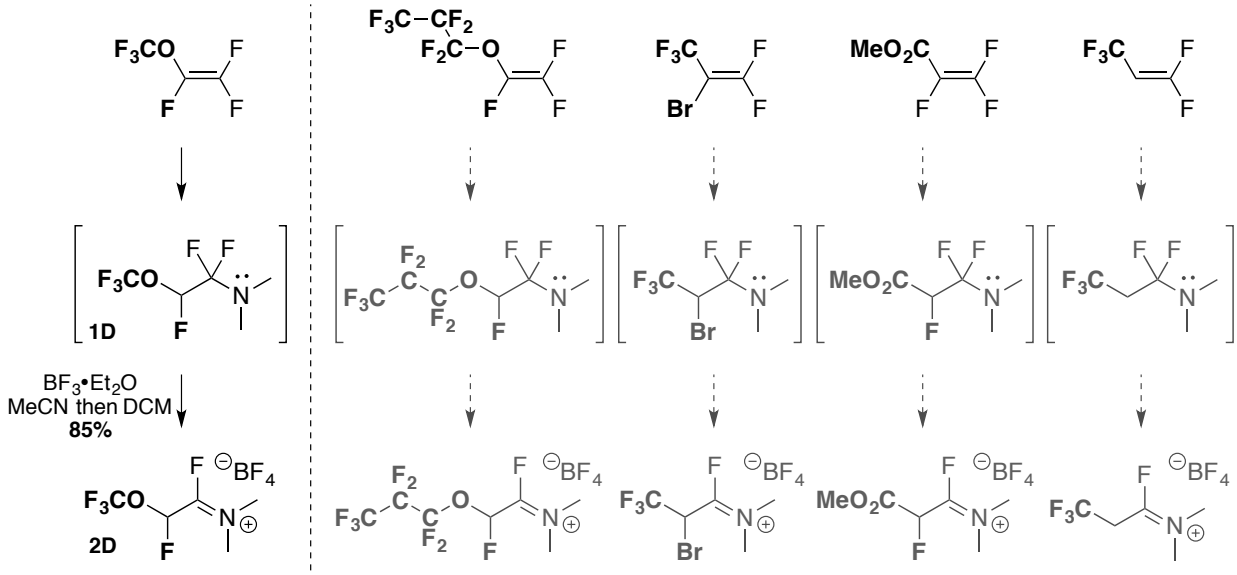


Figure II.15: Other FARs potentially accessible using the procedure developed for 1D.

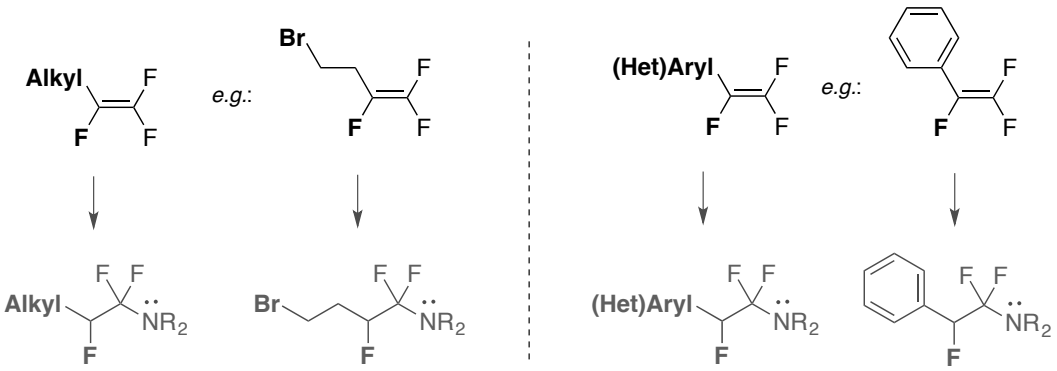


Figure II.16: Possibilities of further development of FAR chemistry.

Upon starting the PhD project, one project was already initiated, and I could start to prepare new bis-fluorinated building blocks in the context of this project. The strategy, based on the use of fluorinated azines, was supposed to enable a new access to 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles, as these compounds were formerly very difficult to access; a strategy reported by our group enabled the preparation of 3,5-bis(fluoroalkyl/aryl)-*N*H-4-pyrazole carboxylates, and only two examples of *N*-*tert*-butyl pyrazoles were deprotected under harsh conditions to access the *N*H-products (compounds **II.18**, top, Scheme II.7).

3. Development of novel fluorinated pyrazole building blocks

a) Azine route

The strategy to access unprecedented 3,5-bis(fluoroalkyl)-*N*H-pyrazole building blocks was based on the use of fluorinated azines, which had to be prepared efficiently and to be further reacted with activated FARs. An intramolecular cyclization was expected to occur under acidic conditions (Figure II.17). The new FAR was not applied to this chemistry as it was simultaneously developed.

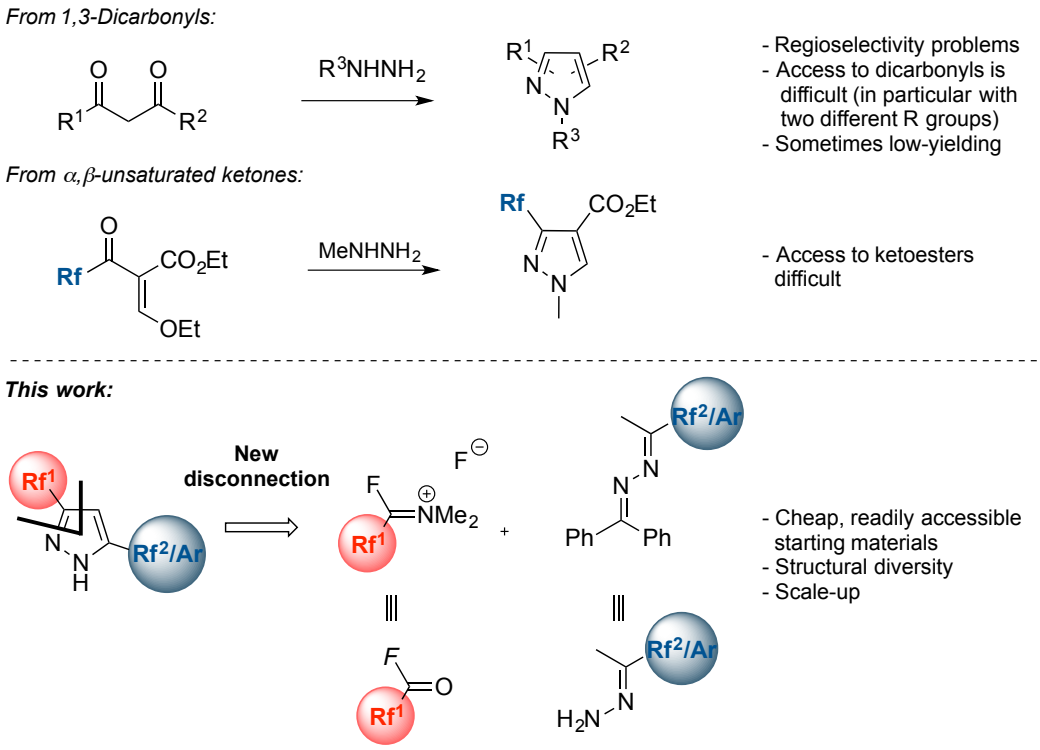
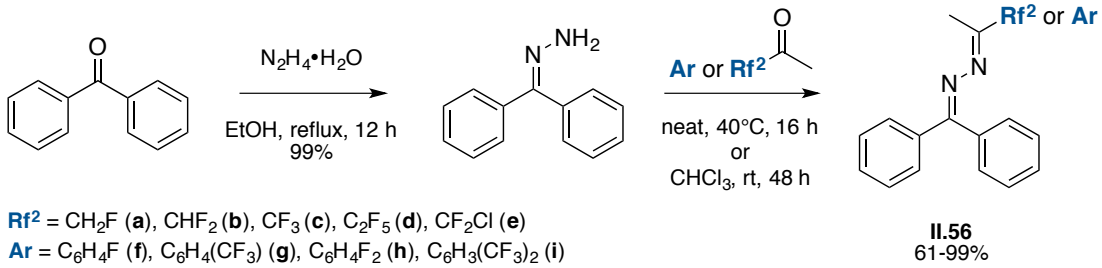


Figure II.17: New disconnection strategy to access 3,5-bis(Rf)-*N*H-pyrazole building blocks

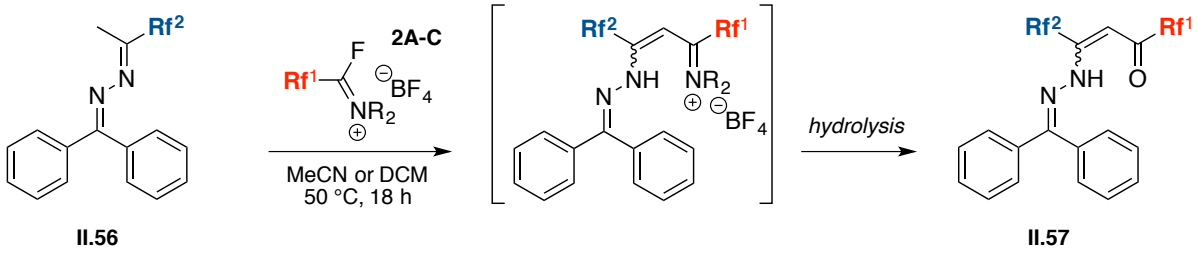
The preparation of the fluorinated azines was straightforward, provided that the procedure was efficiently applied. Indeed, the introduction of highly volatile fluorinated ketones into a sealed system has to be achieved using cooled syringes and fluorinated ketones. The best way is to place both into a dry-ice container during 10-15min, and to inject rapidly the fluorinated ketone into the sealed system.
The quantitative preparation of benzophenone hydrazone is known in the literature. Its condensation with fluorinated ketones was achieved very efficiently. With fluoroalkyl ketones, the reaction occurred without solvent in a sealed vial at 40 °C overnight. For aryl ketones, the reaction proceeded in chloroform at room temperature over two days (Scheme II.15).



Scheme II.15: Preparation of fluoro-alkyl/aryl azines II.56a-i from benzophenone hydrazone.

With these fluorinated azines in hand, we studied the formation of 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles. In order to understand better the reactivity of FARs, the fluoroalkyl azines **II.56a-e** were condensed with activated FARs **2A-C** and several intermediates were hydrolysed and isolated. As TFEDMA previously demonstrated its efficiency, a single example was isolated with high yield (**II.57A.b**). A focus was placed on both Yarovenko and Ishikawa reagents (**1B-C**); results showed a lower overall efficiency, especially with either mono-fluoro azine **II.56a** or with highly fluorinated azine **II.56d**, but also when using the bulkier iminium **2C** (entries 2, 5 and 6-8, Table II.1). It seems that the vinamidinium salt is unstable when bearing CH_2F/C_2F_5 groups, as well as *N*,*N*-diethyl chains and large Rf groups. In general, azines **II.56b** and **c** provided the best results (entries 1, 3, 4, Table II.1).

Table II.1: Preparation of β-(diphenylmethylidene)-bis(fluoroalkyl)-enones II.57



Entry	Cpd.	Rf^1	Rf^2	Yield (%)
1	**II.57A.b**	CHF_2	CHF_2	81%
2	**II.57B.a**	CHFCl	CH_2F	39%
3	**II.57B.b**		CHF_2	91%
4	**II.57B.c**		CF_3	85%
5	**II.57B.d**		C_2F_5	12%
6	**II.57C.a**	$CHFCF_3$	CH_2F	58%
7	**II.57C.b**		CHF_2	52%
8	**II.57C.c**		CF_3	46%

The reaction occurs *via* the enamine tautomer of azines **II.56** formed in solution, which attack the electrophilic activated FARs **2A-C**. The resulting vinamidinium formed (after HF release) can be hydrolysed by an aqueous dilute HCl solution (1-2 mol/L). Importantly, activated FARs **2B-C** provided better results when used in DCM instead of MeCN, at the opposite of **2A**, which is highly efficient in MeCN. These products represent analogues of unsymmetrical 1,3-diketones, (usually difficult to prepare, volatile and low yielding). They demonstrate a nice tendency to crystallize, and crystallographic analyses showed a *Z*-configuration, due to a favourable H-bond interaction between NH and O atoms of the enamino-ketone moiety (Figure II.18). A twist of one phenyl ring can also be observed to diminish the steric interactions within the overall structure. The formation of hydrates of fluoroalkyl acyl moieties was never observed, and the most favourable tautomer observed in solid state was always the enamino-ketone motif.

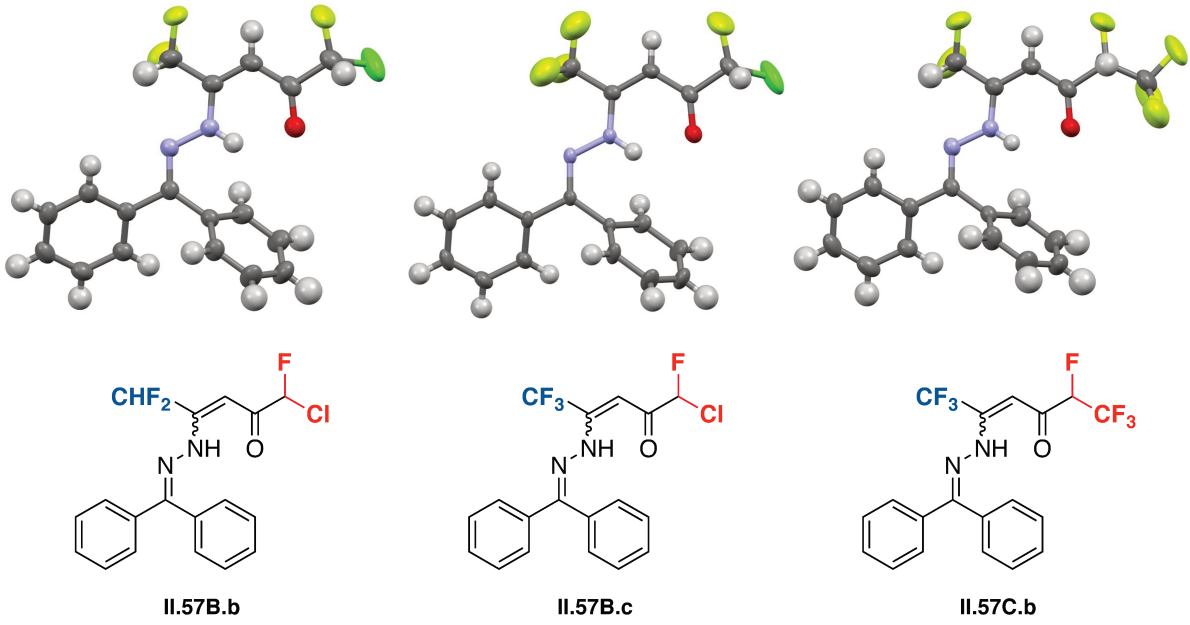


Figure II.18: Crystallographic analyses of single crystals of compounds II.57B.b (left), II.57B.c (centre, unpublishable) and II.57C.b (right).

Vinamidinium intermediates were treated with concentrated HCl (12N) after being prepared *in situ*, to trigger an intramolecular cyclization after hydrolysis of the benzophenone moiety and nucleophilic attack of the resulting hydrazinyl part onto the electrophilic β-fluoro iminium. This step provided the desired *N*H-pyrazoles **II.58** with moderate to excellent yields (Table II.2).

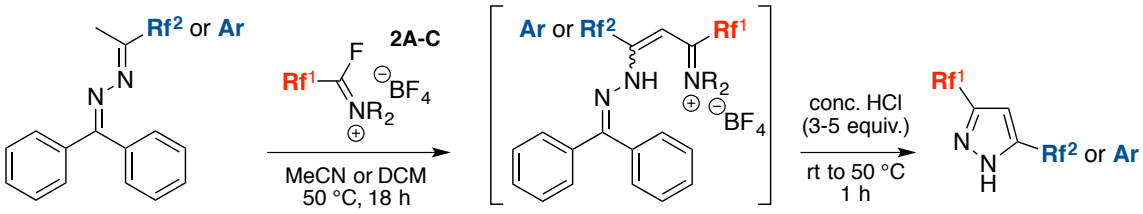
Several examples of products **II.58** were prepared from vinamides **II.57** to compare the reactivity of both vinamides and vinamidiniums. In the case of these vinamides, heating was required to complete the reaction. The cyclization of several vinamides **II.57B-C** was achieved using concentrated HCl (3-5 equiv.) in MeCN at 50 °C for 1-2h, showing a lower reactivity of the vinamide in comparison with the vinamidinium.

The efficiency of this stepwise reaction can be influenced by several parameters (Figure II.19):

- The nucleophilicity of the starting imine **II.56**.
- The stability of the vinamidinium intermediate.
- The steric hindrance of the fluoro iminium moiety considering the nucleophilic attack of the hydrazinyl moiety.

The resulting 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles **II.58** are potentially found under two tautomeric forms in solution, and it is difficult to determine the position of the proton. One example (**II.58B.b**) provided a single crystal with low-resolution crystallographic parameters (consequently not publishable). However, one can observe that the position of the *N*H was constant within the crystal, by looking at the packing structure. This means the position of the *N*H is constant, but probably depends on electronic effects of both fluoroalkyl/aryl substituents (Figure II.20).

Table II.2: One pot synthesis of unprecedented 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles II.58



Rf^1 = CHF_2 (**A**), CHFCl (**B**), $CHFCF_3$ (**C**)
Rf^2 = CH_2F (**a**), CHF_2 (**b**), CF_3 (**c**), C_2F_5 (**d**), CF_2Cl (**e**)
Ar = C_6H_4F (**f**), $C_6H_4(CF_3)$ (**g**), $C_6H_4F_2$ (**h**), $C_6H_3(CF_3)_2$ (**i**)

Entry	Cpd.	Rf^1	Rf^2/Ar	Yield (%)
1	**II.58A.b**	CHF_2	CHF_2	74%
2	**II.58A.c**		CF_3	83%
3	**II.58A.d**		C_2F_5	51%
4	**II.58A.e**		CF_2Cl	31%
5	**II.58A.f**		4-fluoro-C_6H_4	53%
6	**II.58A.g**		4-(CF_3)-C_6H_4	42%
7	**II.58A.h**		3,5-difluoro-C_6H_3	31%
8	**II.58A.i**		3,5-bis(CF_3)-C_6H_3	42%
9	**II.58B.a**	CHFCl	CH_2F	64%
10	**II.58B.b**		CHF_2	69%
11	**II.58B.c**		CF_3	47%
12	**II.58C.a**	$CHFCF_3$	CH_2F	40%[a]
13	**II.58C.b**		CHF_2	93%[a]
14	**II.58C.c**		CF_3	93%[a]

a ^{19}F NMR yield using fluorobenzene as internal standard.

Pyrazoles **II.58** were usually unstable upon storage and volatile compounds, and ^{19}F-NMR yields were used in most complex cases (entries 12-14, Table II.2).

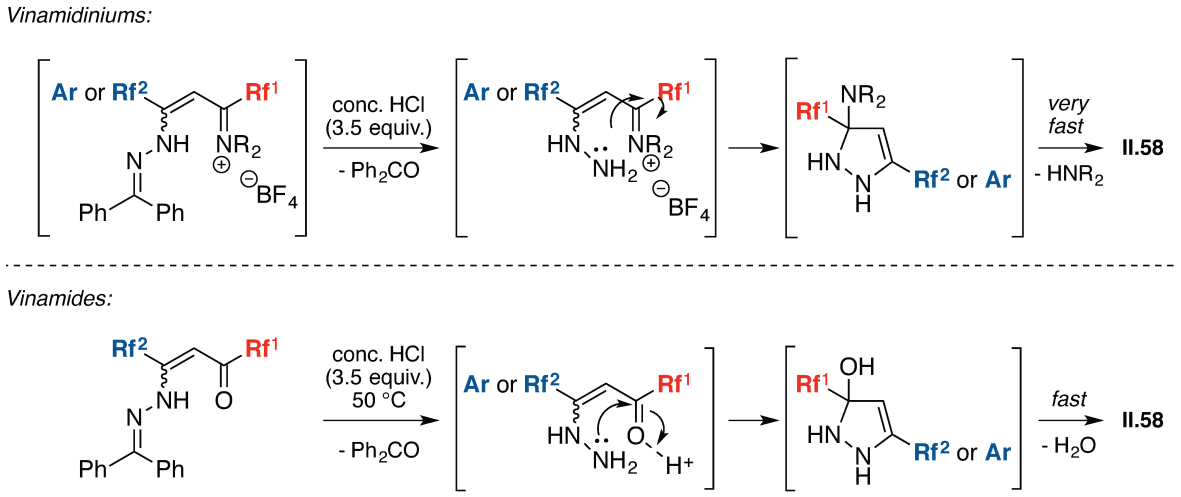


Figure II.19: Possible mechanism for the intramolecular cyclization from vinamidinium intermediates (top) or vinamides II.57 (bottom)

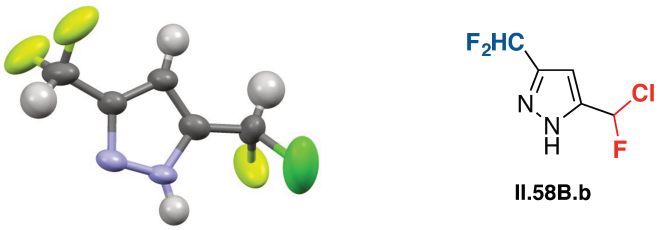


Figure II.20: Crystallographic analysis of a single crystal of compound II.58B.b (unpublishable)

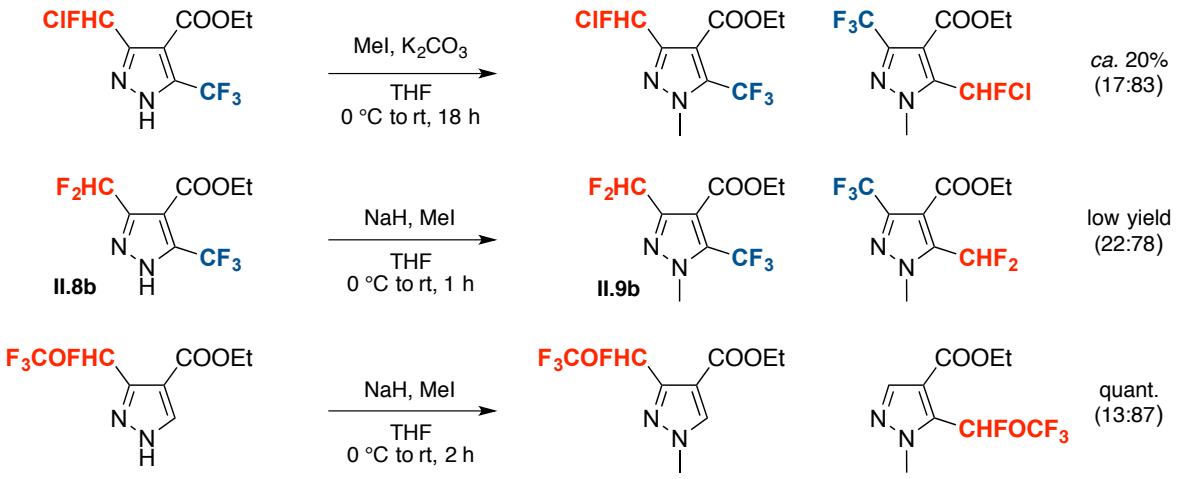
These pyrazole building blocks are rather difficult to handle, as they are highly volatile and must be stored under a cold and inert atmosphere. Their purification is rather challenging, as they are almost UV-inactive. The use of volatile solvents (usually pentane and diethyl ether) is highly recommended, and the concentration under vacuum is risky. Avoiding the use of the vacuum pump is recommended, using only the water bath for the evaporation of previously mentioned solvents. In the cases where the pyrazole ring formation was highly inefficient (especially with azines **II.56a** and **d**), an excess of FAR was used. The remaining hydrolysed FARs **3B-C** were difficult to remove either by flash chromatography or distillation under reduced pressure (using Hickmann apparatus). Another drawback of this method is the use of benzophenone; its complete removal from compounds of moderate polarity is difficult.
This strategy still represents the first method to access the challenging 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles **II.58** with high efficiency in the majority of the cases. This project was summarized in an article published in 2015:

« A general approach towards *N*H-pyrazoles that bear diverse fluoroalkyl groups by means of fluorinated iminium salts », E. Schmitt, G. Landelle, J.-P. Vors, N. Lui, S. Pazenok, F. R. Leroux, *Eur. J. Org. Chem.* **2015**, 6052-6060.

However, to consider an industrial application, avoiding the use of difficult-to-remove auxiliary such as benzophenone would be a great improvement. We decided to develop an alternative strategy, which is atom economic and with larger scope of application. This new project will be discussed in the following part.

b) Ketimine route

After developing an easy access to unprecedented 3,5-bis(fluoroalkyl/aryl)-*N*H-pyrazoles **II.58**, a more general approach was desired, in order to increase the diversity of accessible structures. Another aspect of this new project was the selective introduction of a variety of *N*-substituents onto such 3,5-bis(fluoroalkyl/aryl)-pyrazoles; not only the alkylation/arylation of such electron-poor pyrazole can be difficult, but the regioselectivity can be very low depending upon the fluoroalkyl groups located on the pyrazole ring.
Several attempts were achieved, and proved that regioselective methylation of *N*H-pyrazoles is difficult, and mostly influenced by thermodynamic factors (Scheme II.16):

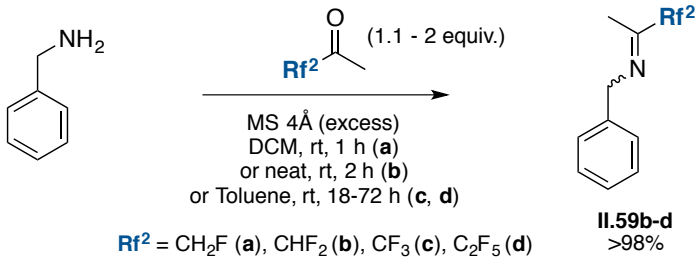


Scheme II.16: Attempts of methylation of various *N*H-pyrazoles

The objective was to access more efficiently to *N*H-pyrazoles and to provide regioselectively to *N*-functionalized pyrazoles. The introduction of other functional groups on position 4 (the ethyl ester was already available) was also an objective, in order to complete the possibilities of substitution pattern. This strategy has been recently patented.[68]

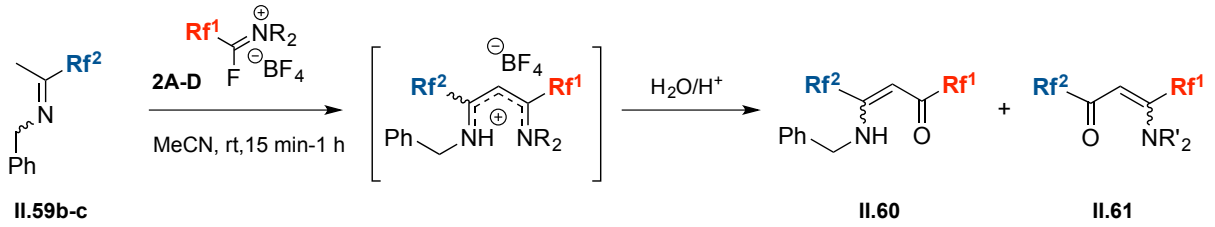
To replace the fluorinated azines **II.56** (and the subsequent purification issues relative to benzophenone), another type of fluorinated imines were investigated. Imines resulting from the condensation of fluorinated ketones with primary amines were targeted. *N*-benzylamine was defined as starting amine, as its removal could be much easier than benzophenone. The synthesis of three examples of fluorinated *N*-benzyl ketimines **II.59b-d** was achieved following a procedure reported in the literature using molecular sieves as dehydrating agent[69] (Scheme II.17).

Mono-fluoro ketimine **II.59a** was prepared but this ketimine was not efficient in further reactions with activated FARs and could not provide any desired pyrazole with sufficient yield and purity to be included in the project. The ketimine bearing a CH_2F group seems prone to either elimination or side reactions. After their efficient preparation, fluorinated ketimines **II.59b-d** were reacted with activated FARs **2A-D** (including the new FAR recently developed). Similarly to the first approach, the vinamidinium intermediates were very rapidly formed after nucleophilic attack of ketimines **II.59b-c** onto activated FARs **2A-D**, and after hydrolysis the vinamides **II.60** and **II.61** were isolated as *E*/*Z* mixtures (Table II.3).



Scheme II.17: Preparation of fluorinated ketimines II.59

Table II.3: Preparation of vinamides II.60 and II.61



Entry	Ketimine	Vinamide	Rf^1	Rf^2	R'	Conv. (%)	Yield (**II.60** / **II.61**) (%)
1	**II.59b**	**II.60A.b** / II.61A.b	CHF_2	CHF_2	Me	99%	79% / 0%
2	**II.59c**	**II.60A.c** / II.61A.c	CHF_2	CF_3	Me	99%	74% / 0%
3	**II.59b**	**II.60B.b / II.61B.b**	CHFCl	CHF_2	Et	n.d.	31%[c] / 17%
4	**II.59b**	**II.60C.b / II.61C.b**	$CHFCF_3$	CHF_2	Et	88%	[25% / 18%[b]][a]
5	**II.59b**	**II.60D.b** / II.61D.b	$CHFOCF_3$	CHF_2	Me	92%	83% / 0%

a: 65/35 mixture. b: isolated pure after micro-distillation. c: isolated pure after chromatography.

Regarding the various FARs tested, one can observe a rapid and high conversion when using FARs **2A** and **2D** (*N*,*N*-dimethyl FARs, entries 1, 2, 5, Table II.3) in addition with very high isolated yields vinamides **III.40** selectively prepared (entries 1, 2, 5, Table II.3). The use of activated FARs **2B-C** led to longer reaction time and lower conversion (entries 3, 4, Table II.3). This results from a lower reactivity of **2B** and **2C** (before the formation of the vinamidinium) and of the resulting intermediate (before the hydrolysis).
The hydrolysis of *N*,*N*-dimethyl-vinamidinium intermediates occurred readily at the desired iminium position, as the *N*,*N*-dimethyl iminium moiety is highly reactive, less sterically hindered and the release of gaseous dimethylamine is easier than diethylamine. The steric parameter can also be considered, as both Rf^1 and NR'_2 are bulkier with FARs **2B** and **2C**. For the other cases, the positive charge is delocalized along the vinamidinium, and the discrimination between both electrophilic centres is not similar. The hydrolysis can partially occur on the *N*-benzyl iminium moiety, providing opposite vinamides **II.61** (entries 3, 4, Table II.3). To increase the reactivity of these FARs, the preparation of their *N*,*N*-dimethyl analogues could be achieved using previously described procedure.

The resulting mixture of vinamides **II.60** and **II.61** (entries 3, 4, Table II.3) was difficult to separate, and flash chromatography was combined with reduced pressure distillation to achieve a correct separation. The crystallographic analysis of compound **II.60A.b** showed a *E*-configuration in solid state, differently than azine vinamides **II.57**. The H-bonding between *N*H and O is not present (Figure II.21).

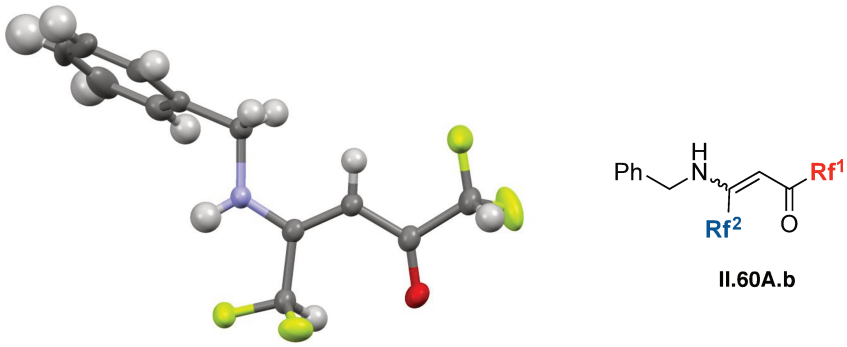
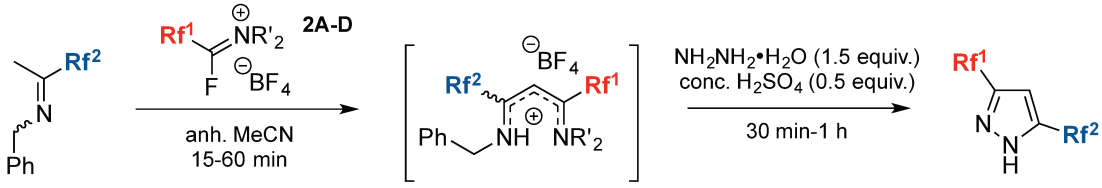


Figure II.21: Crystallographic analysis of a single crystal of compound II.60A.b

After preparing the vinamides intermediates **II.60** et **II.61**, proving that the ketimines **II.59** were compatible with activated FARs, the objective was to reproduce the results from the azine route to demonstrate the better efficiency of our new method for the preparation of 3,5-bis(fluoroalkyl)-*N*H-pyrazoles **II.58** (shown in Table II.2). For this purpose, the vinamidiniums formed *in situ* were treated with hydrazine hydrate, rapidly followed by addition of concentrated H_2SO_4 (for acidic assistance, avoiding excessive presence of water); the results were very promising (Table II.4):

Table II.4: Results for the preparation of 3,5-bis(fluoroalkyl)-*N*H-pyrazoles II.58 using the ketimine strategy



II.59 **II.58**

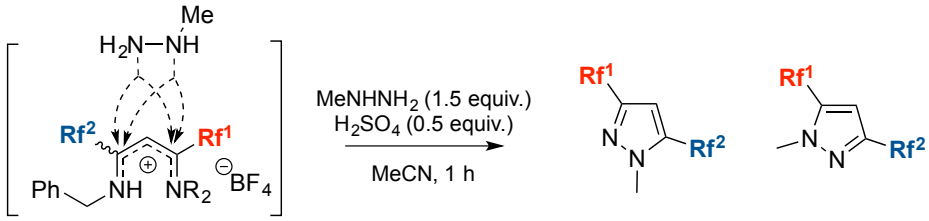
Rf^1 = CHF_2 (**A**), CHFCl (**B**), $CHFCF_3$ (**C**), $CHFOCF_3$ (**D**)
Rf^2 = CHF_2 (**b**), CF_3 (**c**), C_2F_5 (**d**)

Entry	Cpd.	Rf^1	Rf^2	Yield:
1	**II.58A.b**	CHF_2	CHF_2	99%[a]
2	**II.58A.c**		CF_3	99%[a]
3	**II.58A.d**		C_2F_5	99%[a]
4	**II.58B.b**	CHFCl	CHF_2	81%[a,b]
5	**II.58B.c**		CF_3	30%[a,b]
6	**II.58C.b**	$CHFCF_3$	CHF_2	96%[a]
7	**II.58C.c**		CF_3	27%[a]
8	**II.58D.b**	$CHFOCF_3$	CHF_2	85%
9	**II.58D.c**		CF_3	81%[a]
10	**II.58D.d**		C_2F_5	99%[a,b]

a: ^{19}F NMR yield using PhF as internal standard. b: After 18h more.

The examples using TFEDMA were more efficiently prepared than in the previous method (entries 1-3, Table II.4). New pyrazoles prepared from the new FAR **2D** were very efficiently prepared even with highly electron-withdrawing groups (entries 8-10, Table II.4), showing very good stability. The reaction time was usually much shorter. Pyrazoles **II.58A.c** and **II.58A.d** (entries 2-3, Table II.4) are identical to products reported earlier in our group (**II.18b-c**, Scheme II.7) but prepared a single step.
Once again, the use of fluoro iminiums **2B-C** provided lower results, except with the most efficient ketimine **II.59b** (entries 4, 6, Table II.4). With ketimines **II.59c-d**, the high electron-withdrawing effect of CF_3 and C_2F_5 probably prevents the formation of the corresponding vinamidinium with less reactive FARs **2B-C**, and the cyclization is also disturbed by higher steric hindrance. In these attempts the FARs **2B-C** were not precipitated, explaining the lower yield. The reactivity of FARs **2A** and **2D** is higher than **2B-C**.

Table II.5: Results for the preparation of 3,5-bis(fluoroalkyl)-*N*-methyl pyrazoles II.62 and II.63 using the ketimine strategy



Rf^1 = CHF_2 (**A**), CHFCl (**B**), $CHFCF_3$ (**C**), $CHFOCF_3$ (**D**)
Rf^2 = CHF_2 (**b**), CF_3 (**c**), C_2F_5 (**d**)

Entry	Cmpd.	Rf^1	Rf^2	Yield:	Ratio **II.62 / II.63**
1	**II.62A.b**	CHF_2	CHF_2	90%[a]	-
2	**II.62A.c** **II.63A.c**		CF_3	>99%[a,b]	85/15
3	**II.63A.c**			From **II.60A.c**: 96%	0/100
4	**II.62A.d** **II.63A.d**		C_2F_5	>99%[a]	87/13
5	**II.62B.b** **II.63B.b**	CHFCl	CHF_2	45%[a,c]	73/27[e]
6	**II.62C.b** **II.63C.b**	$CHFCF_3$	CHF_2	84%[a,d]	31/69
7	**II.62D.b** **II.63D.b**	$CHFOCF_3$	CHF_2	99%[a,d]	71/29
8	**II.62D.c**		CF_3	66%[a]	100/0
9	**II.62D.d**		C_2F_5	81%[a,c]	100/0

a: ^{19}F NMR yield using PhF as internal standard. b: Only 0.1 equiv conc. H_2SO_4 used. c: After 18 h. d: Separated by silica-gel chromatography. e: Reproducibility issues.

The next objective was to achieve the cyclization step between vinamidinium intermediates and methyl hydrazine. The regioselectivity of the methyl hydrazine addition was crucial, as it is often difficult to separate the pyrazole regioisomers. The synthesis of variously substituted pyrazoles was achieved similarly to the *N*H-series (see Table II.5). Hydrazines possess two nucleophilic positions (NH_2 or NH) which can both attack two electrophilic fluoro iminium centres (*N*,*N*-dialkyl iminium and *N*H-benzyl iminium), explaining the formation of two regioisomers.
In the Table II.5 are recorded the results from the addition of methyl hydrazine onto vinamidinium intermediates prepared *in situ*. For FARs **2A** and **2D**, the ratios observed are ranging from 71/29 to 100/0, with several regiospecific examples (entries 8, 9). The major regioisomer produced in these reactions is formed *via* the addition of NH_2 moiety of methyl hydrazine onto the most reactive *N*,*N*-dimethyl iminium moiety.

The synthesis of pyrazoles resulting from the reaction between highly fluorinated ketimines **II59.c-d** and FARs **2B-C** could not be prepared due to low reactivity of both partners. Moreover, for the efficient examples, the regioselectivity is low. The activated Yarovenko reagent **2B** provided one pyrazole (entry 5, Table II.5) with a ratio of regioisomers not reproducible. For the Ishikawa iminium salt **2C**, the ratio was reversed (31/69, entry 6, Table II.5); these observations illustrate the larger bulkiness of *N*,*N*-diethyl chains.
The kinetics of the cyclization being less favourable, the nucleophilic NH part of hydrazine can attack the *N*,*N*-diethyl iminium despite of the bulkiness of the methyl group. Another hypothesis is that the NH_2 part can attack the opposite *N*H-benzyl iminium due to a lower reactivity of the *N*,*N*-diethyl one.
The pyrazoles **II.62A.b-d** are identical to products reported earlier in our group (**II.15a-c**, Scheme II.7) but are prepared in a single step.

The various possibilities of nucleophilic attack and subsequent ring closure are summarized in Figure II.22. For steric reasons, the attack of NH part of methyl hydrazine seems disfavoured (paths A and D, Figure II.22). The most favourable path is B (when R = methyl), as it provides the major regioisomer *via* the more favourable steps. However, when NR_2 becomes bulkier (R = ethyl), both electrophilic centres reactivities are closer, and the iminium is stabilized by the inductive effect of the larger chains. These hypotheses were in concordance with computational calculations achieved by Dr. Pierre Genix (Bayer CropScience, Lyon).
This computational chemist initially rationalized the regioselectivity of the methyl hydrazine addition into the vinamidinium involved in the synthesis of DFMMP (Scheme II.6); by comparing the relative energies of the possibly formed cations (resulting addition of methyl hydrazine onto the electrophilic centre and elimination of $HNMe_2$), he postulated that the cation being the energetically more favoured results from the attack of the most nucleophilic NH part of methyl hydrazine onto the sterically less hindered iminium. This configuration avoided the presence of adjacent fluoroalkyl group close to the cation (top, Figure II.23).

However, in the case of bis(fluoroalkyl) vinamidiniums, the conclusions are different. As the enamino-hydrazinyl cation intermediates involved in this reaction are very complex to consider for computational calculations, a simplified and symmetrical cationic transition states bearing two dimethylamino and two CF_3 groups was preferred. The conclusion is that the cation resulting from elimination of $HNMe_2$ is more favourable when the NH_2 moiety attacks (avoiding steric clash between CH_3 and CF_3 groups), providing a *syn*-intermediate ready for the ring closure step (bottom, Figure II.23):

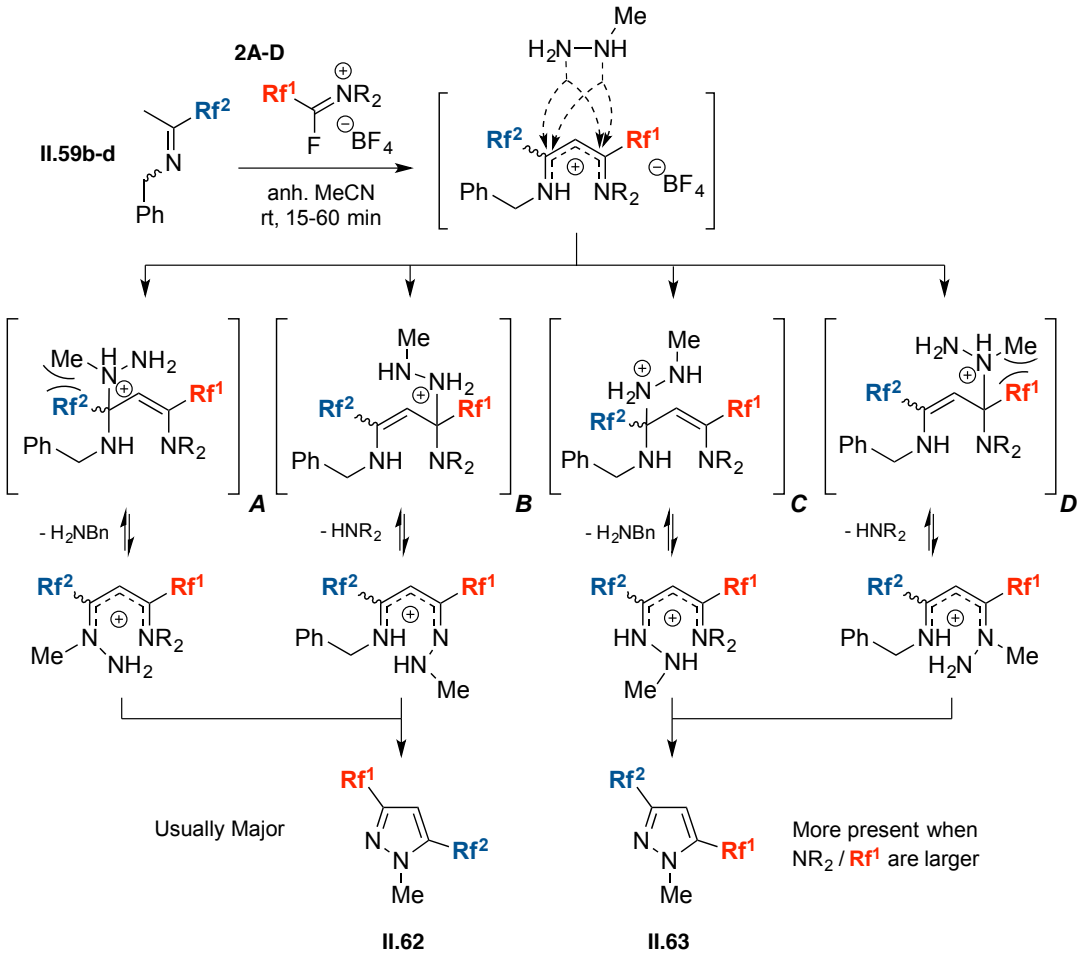


Figure II.22: Possible mechanistic pathways for the pyrazole ring formation *via* nucleophilic attack of methyl hydrazine onto bis(fluoroalkyl) vinamidiniums

It seems that steric parameters are highly influencing the addition of methyl hydrazine onto bis(fluoroalkyl) vinamidiniums. This observation cannot be extended to other differently substituted hydrazines (phenyl hydrazine, BOC-hydrazide, etc), but offers a good explanation for the results obtained in this project. One example of cyclization of vinamide **II.60A.c** with methyl hydrazine was included, as it provided an extremely interesting result. The use of vinamide instead of the corresponding vinamidinium completely reversed the regioselectivity of the reaction, and pyrazole **II.63A.c** was isolated in 96% yield and complete regioselectivity (entry 3, Table II.5).

In the presence of a single enamino group (from the enamino ketone moiety), the iminium tautomer is the most electrophilic species within the vinamide, and as previously exemplified, the attack of NH_2 is favoured in the case of a fluoroalkyl iminium group. Path B is the favoured pathway and provides only the opposite pyrazole (Figure II.24). All examples were not be achieved by lack of time, but this strategy could allow for the fully regioselective preparation of certain bis(fluoroalkyl)pyrazoles when the vinamidinium strategy does not provide a satisfying regioselectivity.

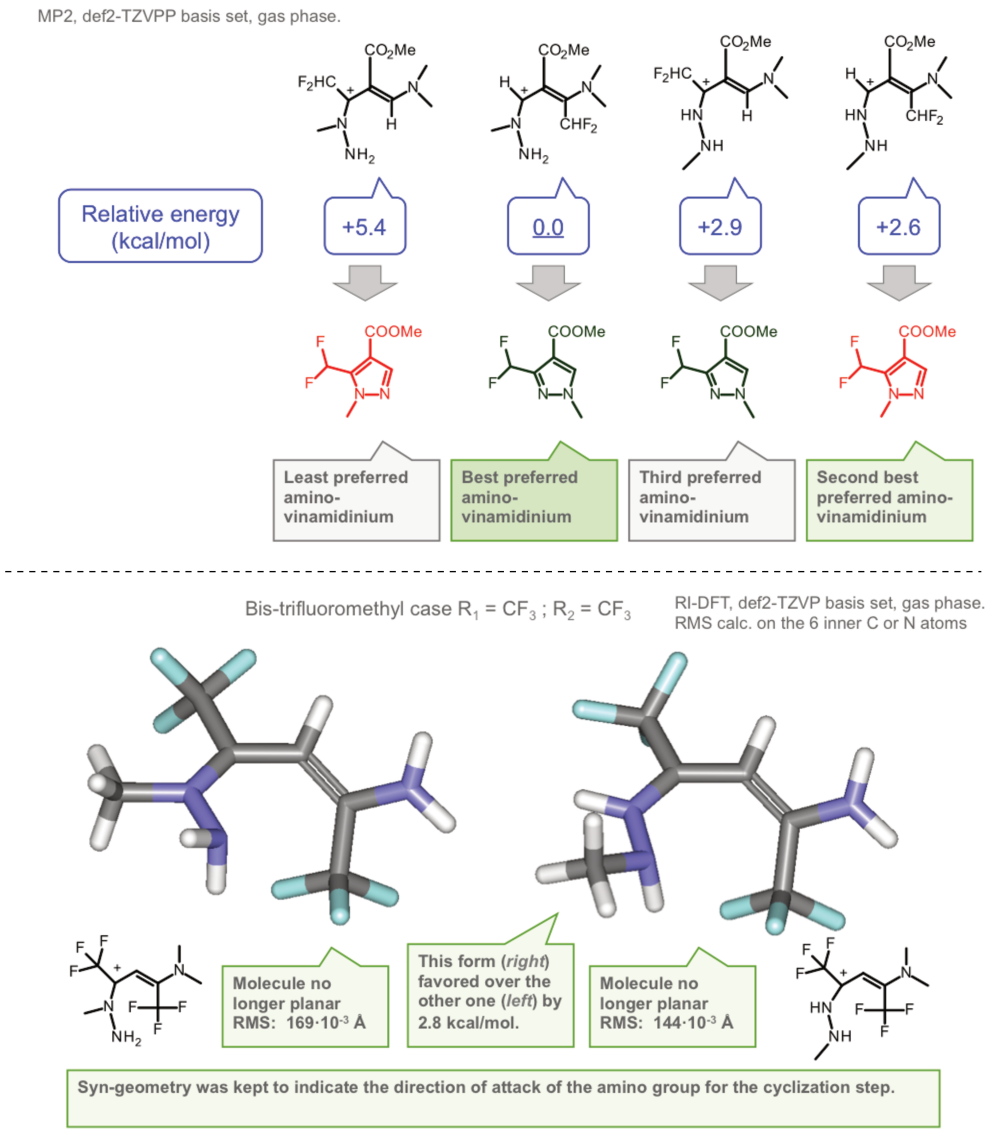


Figure II.23: Computational approach to explain the regioselectivity of methyl hydrazine onto bis(fluoroalkyl) vinamidiniums (Dr. P. Genix, Bayer CropScience, Lyon)

After the development of two powerful strategies to access unsymmetrical bis(fluoroalkyl)-*N*H and *N*Me pyrazoles, the next objective was to introduce diversity at the *N*-position. For this purpose, symmetrical bis-CHF_2 pyrazoles were considered to avoid the formation of regioisomers, as this aspect has been discussed previously. The vinamidinium strategy was initially used and good results were obtained with classical alkyl and aryl hydrazines, but for both more sterically hindered or electron-poor aryl/heteroaryl hydrazines, almost no reaction was observed. To circumvent this issue, microwave reaction conditions were developed starting from vinamides **II.60** and **II.61** in presence of hydrazines and concentrated H_2SO_4 in toluene or MeCN. Finally, variously *N*-substituted pyrazoles **II.64a-f** were obtained in moderate to excellent yields (Scheme II.18). Several limitations were observed, such as non-compatibility with acid-labile groups (BOC, tosyl, *t*Bu, benzoyl under certain conditions, etc.) and sluggish reactions (especially **II.64f**). Despite that, these results were really satisfying.

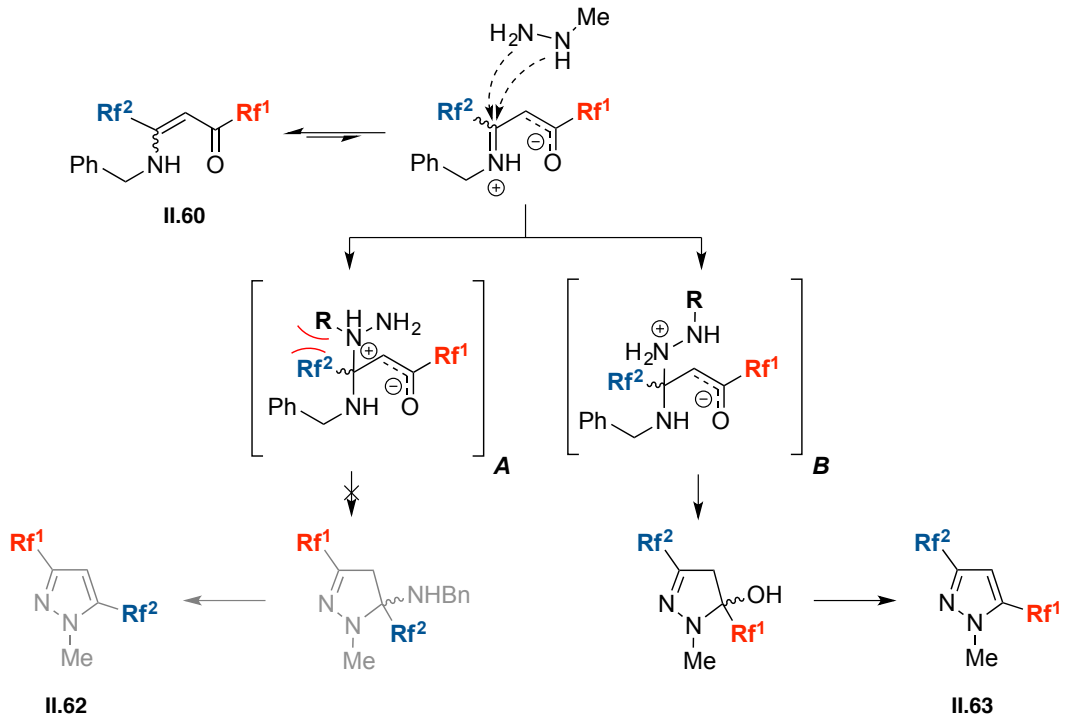
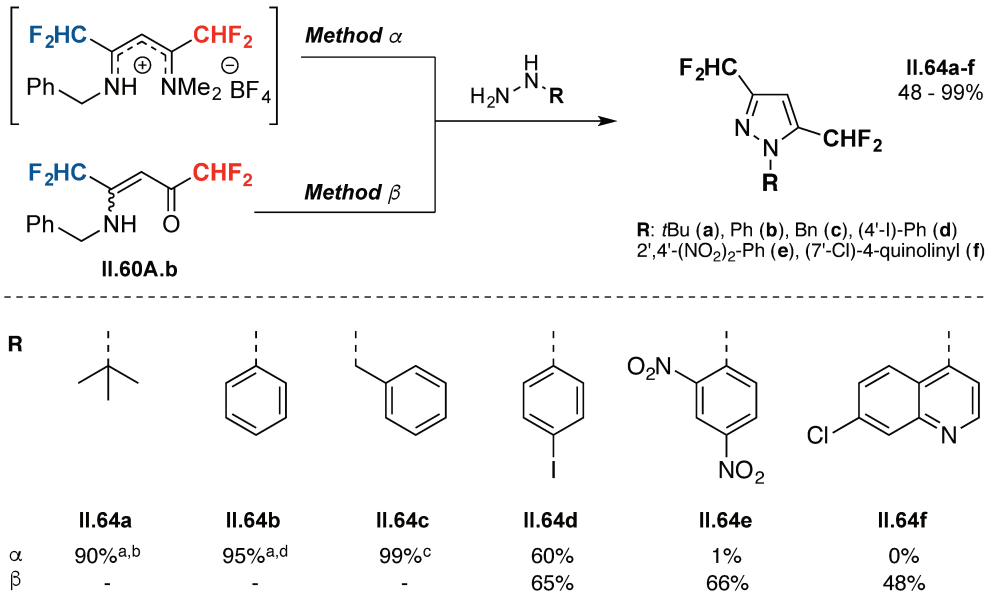


Figure II.24: Possible mechanistic pathways for the pyrazole ring formation *via* nucleophilic attack of methyl hydrazine onto bis(fluoroalkyl) vinamides

When using electron poor or bulky hydrazines, interesting side-products were formed in good yields. A possible pathway is proposed for this side-reaction (Figure II.25).

As reported by several groups, fluoroalkyl pyrazoles can be prepared from fluorinated 1,3-diketones or analogues and hydrazines, but fluorinated 5-hydroxypyrazolines are often not dehydrated under the reaction conditions.[70-72] The vinamidiniums or vinamides **II.60** can be regarded as bis(fluoroalkyl) 1,3-diiminiums and 1,3-ketoiminiums, and they were reacted with various hydrazines. In our case, the presence of an excess of tertiary amine was required to complete the reaction, and the previous examples provided easily aromatic pyrazoles, as the inductive effect of *N*-substituents stabilize the partial positive charge resulting from the departure of the leaving group. Eventually, in the presence of H-bonding *N*-substituents (benzoyl, BOC, carbamyl, 2-pyridinyl, tosyl), the dehydration/deamination step was disfavoured resulting from the adjacent electron-withdrawing fluoroalkyl group. Electron-withdrawing groups enhance the partial positive charge whereas H-bonding stabilizes the pyrazoline form. The aromatization is consequently limited thermodynamically (Figure II.26).



R	II.64a	II.64b	II.64c	II.64d	II.64e	II.64f
α	90%[a,b]	95%[a,d]	99%[c]	60%	1%	0%
β	-	-	-	65%	66%	48%

Method α: hydrazine, conc. H_2SO_4, MeCN, rt - 50 °C, 1 h. **Method** β: hydrazine, conc. H_2SO_4, toluene/MeCN, 120–140 °C, microwave, 0.5-2 h. a: ^{19}F NMR yield using PhF as internal standard. b: *t*Bu sensitive to excess of conc. H_2SO_4 at 50 °C. *N*-H pyrazole **II.58A.b** partially formed. c: Et_3N used instead of H_2SO_4. d: After 18 h.

Scheme II.18: Various *N*-substituted pyrazoles prepared from corresponding hydrazines

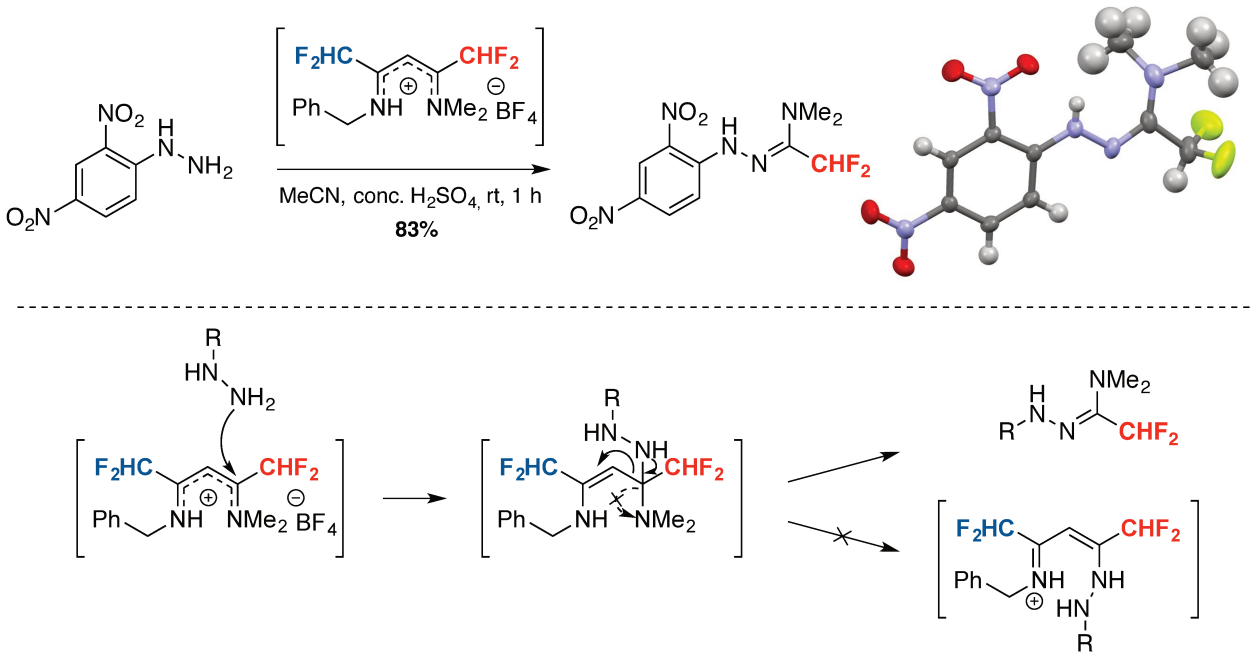


Figure II.25: Observed side-reaction product and crystallographic analysis confirming the structure (top); mechanistic proposal for the formation of this type of side-products (bottom)

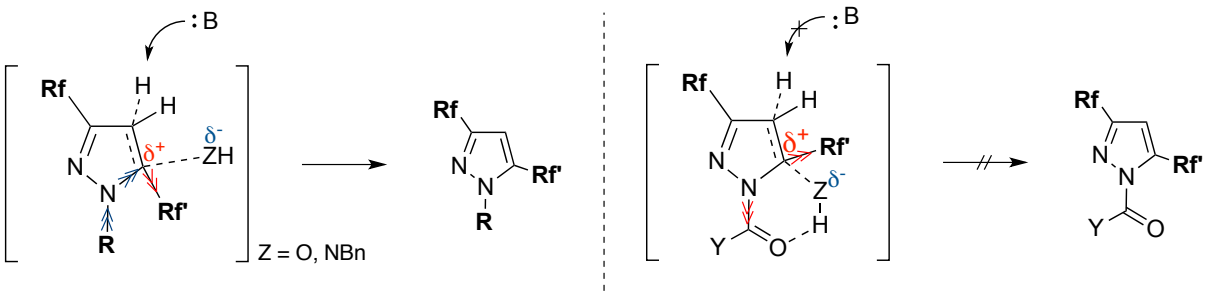


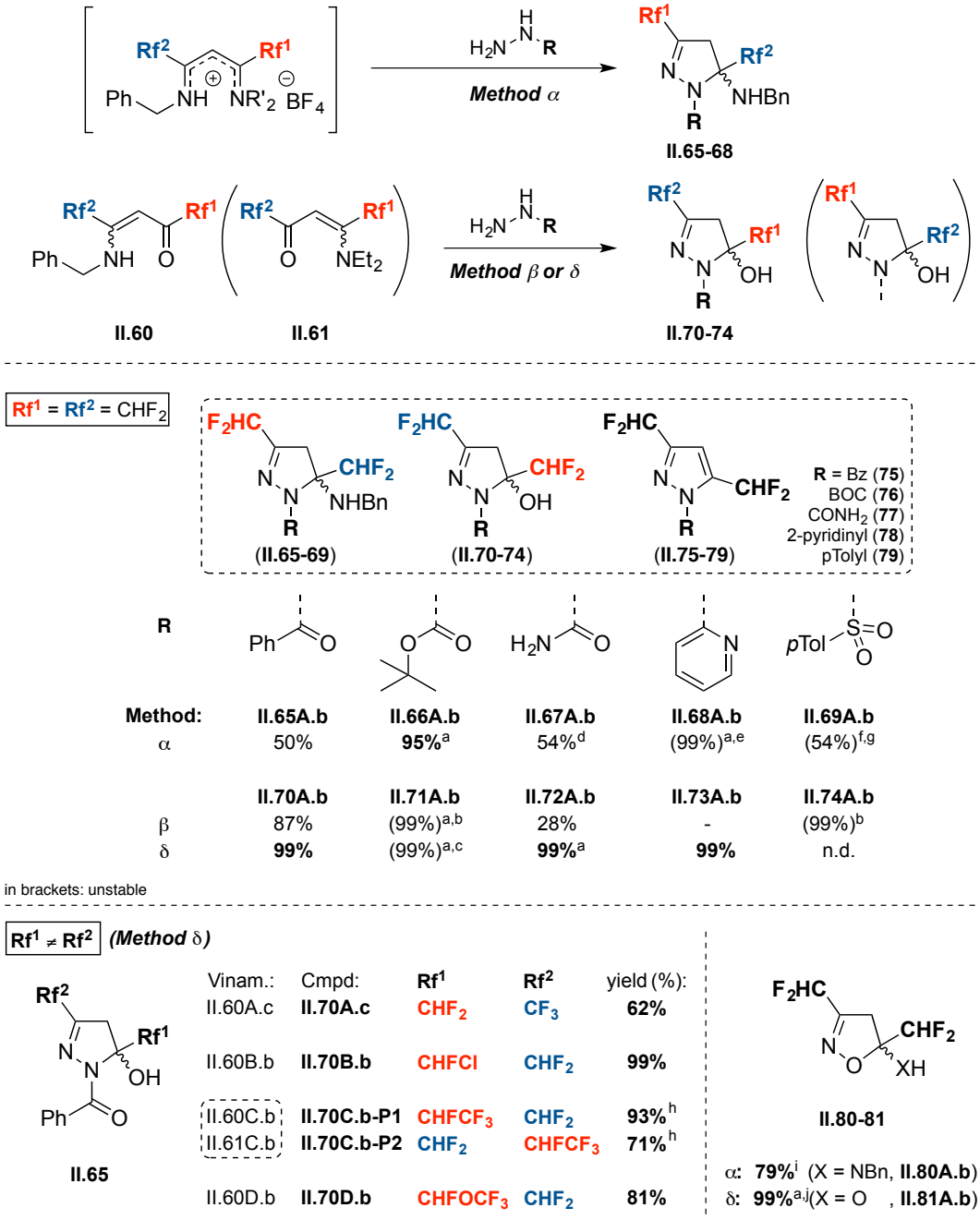
Figure II.26: Effect of electron withdrawing *N*-substituent on the aromatization of the pyrazoline intermediates.

Several pyrazolines were isolated and demonstrated an excellent stability (*e.g.*: **II.66A.b**, **II.70A.b**, **II. 72A.b**, **II. 73A.b**, Scheme II.19, centre). These experiments demonstrate that the opposite reactivities of vinamidiniums and vinamides, considering a preferential nucleophilic attack of the NH_2 part of methyl hydrazine.
5-(*N*-benzylamino)pyrazolines **II.65-69** were selectively prepared from corresponding vinamidiniums (**Method α**), and 5-hydroxypyrazolines **II.70-74** were prepared from corresponding vinamides (**Method β**). Using a fluorinated polar protic solvent (hexafluoropropan-2-ol, HFIP) made a critical improvement in this reaction (**Method δ**). This non-nucleophilic and highly H-bonding solvent proved high compatibility with the preparation of 5-hydroxypyrazolines **II.70-74** without any acidic assistance providing excellent yields.

Method δ was applied to unsymmetrical vinamides **II.60** (and **II.61)**; as a result, five different unsymmetrical 5-hydroxypyrazolines **II.70** were selectively formed with yields ranging from 62 to 99% (bottom left corner, Scheme II.19). The *N*-benzyl iminium (formed *in situ*) being more electrophilic than the fluoroalkyl ketone and the NH_2 moiety attacks selectively this position. The mixture of vinamides **II.60C.b/II.61C.b** (65:35) provided respectively a mixture of pyrazolines **II.70C.b-P1/P2** further separated by chromatography (68:32) with almost complete conservation of the initial ratios.

The synthesis of the corresponding isoxazolines has been achieved similarly by replacing hydrazines by hydroxylamine (aqueous or hydrochloride). 5-(*N*-benzylamino)-isoxazoline **II.80A.b** (**Method α**) and 5-(hydroxy)-isoxazoline **II.81A.b** (**Method δ**) were isolated in very good yields. This demonstrates that the more nucleophilic nitrogen attacks the most electrophilic iminium group in both starting vinamidinium salt and vinamide **II.60A.b** (the vinamide is in equilibrium with its keto iminium analogue) (bottom right corner, Scheme II.19). The stabilization of the non-aromatic isoxazoline form is permitted by either 1,4-H-bonding interactions or intermolecular H-bonding interactions.

Another observation relative to the preparation of *N*-carbamyl pyrazoline **II.67a** is the formation of two interesting side-products. This is due to the presence of three nucleophilic centres in the semi-carbazide, leading to different possible reaction outcomes. Considering the results, the kinetically more reactive centre is the NH_2 of the urea core. Its adjacent nucleophilic NH is achieving the pyrazole ring formation. But it can also attack first the iminium group, and the ring closure can lead to *N*-amino bis(fluoroalkyl) pyrimidinone side-products (Scheme II.20). This could not be observed when replacing the semi-carbazide by *N*-methyl urea, proving the electron-donating ability of the terminal NH_2 (attached to NH) of the semi-carbazide. A protection strategy could lead selectively to such bis(fluoroalkyl) pyrimidin-2-ones.

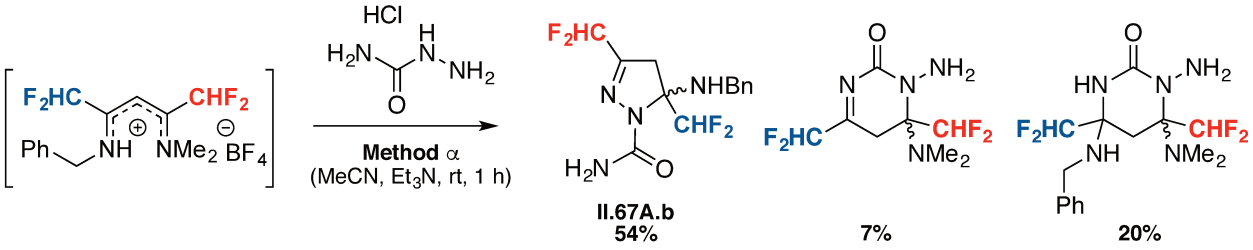


Method α: hydrazine, conc. H_2SO_4, MeCN, 20 °C, 1–18 h. **Method β**: hydrazine, conc. H_2SO_4, toluene/MeCN, 120–140 °C, microwave, 0.5–2 h. **Method δ**: hydrazine, HFIP, 100-140 °C, 0.5–5 h.

a: ^{19}F NMR yield with PhF as internal standard. b: R group cleaved between 120 and 150 °C. *N*H-pyrazole **II.58A.b** formed. c: R group cleaved between 80 and 120 °C. *N*H-pyrazole **II.58A.b** formed. d: Et_3N used to enhance hydrazine solubility, no further H_2SO_4 added. e: Pyrazole **II.78** was isolated directly. f: No conc. H_2SO_4 used. g: *N*-(*p*Tolyl)-pyrazole **II.79** was separated by chromatography from pyrazoline **II.69A.b** (29% isolated). h: Pyrazolines **II.70C.b-P1** and **II.70C.b-P1** were prepared from a 65/35 mixture of **II.60C.b**/**II.61C.b** and separated by chromatography. i: Hydroxylamine (50wt.% aq.) used instead of hydrazine. j: Hydroxylamine·HCl used instead of hydrazine. *: Mixture of diastereoisomers formed.

Scheme II.19: Regioselective preparation of 5-*N*-benzylamino- and 5-hydroxy pyrazolines and isoxazolines

The H-bonding capacity of pyrazolines **II.65-74** and isoxazolines **III.80-81** allowed the rapid formation of single crystals in many examples, which provided structural confirmation after crystallographic analysis (Figure II.27). One example of addition of BOC-hydrazide onto a vinamidinium prepared *in situ* from a *N*,*N*-dimethyl analogue of FAR **2C** (**Method** α) provided the *N*H-pyrazole **II.58C.b** with 57% yield, but another fraction provided an analogue of pyrazoline **II.65C.b-P2** (centre top structure, Figure II.27).



Scheme II.20: Side-products observed during the preparation of pyrazoline II.67A.b

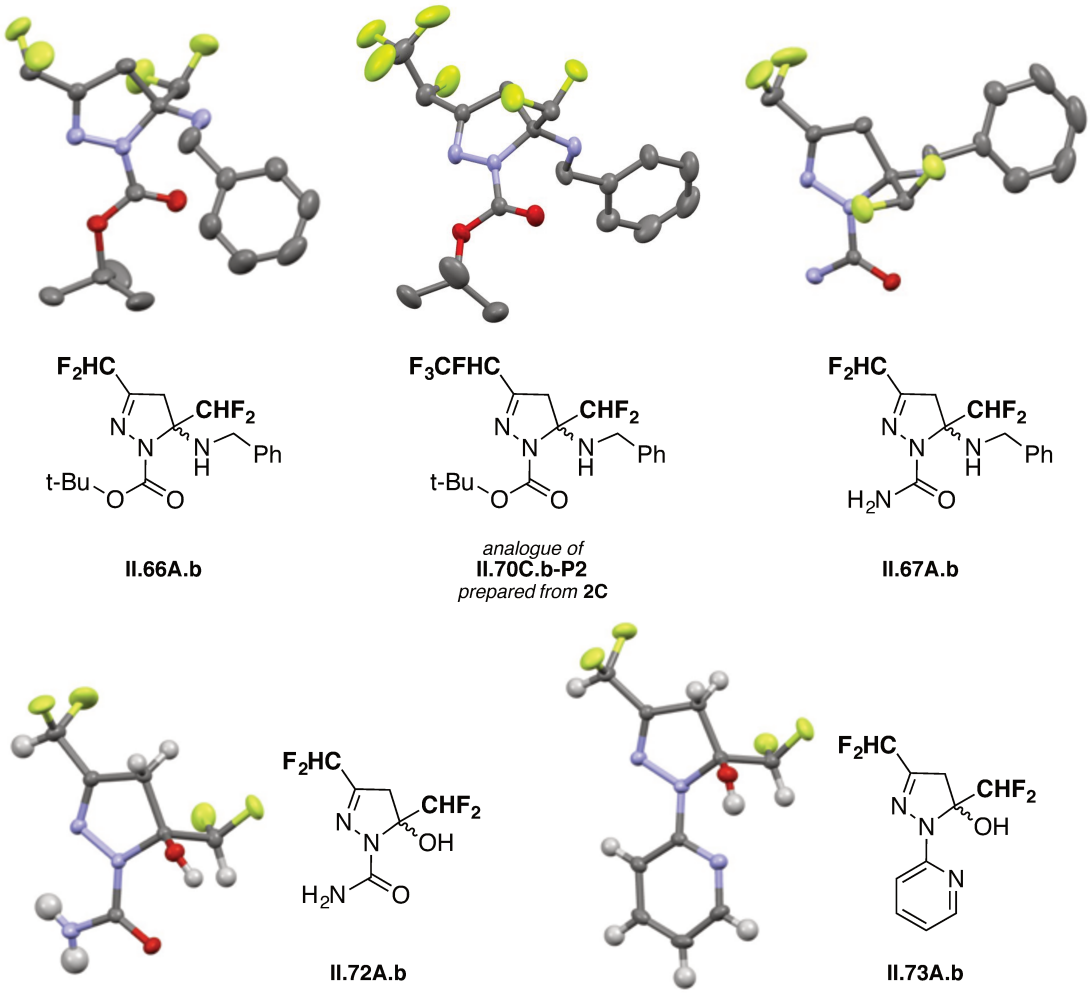
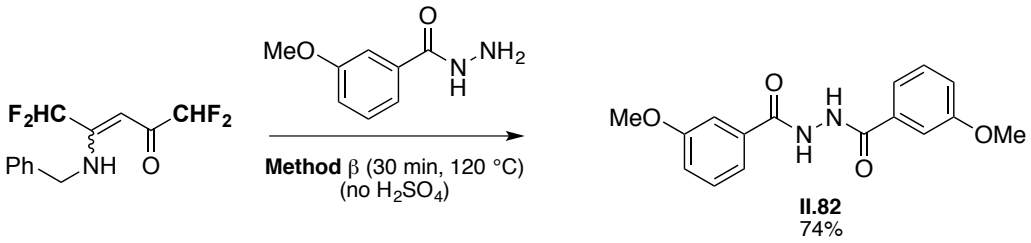


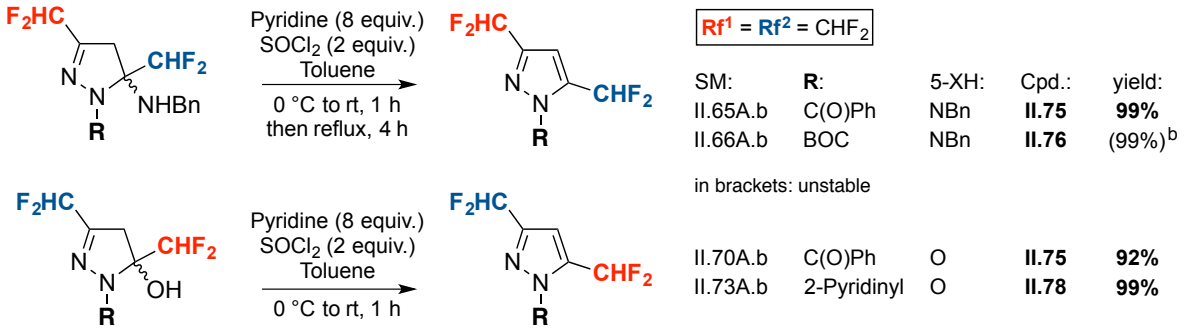
Figure II.27: Crystallographic analysis of several examples of pyrazolines

Surprisingly, whereas benzoyl hydrazine proved efficient in the synthesis of pyrazolines, the use of 4'-methoxybenzoyl hydrazine (or *m*-anisic hydrazide) never provided any desired pyrazoline or pyrazole. Instead, another side product was quantitatively formed (Scheme II.21). The resulting compound **II.82** was previously described in the literature[73].



Scheme II.21: Side product II.82 isolated from a reaction with *m*-anisic hydrazide (known in the literature).

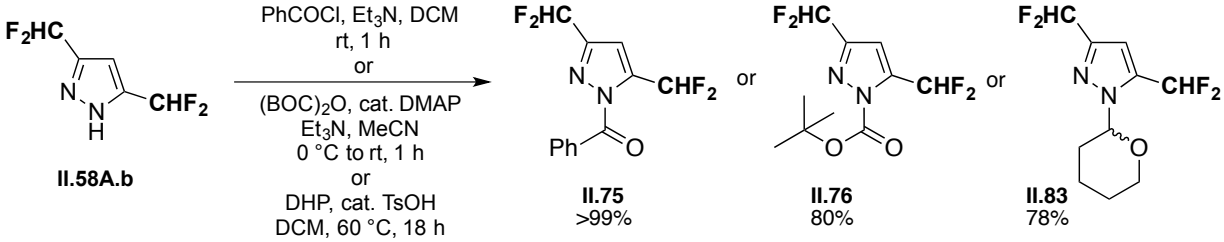
According to literature reports, we successfully aromatized a selection of bis(fluoroalkyl) pyrazolines **II.65-74** under basic conditions (pyridine in excess) using thionyl chloride ($SOCl_2$). Reflux heating was required for the aromatization of *N*-benzoyl-5-(*N*-benzylamino)pyrazoline **II.65A.b** to pyrazole **II.75**, and similarly for the *N*-(BOC) analogue **II.66A.b,** which provided quantitatively the *N*H-pyrazole **II.58A.b** due to the thermal instability of the BOC group. *N*-Benzoyl-5-hydroxypyrazoline **II.70A.b** and *N*-(2-pyridinyl)-5-hydroxy-pyrazoline **II.73A.b** were readily and quantitatively dehydrated at room temperature to yield the corresponding pyrazoles **II.75** and **II.76** (Scheme II.22).



a: ^{19}F NMR yield with PhF as internal standard. b: Pyrazole **II.58A.b** formed after BOC-cleavage.

Scheme II.22: Dehydration of several examples of pyrazolines.

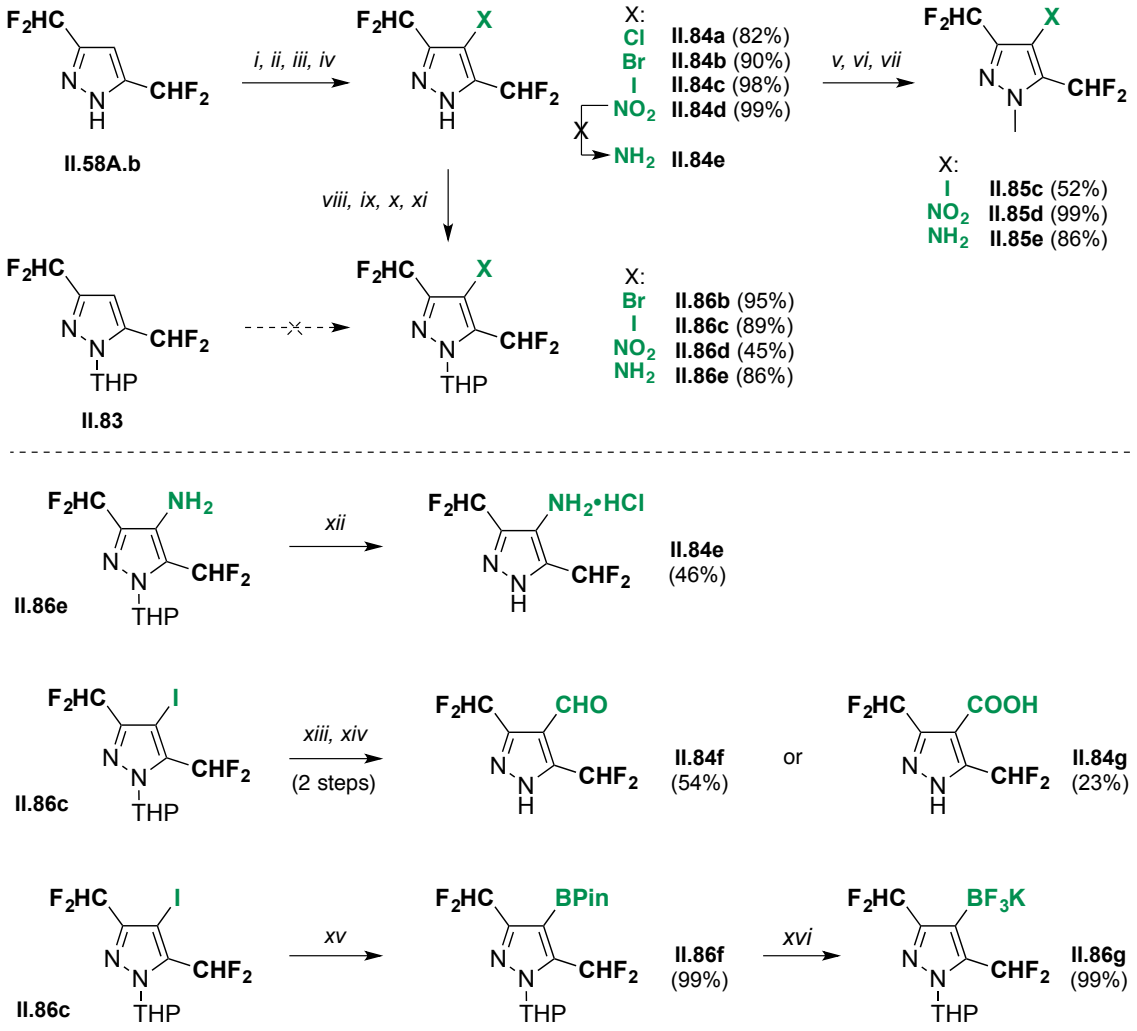
The symmetrical *N*-benzoyl pyrazole **II.75**, *N*-BOC-pyrazole **II.76** (unstable) and *N*-THP pyrazole **II.83** were also prepared from *N*H-pyrazole to access the reference compounds of variously *N*-protected pyrazoles, for further studies concerning the functionalization of the remaining position 4 (Scheme II.23):



Scheme II.23: *N*-protection of symmetrical pyrazole II.58A.b

c) Functionalization of position 4

After having developed a very powerful method to access various symmetrical and unsymmetrical bis(fluoroalkyl) pyrazoles with a large scope for *N*-substituents, another objective was to introduce more variety in the position 4 of bis(fluoroalkyl)-pyrazoles. The introduction of ethyl ester was already reported in our group,[35, 36] and other functional groups were targeted (halides, carbonyl groups, amino groups, etc.). The overall results are summarized below (Scheme II.24):



i : aq. NaOCl, AcOH, rt, 18 h. *ii* : cat. Fe, Br_2, 100 °C, 1 h. *iii* : I_2, CF_3COOAg, DCM, -15 °C to rt, 4 h. *iv* : HNO_3, H_2SO_4, 115 °C, 15 min, microwave. *v* : **II.84c**, MeI, Et_3N, DCM, rt. *vi* : **II.84d**, MeI, Et_3N, DCM, rt, 18 h. *vii* : **II.85d**, cat. Pd/C, H_2, EtOH, rt, 1 h. *viii* : **II.84b**, DHP, cat. TsOH, DCM, 50 °C, 18 h. *ix* : **II.84c**, DHP, cat. TsOH, DCM, rt, 18 h. *x* : **II.84d**, DHP, cat. TsOH, DCM, rt, 18 h. *xi* : **II.86d**, cat. Pd/C, H_2, EtOH, 50 °C, 18 h. *xii* : 2N HCl in Et_2O, rt, 30 min. *xiii* : 1) *i*PrMgCl•LiCl solution in THF, -30 °C, 1 h. 2) DMF, -30 °C to rt, 1 h. 3) conc. HCl, EtOH, rt, 72 h. *xiv* : 1) *i*PrMgCl•LiCl solution in THF, -30 °C, 1 h. 2) dry CO_2, -30 °C to rt, 1 h. 3) 1N HCl. *Then rapidly* 3) cat. conc. HCl, MeOH, rt, 1 h. *xv* : 1) *i*PrMgCl•LiCl solution in THF, -30 °C, 1 h. 2) *i*PrO-B(pin), -30 °C to rt, 1 h. *xvi* : aq. KHF_2, MeOH, rt, 30 min.

Scheme II.24: Summary of results of functionalization of the remaining position 4

The direct metallation of position 4 of pyrazoles **II.58A.b** or **II.83** did not provide the desired functionalized compounds. Similarly, the halogenation of THP-protected pyrazole **II.83** failed, showing that the electrophilic aromatic substitution is much more efficient using *N*H-pyrazoles **II.58** than with *N*-functionalized analogues. The fluorination of *N*H- or *N*-THP pyrazoles (**II.58A.b** and **II.83**) failed to occur in the position 4. Instead, in the case of **II.83**, the fluorination of other positions was observed in alpha of the THP oxygen. The metallation of **II.86c** followed by addition of electrophilic fluorination reagents (Selectfluor, 1-fluoropyridinium triflate) failed to fluorinate selectively the position 4.

The preparation of both pyrazole carboxaldehyde **II.84f** and pyrazolic acid **II.84g** was a very challenging task, and complete the access to pyrazolic acids described in Scheme II.18. They have been prepared from the 4-iodo-*N*-THP pyrazole **II.86c**, which formed the corresponding Grignard intermediate after treatment in THF at -30 °C with the turbo Grignard reagent (*i*PrMgCl•LiCl solution), and trapping with DMF or dry ice. The resulting THP-protected pyrazole carboxaldehyde and pyrazolic acid are both highly sensitive and decompose rapidly, and must be deprotected quickly in acidic media. The access to boronic ester **II.86f** and potassium trifluoroborate salt **II.86g** is interesting for further cross-coupling reactions. Similarly, the preparation of the 4-amino pyrazole hydrochloride salt **II.84e** is much more difficult than the methylated analogue **II.85e**. Interestingly, the nitropyrazole **II.84d** formed a single crystal showing its semi-hydrate character as a crude, whereas it is amorphous after silica gel purification. Its *N*-THP analogue was also confirmed by crystallographic analysis (Figure II.28).

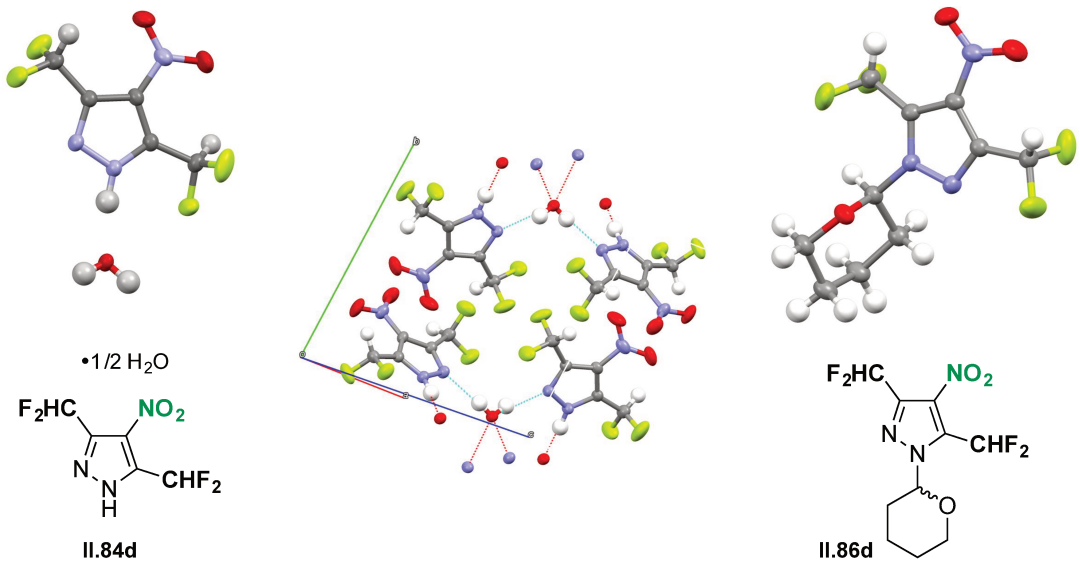


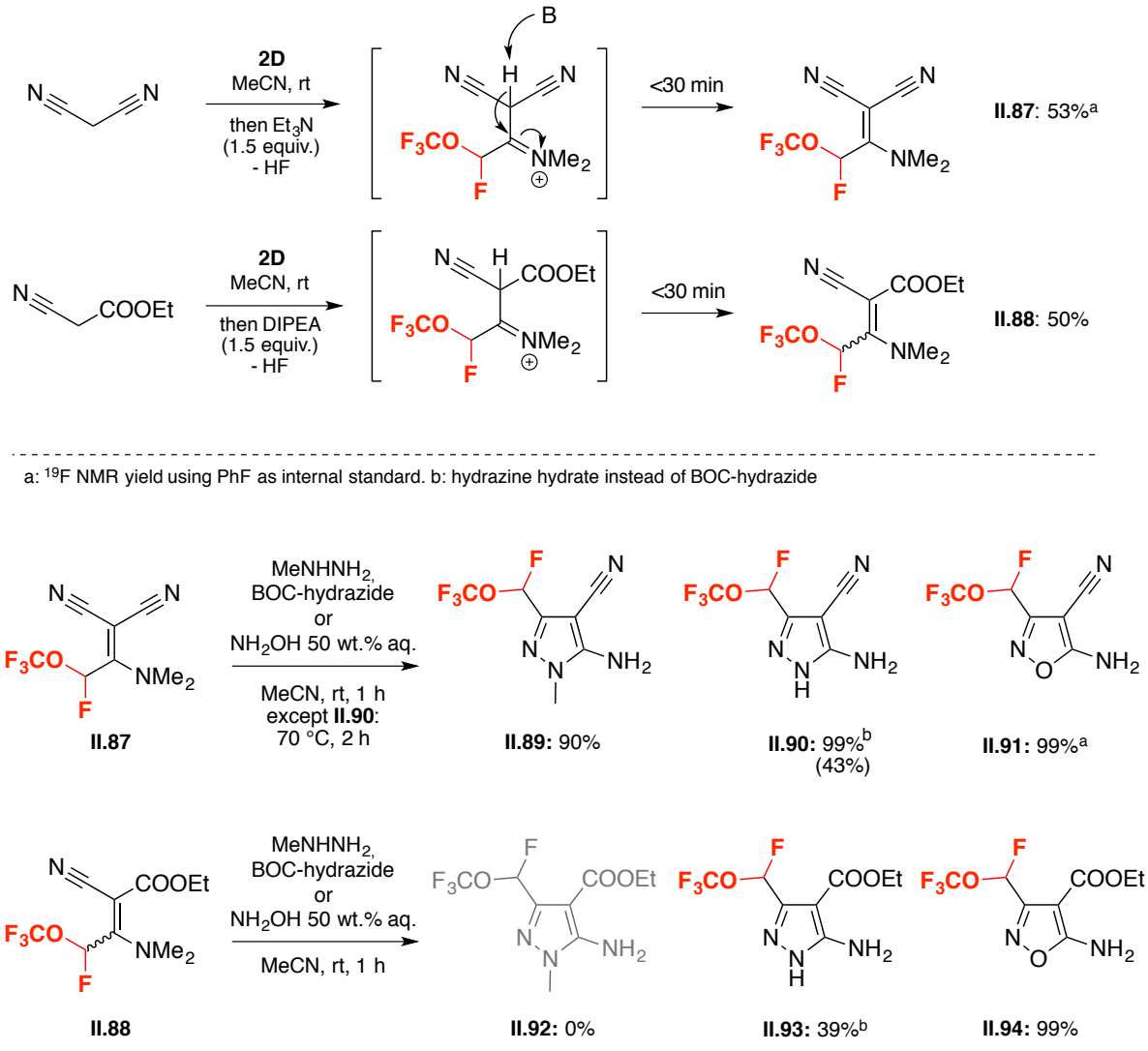
Figure II.28: Crystallographic analysis of single crystals of nitropyrazoles II.84d (crude, left; packing, centre) and II.86d (right)

A complete investigation was achieved concerning the synthesis of 3,5-bis(fluoroalkyl)pyrazoles *via* two complementary methods. A large variety of pyrazoles can be prepared with control of the fluoroalkyl groups introduced in both position 3- and 5-, but also with extended possibilities of *N*-substitution, and further possibility of functionalization of the position-4.
The addition of methyl hydrazine has been rationalized with the help of a computational chemist (from Bayer CropScience), and could help further in the rationalization of other types of hydrazines. These results were published this year, and was designed as an inside back cover of the corresponding issue. « A Major Advance in the Synthesis of Fluoroalkyl Pyrazoles: Tuneable Regioselectivity and Broad Substitution Patterns », E. Schmitt, A. Panossian, J. P. Vors, C. Funke, N. Lui, S. Pazenok, F. R. Leroux, *Chem. Eur. J.* **2016**, *22*, 11239-11244.

d) Application of the new FAR for novel ($CHFOCF_3$)-Heterocycles

Similarly to TFEDMA in its activated form (**2A**), the new FAR was confronted with CH-acidic substrates and *N*,*N*-dimethylaminoacrylate to access analogues of the CHF_2 compounds presented earlier in this chapter, and proved the efficacy of this FAR.

After similar Lewis acid activation, the new FAR **2D** was used to prepare fluoroalkyl heterocycles similarly to TFEDMA (see II.D.1.b). It was reacted with CH-acidic substrates to access intermediates **II.87-88** with much more moderate yields. However, they efficiently provided 5-amino-4-pyrazole carbonitriles and carboxylates bearing a $CHFOCF_3$ motif in position 3 (**II.89-94**) after cyclization, similarly to Scheme II.13.



Scheme II.25: Preparation of key adducts II.87 and II.88 (top);
Synthesis of 3-$CHFOCF_3$-5-amino-4-pyrazole or isoxazole carbonitriles or carboxylates II.89-94 (bottom)

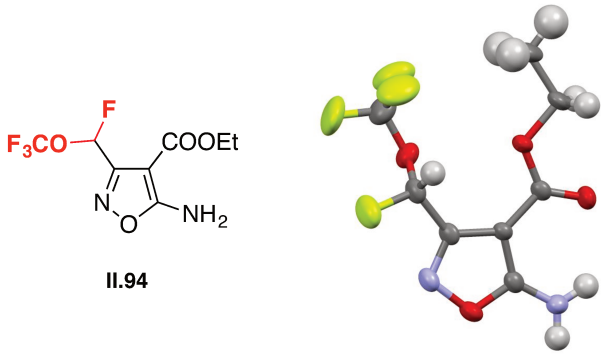
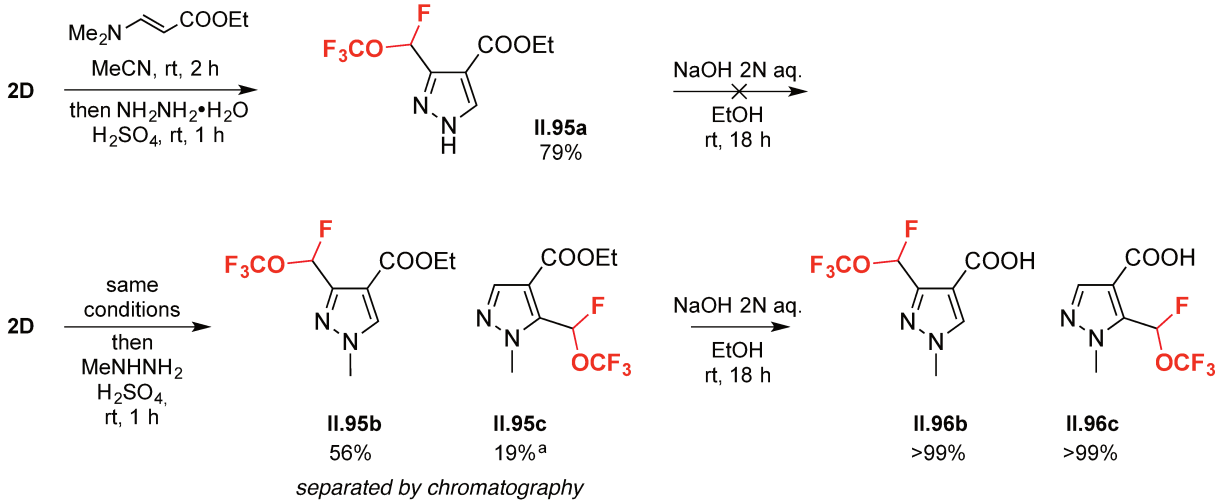


Figure II.29: Crystallographic analysis of a single crystal of compound II.94

Importantly, the use of hydrazine hydrate provided moderate yields for the preparation of NH-pyrazoles **II.90** and **II.93**. The use of BOC-hydrazide solved this problem in the case of **II.90** by preparing a *N*-BOC pyrazole, spontaneously deprotected during the purification by flash chromatography. Another difference is the impossibility to prepare the example **II.92**; in this specific case, only traces of the pyrazole were observed. No explanation could be hypothesized, and in the meantime, the isoxazole **II.94** provided crystallographic analysis confirming the formation of expected heterocycles (Figure II.29). An illustration of the similar reactivity of **2D** with **2A** is the preparation of bis(fluoroalkyl)pyrazoles using the new FAR reported in the "Ketimine route" section of this manuscript (entries 8-10, Table II.4 and entries 7-9, Table II.5).

The preparation of analogues of the key intermediate of Bixafen® was achieved using **2D** (**II.95b**, Scheme II.26).

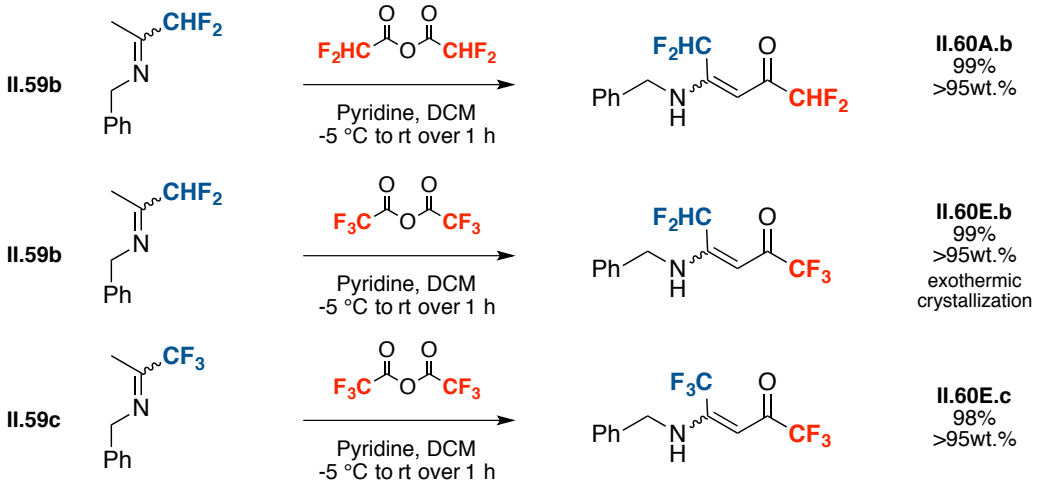


Scheme II.26: Efficient preparation of *N*H- and *N*Me-analogues of DFMMP (see Scheme II.6)

In the *N*-methyl series, both regioisomers **II.95b** and **II.95c** were separated after silica gel chromatography purification using a very slow gradient of diethyl ether in pentane in a large column. Each regioisomer has been saponified separately to provide the corresponding carboxylic acids **II.96b** and **II.96c**. An article concerning these results will be submitted in due course for publication. After investigating in details the potential of FARs for the synthesis of fluoroalkylated arenes and heterocycles, we decided to develop new access to fluoroalkyl heterocycles without the use of FARs. These results are described in the following part of this chapter.

e) Access to mono- and bis-fluoroalkyl heterocycles without FARs

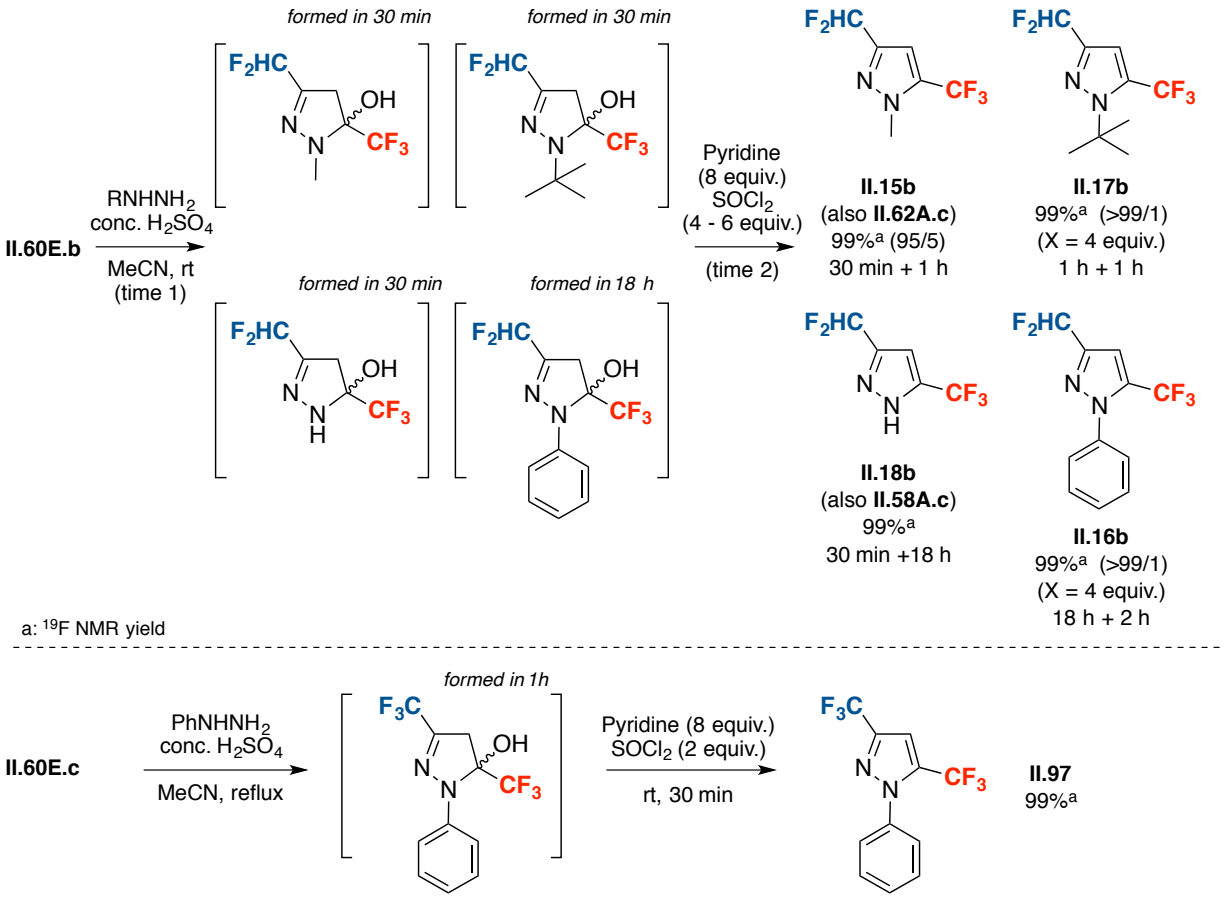
After using FARs for the efficient preparation of various acylated arenes and mono- and bis-fluoroalkylated heteroarenes, the next objective was to prepare efficiently mono- and bis-fluoroalkyl heteroarenes without the use of FARs. For this purpose, we decided to use fluorinated ketimines **II.59** in combination with more easily accessible electrophilic fluorinating reagents. Bis(fluoroalkyl) vinamides **II.60** were prepared using fluorinated anhydrides under basic conditions. This strategy allowed for the preparation of two unprecedented vinamides (**II.60E.b** and **II.60E.c**), and improved the result in the preparation of vinamide **II.60A.b** (Scheme II.27):



Scheme II.27: Facile preparation of bis-fluoroalkyl vinamide II.60A.b (top, see Table II.3) and both unprecedented II.60E.b (middle), and II.60E.c (bottom)

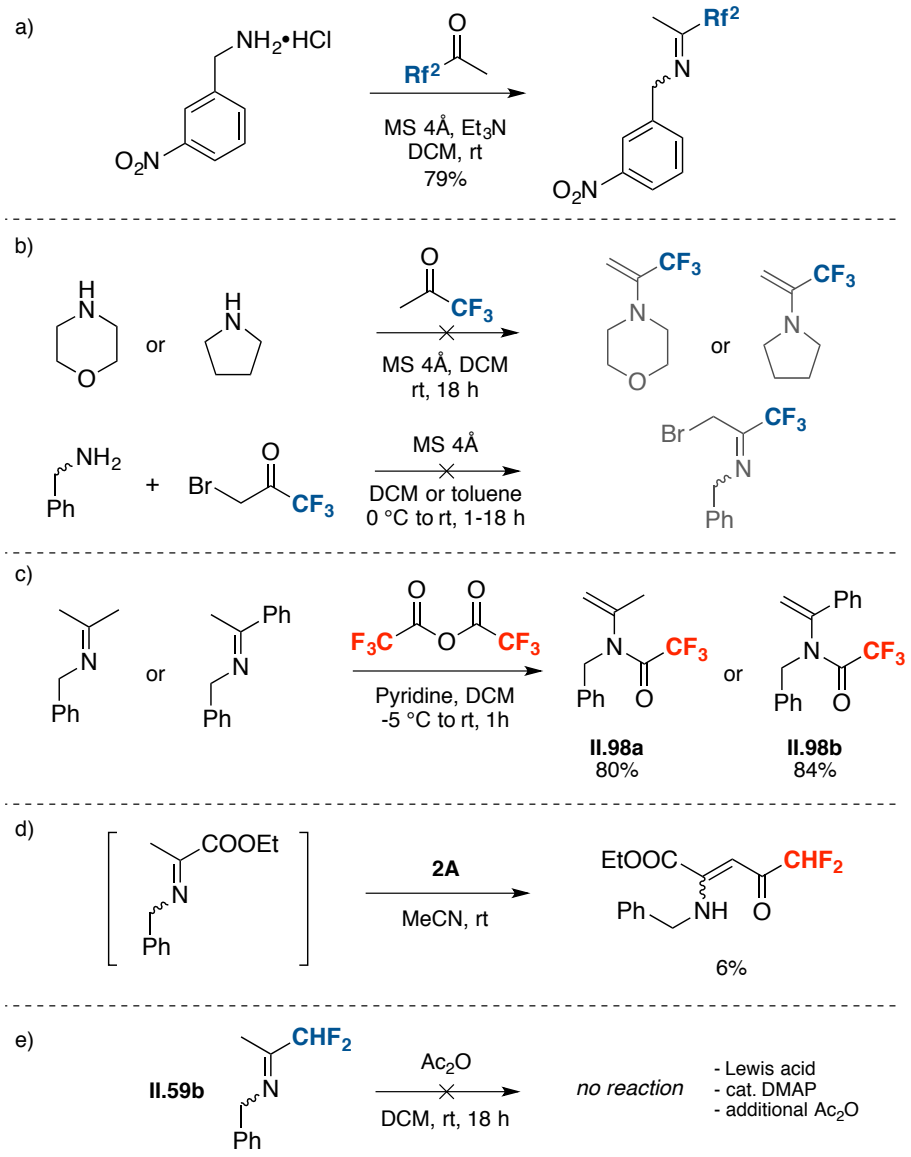
As these vinamides did not allow for the synthesis of several examples of bis(fluoroalkyl) pyrazoles in our previously described article, their synthesis was achieved. The vinamides formed in a first step the corresponding 5-hydroxy pyrazolines after addition of the hydrazines, before dehydration conditions were applied *in situ*. Thus, the preparation of pyrazoles **II.15b** (identical to **II.62A.c**, Table II.5)**, II.16b, II.17b** and **II.18b** (identical to **II.58A.c**, Table II.4) was reproduced with much higher yield (in comparison with our recent report)[35] using very simple reaction conditions (top, Scheme II.28). Meanwhile, the preparation of bis(CF_3)-*N*-phenyl pyrazole **II.97** was much more efficient than in previous reports from the literature, where volatile and highly toxic bis(CF_3)-1,3-diketone is used with lower yield (bottom, Scheme II.28).

To access mono-fluoroalkyl vinamides, several reactions involving fluorinated or non-fluorinated imines and fluorinating reagents (anhydrides, alkyl oxalyl chlorides) were attempted. Functionalized fluorinated ketimines were supposed to influence the pyrazole formation step, and one example was prepared starting from *m*-NO_2-benzylamine but was not further exploited (a, Scheme II.29). The synthesis of other types of fluorinated ketimines has been attempted without success, especially from halogenated fluoroalkyl ketones (corresponding ketimine was reported with poor yield,[74] but it was impossible to prepare this example with sufficient purity to be reacted with activated FARs), or using other amines than benzylamine. Unfortunately, these attempts failed (b, Scheme II.29). The reaction between non-fluorinated ketimines and fluorinated anhydrides was attempted, inspired by the highly efficient examples of Scheme II.27. However, *N*-acylation products **II.85a-b** were selectively formed. These unprecedented compounds have not been further used so far (c, Scheme II.29).



Scheme II.28: Preparation of the corresponding bis(fluoroalkyl) pyrazoles from both unprecedented vinamides II.60E.b and II.60E.c (top); facile synthesis of a challenging bis-CF_3-pyrazole reported in the literature (bottom)

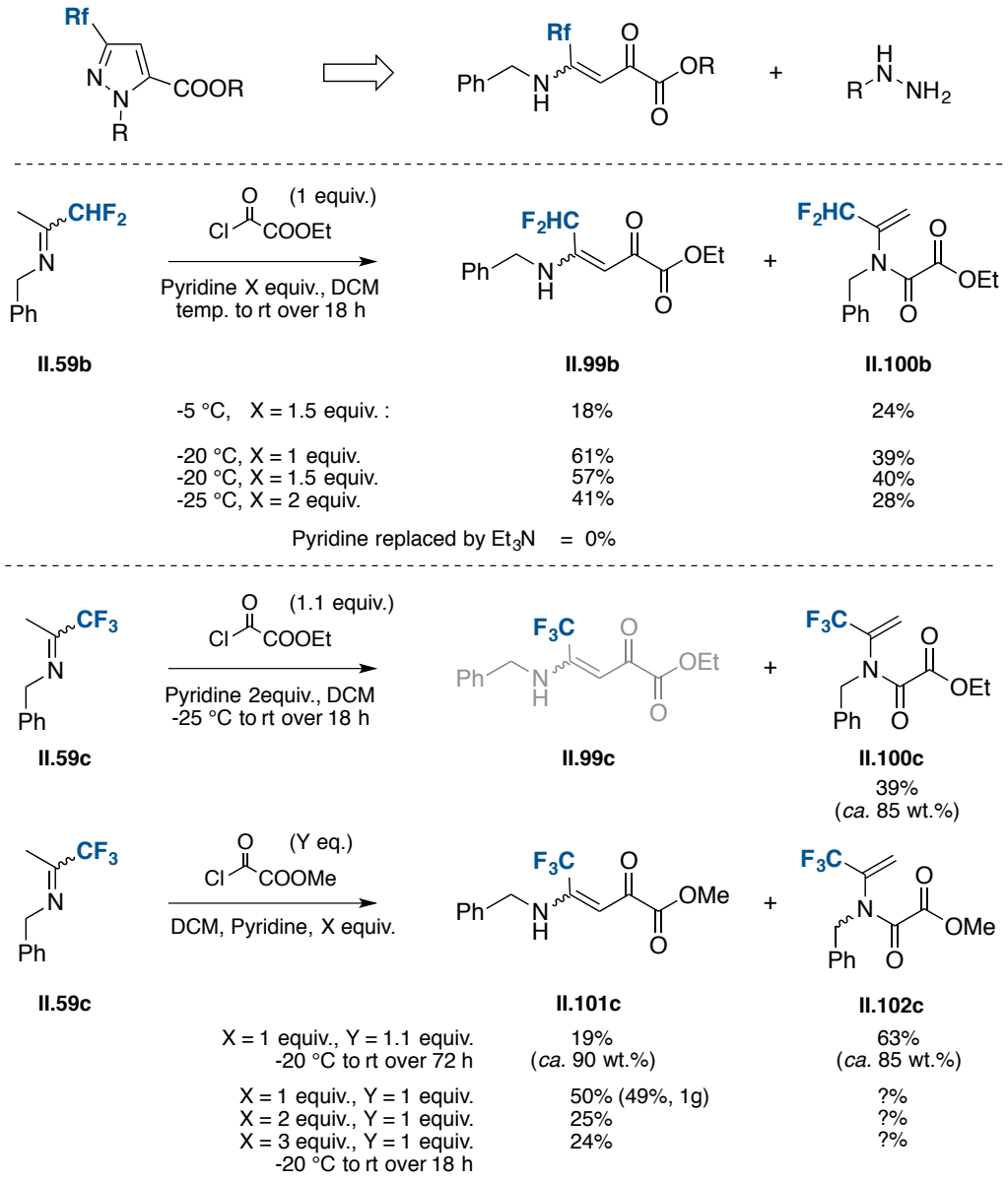
The preparation of a ketimine functionalized with an ester group was attempted but proved to be difficult, starting from benzylamine and ethyl pyruvate (both distilled prior to use) and using previously described conditions. The crude mixture resulting from this imine synthesis was engaged in a reaction with activated TFEDMA **2A** using conditions reported as **Method α**. A small amount of the desired vinamide was isolated with low purity, but this reaction has to be ameliorated (d, Scheme II.29). The fluorinated ketimine **II.59b** was reacted with acetic anhydride, but no reaction occurred at all despite the addition of Lexis acid (boron trifluoride diethyl etherate), of a catalytic amount of DMAP, or of excess of acetic anhydride (e, Scheme II.29).



Scheme II.29: Various parallel attempts concerning the "Ketimine route" project

Finally, the condensation of fluorinated ketimines with alkyl oxalyl chlorides was investigated, in order to access mono-fluoroalkyl vinamides **II.99**. The fluorinated ketimines **II.59b** and **II.59c** were separately investigated, as both compounds displayed different reactivity towards ethyl- and methyl-oxalyl chlorides (Scheme II.30).

The ketimine **II.59b** reacted efficiently with ethyl oxalyl chloride, but after a closer analysis, the selectivity between *C*- and *N*-acylation revealed to be poor. In the best example, the desired vinamide **II.99b** was formed up to 61%. The ketimine **II.59c** reacted also with ethyl-oxalyl chloride but only the undesired CF_3-propenyl amino-oxoacetate side-product **II.100c** was isolated. When switching to methyl-oxalyl chloride, the desired vinamide **II.101c** was formed in mixture with CF_3-propenyl amino-oxoacetate side-product **II.102c**. Both products were separable by chromatography. Long reaction time seems to favour the side product **II.102c**, probably due to a rearrangement of the desired vinamide providing the thermodynamically more stable side-product (Scheme II.30). These results are not optimized, but the desired vinamides were employed in the synthesis of valuable 3-fluoroalkyl-5-pyrazole carboxylate building blocks **II.103-107** (Scheme II.31).

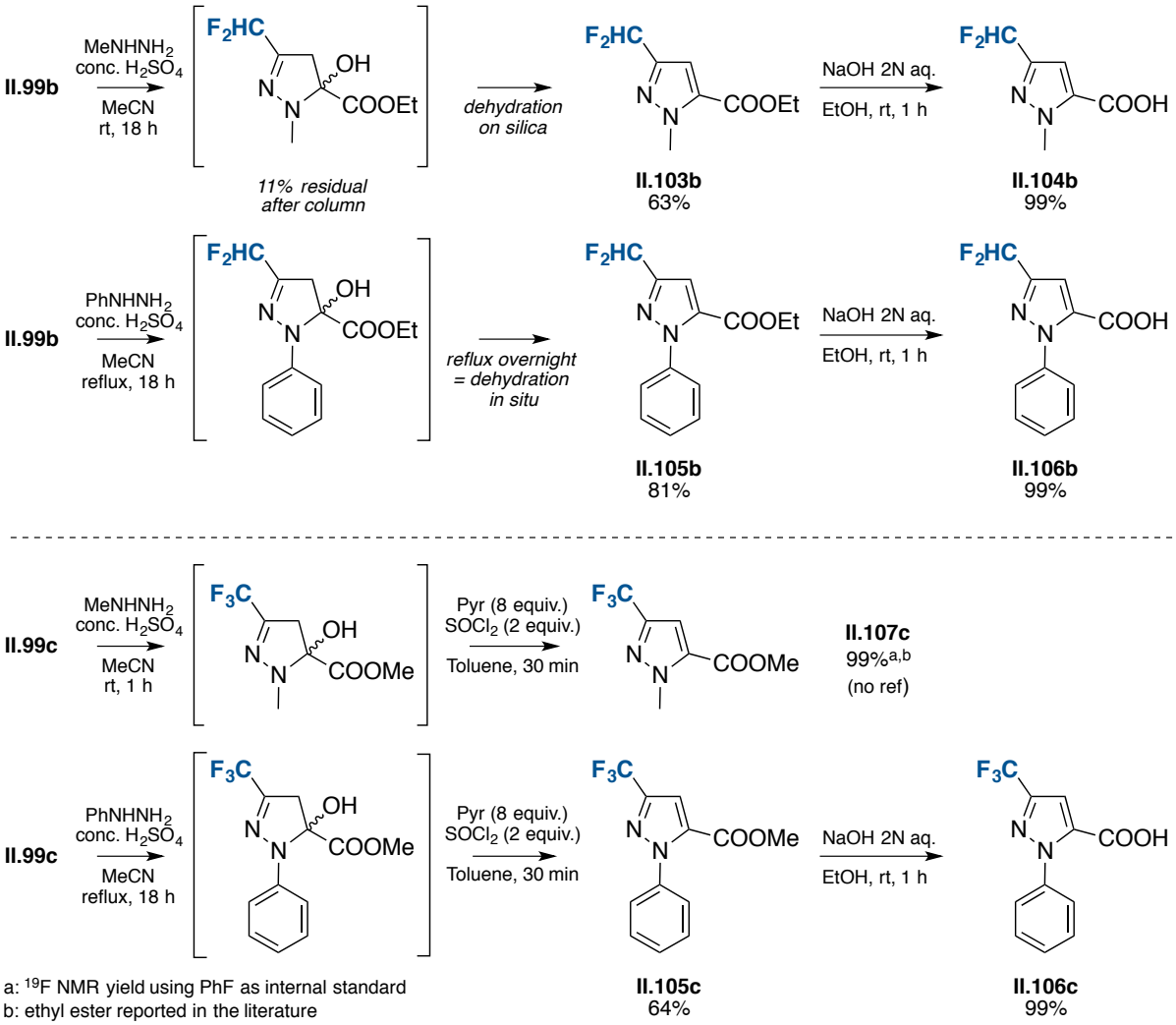


Scheme II.30: Early results for the preparation of key vinamide intermediates

The pyrazole ring formation occurs similarly to Scheme II.28, and for 3-CHF_2-5-hydroxypyrazolines the dehydration is either spontaneous or occurs during the silica gel purification. For the CF_3-analogues, a subsequent addition of pyridine and thionyl chloride is required to allow for the dehydration step.
The pyrazoles **II.103b** and **II.105b** are prepared with good to excellent yields. The yield of the example **II.107c** was measured by ^{19}F NMR analysis the ethyl ester analogue as a reference (both NMR traces are similar by ^{19}F NMR). All pyrazoles were very rapidly saponified, to produce the desired pyrazole carboxylic acids **II.104b**, **II.106b** and **II.107b** with quantitative yields. Former methods to prepare such pyrazole carboxylic acids are not as efficient.

These results have been integrated into a patent recently filed (Bayer CropScience, Monheim / CNRS):

F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates and 3- fluoroalkyl-5-pyrazolecarboxylic acids, *BCS163094* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 13/09/2016).



a: ^{19}F NMR yield using PhF as internal standard
b: ethyl ester reported in the literature

Scheme II.31: Efficient preparation of 3-fluoroalkyl-5-pyrazole carboxylate and carboxylic acid building blocks

E. Conclusion

The necessity to develop new methods of preparation of innovative fluorinated building blocks has been highlighted in this chapter, especially for the introduction of Emergent Fluorinated Substituents (EFSs) into various *N*-based heterocycles. The pyrazole core was defined as the first objective due to the expansion of marketed compounds built around this motif. After previous reports from our group dealing with the synthesis of 3,5-bis(fluoroalkyl)pyrazole carboxylates with the use of Fluoroalkyl Amino Reagents (FARs), we decided to investigate further their potential in organic synthesis. At this period, three FARs were commercially available (TFEDMA, Yarovenko reagent and Ishikawa reagent, **1A-C**).

We achieved a study of the reactivity of TFEDMA (**1A**) (after activation using a Lewis acid, $BF_3.Et_2O$) with a variety of substrates (electron-rich heterocycles and arenes, vinyl ethers and analogues, silyl enol ethers, CH-acidic compounds). A large scope of difluoroacylated heteroarenes and arenes was prepared and the resulting yields were superior to all previous report in the literature for direct difluoroacylation. The use of activated TFEDMA **2A** as difluoromethyl transfer reagent provided a large variety of 3-difluoromethyl heterocycles with a majority of pyrazoles, and also isoxazoles. The resulting unprecedented heterocycles constitute new and easily accessible synthons in life science oriented research.

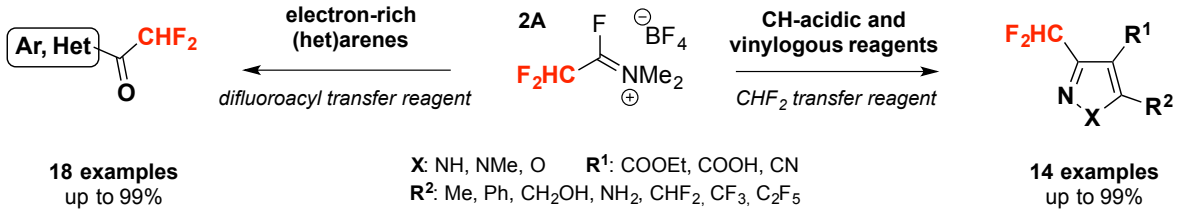


Figure II.30: Study of the versatility of fluoro iminium salts illustrated by the use of TFEDMA

At this point, we developed a procedure for the preparation of a new FAR from perfluoromethyl perfluorovinyl ether. This FAR **1D** was prepared by hydroamination of this liquefied gas with a solution of dimethylamine at low temperature and subsequent Lewis acid activation *in situ*. This FAR proved to be similarly reactive than TFEDMA. Its use provided valuable building blocks, similarly to the first project. This activated FAR showed a quite similar reactivity when compared with **2A**. Innovative pyrazole and isoxazoles bearing a new EFS (-$CHFOCF_3$) have been prepared with good to excellent yields using similar approaches.

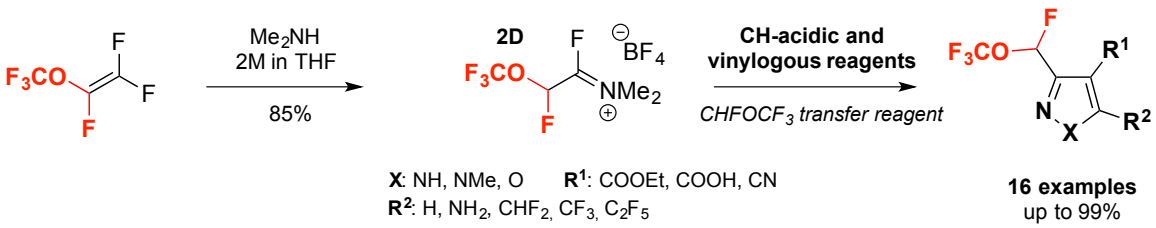


Figure II.31: Use of the new FAR 2D for the preparation of building blocks bearing a new EFS

The interest for bis(fluoroalkyl) synthons (especially pyrazoles) came in parallel, and a new synthetic strategy was developed to access challenging 3,5-bis(fluoroalkyl)-*N*H-pyrazole building blocks; we developed fluorinated azines that were reacted with activated FARs **2A-C**. The resulting intermediates

could be isolated after hydrolysis, or treated with concentrated acid in order to achieve the intramolecular cyclization and the pyrazole ring formation. Innovative 3,5-bis(fluoroalkyl)-*N*H-pyrazoles bearing unsymmetrical fluorinated substituents (mostly EFSs) have been prepared with moderate to excellent yields. Some drawbacks were observed in this approach, as the use of difficult-to-remove benzophenone.

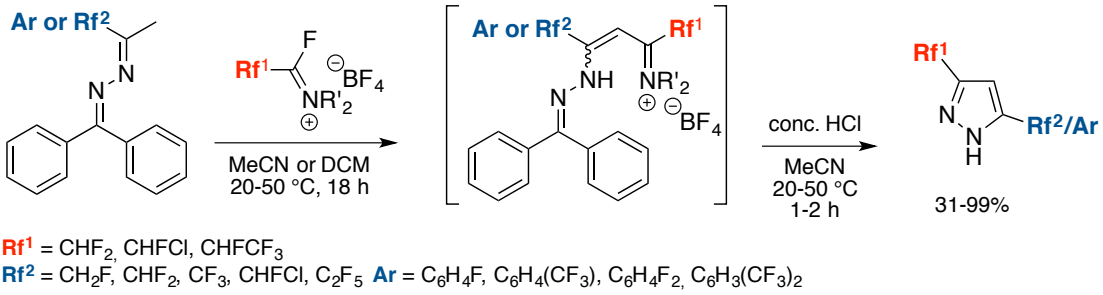


Figure II.32: Preparation of unprecedented 3,5-bis(fluoroalkyl)-*N*H-pyrazoles *via* the azine route

The next objective was to improve the atom economy of the method, while developing a more convenient strategy, especially for the purification step. This strategy was successfully designed, based on the use of fluorinated ketimines. These substrates were readily prepared from simple chemicals (benzylamine and fluorinated ketones), and reacted very quickly with activated FARs; the resulting vinamidinium salts revealed to be very peculiar intermediates, as they could either be treated with hydrazines *in situ* to provide regioselectively the corresponding pyrazoles (**Method α**), or be hydrolysed to provide the corresponding vinamides. These vinamides possessed a completely reversed reactivity towards hydrazines, giving regiospecific access to the opposite regioisomer (**Method β or δ**). The functionalization of the position 4 of bis(fluoroalkyl)pyrazoles was also studied and a broad scope of functional groups have been introduced. (Figure II.33).

Finally, the preparation of mono- and bis-fluoroalkyl pyrazoles without employing FARs was investigated, as fluorinated reagents such as anhydrides are more easily accessible and cheaper than FARs. The preparation of valuable fluoroalkyl building blocks was possible but the efficiency of the intermediate preparation must be optimized.

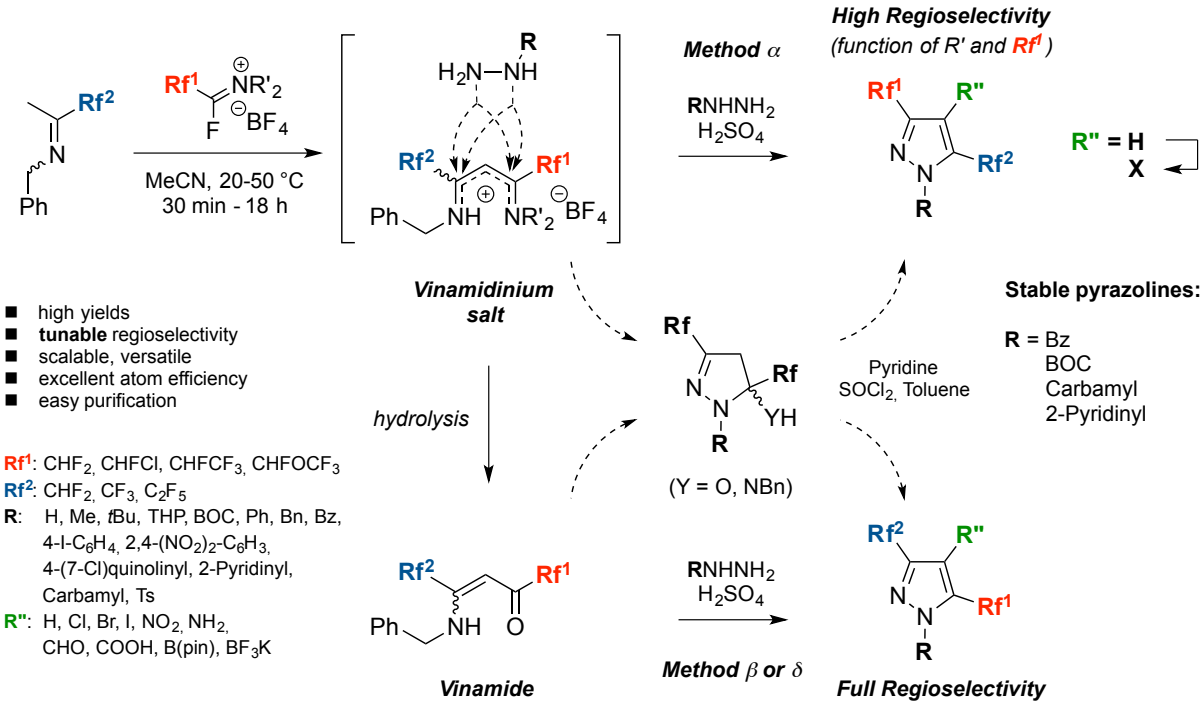


Figure II.33: Summary of "Ketimine route" project giving facile access to 3,5-bis(fluoroalkyl) pyrazoles with various possibilities of functionalization in positions 1, 3, 4 and 5.

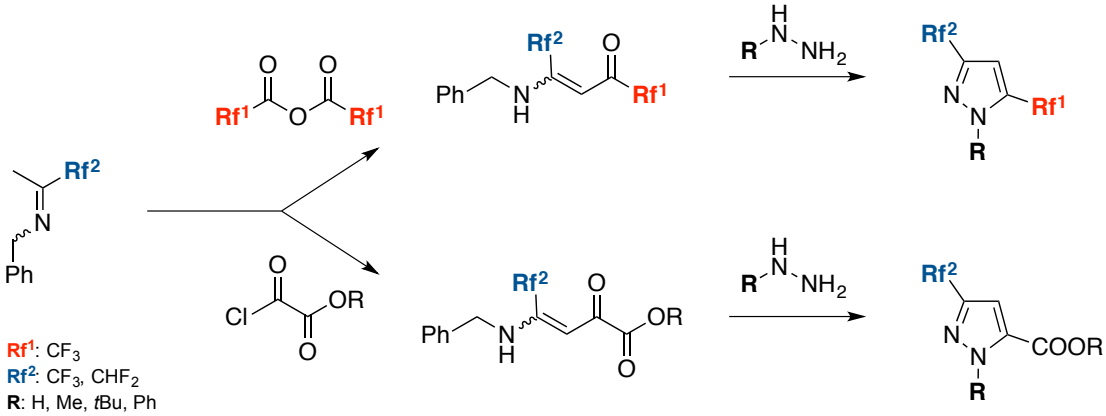


Figure II.34: Preparation of mono- and bis-fluoroalkyl pyrazole building blocks without using FARs

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Chapter III

Fluoroalkyl Amino Reagents for the Synthesis of 6-membered Heterocycles bearing Emergent Fluorinated Substituents

Table of contents

In the previous chapter, it has been described how the use of FARs can conveniently and innovatively provided fluoroalkyl 5-membered *N*-based heterocycles such as pyrazoles, isoxazoles, and probably other examples, which were not discussed but could be produced using similar strategies.

Another type of heterocycles will be discussed, of similar importance for the discovery of new bioactive entities, namely the 6-membered *N*-based heterocycles. More specifically, an interest will be put on the preparation of unprecedented pyrimidines and several pyridines.

The importance of diazine in life science oriented research has been highlighted previously. More specifically, the pyrimidine core has attracted great attention over the last years, due to its large occurrence in a variety of disease treatments, and specifically in antimicrobial treatments, as recently reviewed.[1, 2] Several blockbuster drugs contain a pyrimidine core, *e.g.* Imatinib or Rosuvastatin (Crestor, fourth-highest selling drug in the US, with $5.2 billion sales in 2013) (left and centre, Figure III.1).

In agrochemistry, pyrimidines are also extensively represented, as illustrated with one selected example (right, Figure III.1). These bioactive pyrimidine-based compounds are relatively complex in terms of chemical structure. The synthesis of pyrimidines is well described for decades and has been recently reviewed;[3] it will not be discussed in more details.

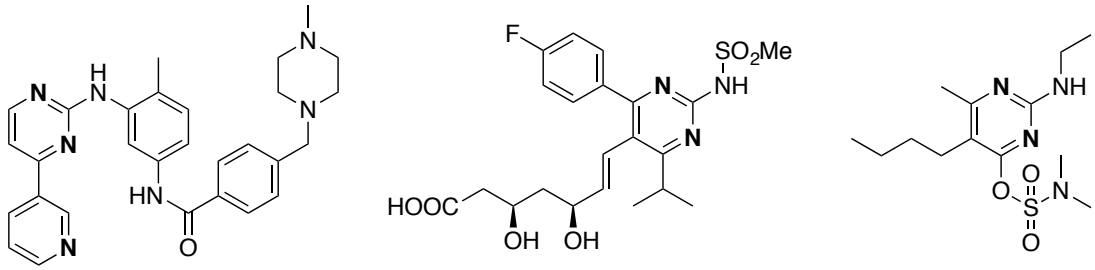


Figure III.1: Examples of pyrimidine-based top-selling drug and agrochemical compounds.

The necessity to developed novel building blocks for the discovery of new bioactive entities has been discussed earlier in this manuscript and is a key aspect of modern research. The preparation of CF_3-containing pyrimidines is well established, and several CF_3-pyrimidine agrochemicals are included in the manuscript as examples of bioactive compounds (Fluacrypyrim Figure I.10, selection of herbicides, Figure I.12). Constant work has been achieved for a long time in the synthesis of CF_3-pyrimidine building blocks. Several relevant examples providing attractive targets for drug discovery,[4] or with applications in agrochemistry (*e.g.*: 2-anilinopyrimidine class[5]).

In this PhD, the focus has been repeated on the preparation of novel 6-membered heterocyclic building blocks containing emergent fluorinated substituents (EFSs); their potential has been discussed in Chapters I and II, however the introduction of EFSs into pyrimidines is scarcely described, which limits the rate of discovery of related highly drug-like fluoroalkyl pyrimidines.

The existing methods for the preparation of mono- or bis- fluoroalkyl pyrimidine building blocks will be discussed and the development of an strategy for the preparation of bis-fluoroalkyl pyrimidines will then be presented in details using FARs. Finally, an opening will be made on the preparation of mono-fluoroalkyl pyrimidines.

A. Synthesis of Fluorinated Pyrimidines – State-of-the-art

As mentioned above, the access to pyrimidines containing one or more EFSs is still a synthetic challenge, at the opposite of CF_3-analogues being state-of-the-art. There is still a need for new strategies to access these valuable building blocks, with potential applications in agrochemistry as well as medicinal research and even material science.

The introduction of EFSs into pyrimidines has been reported in the literature to a limited extent, usually by late stage fluorination using expensive deoxofluorination reagents. However, similar limitations and drawbacks are encountered in comparison with the previously discussed pyrazoles (Chapter III). Nowadays, there is a need for developing general and easily accessible methods for the preparation of such compounds.

As in the previous chapter, a large focus will be placed in the introduction of the -CHF_2 group, very prevalent EFS currently. The strategies for its introduction into pyrimidines will be summarized but are still limited. The synthesis of bis(fluoroalkyl)pyrimidines is even more scarcely described in the literature, but a few results are documented. This led us to design an innovative strategy to fill this empty space in organofluorine chemistry.

One specific report caught our attention. In 2013, Frutos *et al*. reported an interesting method for the synthesis of non-fluorinated pyrimidines from amidines (prepared *in situ* from commercially available carbonitriles) in presence of a vinamidinium salt. This method provides efficiently non-fluorinated pyrimidines, but we have seen that fluoroalkyl vinamidinium salts can be used to prepare fluorinated pyrazoles, and this strategy will be further investigated.[6]

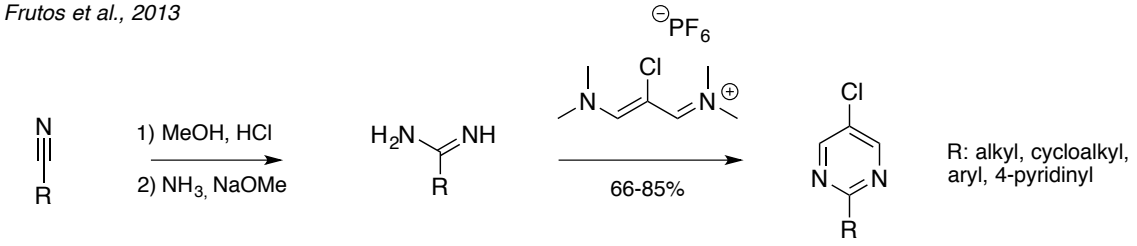


Figure III.2: Preparation of pyrimidines using self-prepared amidines and a vinamidinium salt

1. Mono(difluoromethyl) Pyrimidines

In the literature, many patents can be found describing the multi-step synthesis of complex molecules containing a fluoroalkyl pyrimidine for specific biological applications, but not for small fluoroalkyl pyrimidine building blocks. Moreover, these patents describe deoxofluorination reactions (using expensive reagents such as DAST, Deoxofluor®, etc.) from aldehyde substrates often difficult to prepare. This approach is not adapted for industrial applications for reasons previously cited in this manuscript.[7, 8]

In 2002, Shermolovitch *et al*. reported the preparation of benzylsulfonyl pyrimidine diones by condensation of fluorinated benzylsulfonyl substrates with two equivalents of sodium cyanate. The chlorination of the pyrimidine diones led to functionnalizable pyrimidines, and the desulfonylation was reported with an excess of toxic HMPA under harsh conditions (Figure III.3). This strategy remains very limited, and the preparation of the starting substrates was not detailed.

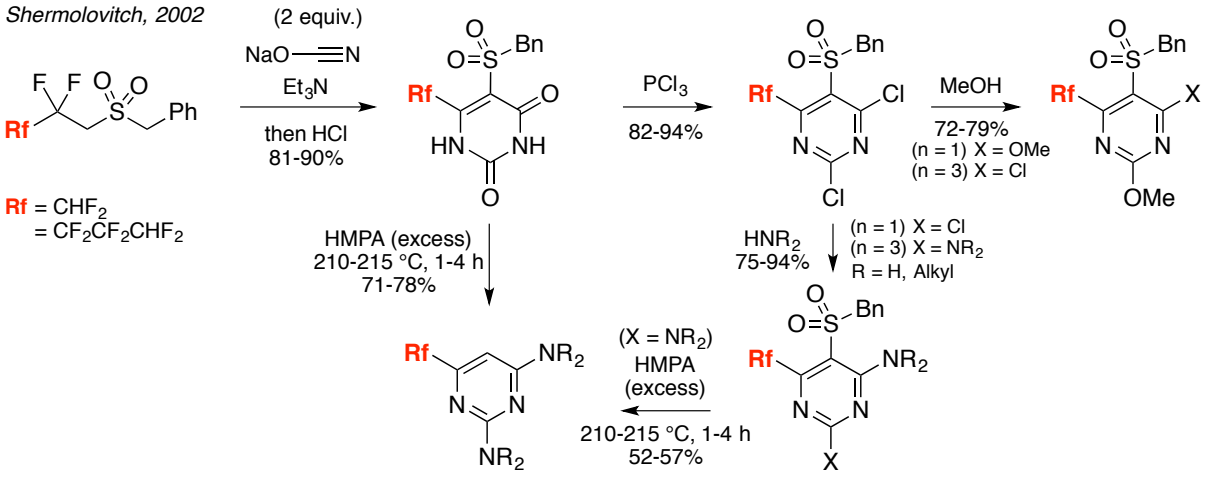


Figure III.3: Construction of pyrimidine dione core from fluorinated benzylsulfonyl substrate

The preparation of fluoroalkyl pyrimidines is usually based on the construction of the pyrimidine core from 1,3-dielectrophiles and 1,3-dinucleophiles (*e.g.*: amidines, ureas).

In 2001, Iaroshenko *et al*. reported the preparation of various fluoroalkyl heterocycles. The CF_2Cl-pyrimidines (and other heterocycles) were prepared from CF_2Cl-1,3-diketones (or β-ethoxyenones) and amidines. A subsequent radical dechlorination was required to access the CHF_2-analogues. In addition, the starting reagents are not easy to prepare (a, Figure III.4).[9] In 2012,

Negoro *et al*. reported a similar pyrimidine ring construction from the preparation of the corresponding pyrimidinone from aryl amidines and fluoroalkyl acetoacetates. A subsequent chlorination provided the chloro pyrimidines. This multi-step procedure is very efficient despite a limited scope (b, Figure III.4).[10]

Burgart *et al*. reported in 2014 the synthesis of 2-SMe pyrimidin-4-ones by condensation of fluoroalkyl acetoacetates and *S*-methylisothiourea sulphate. The nucleophilic substitution of the thiomethyl group by various hydrazines was achieved with moderate yields (c, Figure III.4).[11] Grée *et al*. reported in 2009 the preparation of mono- and difluoromethyl pyrimidines from CHF_2-propargyl ketones. Several examples were synthesized from fluorinated propargyl ketones (prepared by non-selective deoxofluorination of carbonyl analogues) (d, Figure III.4).[12]

In 2009, Iaroshenko *et al*. reported a strategy involving fluorinated chromones providing the corresponding pyrimidines, similarly to their previous work on fluoroalkyl pyrazoles with hydrazines (Scheme II.3). This strategy requires the preparation of chromones (which can be difficult) and its scope is limited to 5-salicyloyl-4-(fluoroalkyl)-pyrimidines (e, Figure III.4).[13] In 2012, Iaroshenko *et al*. reported the preparation of several ribofuranosyl pyrimidines bearing fluoroalkyl groups by condensation of ribofuranosyl amidine hydrochloride with 1,3-dielectrophiles (fluoroalkyl β-mono- or β-diethoxyenones), showing a tolerance to the presence of non-protected carbohydrates.[14]

The preparation of 2-CHF_2-pyrimidines is even more scarcely described. Qin et al. reported in 2001, the preparation of 2-(CHF_2)pyrimidine-4,6-diol by condensation of malonamide and ethyl difluoroacetate under basic conditions, and was used in the preparation of a promising 2-(CHF_2)-pyrimidine-4,7-dione as potential nicotinic acid receptor agonist. This example remains limited in terms of scope (f, Figure III.4).[15]

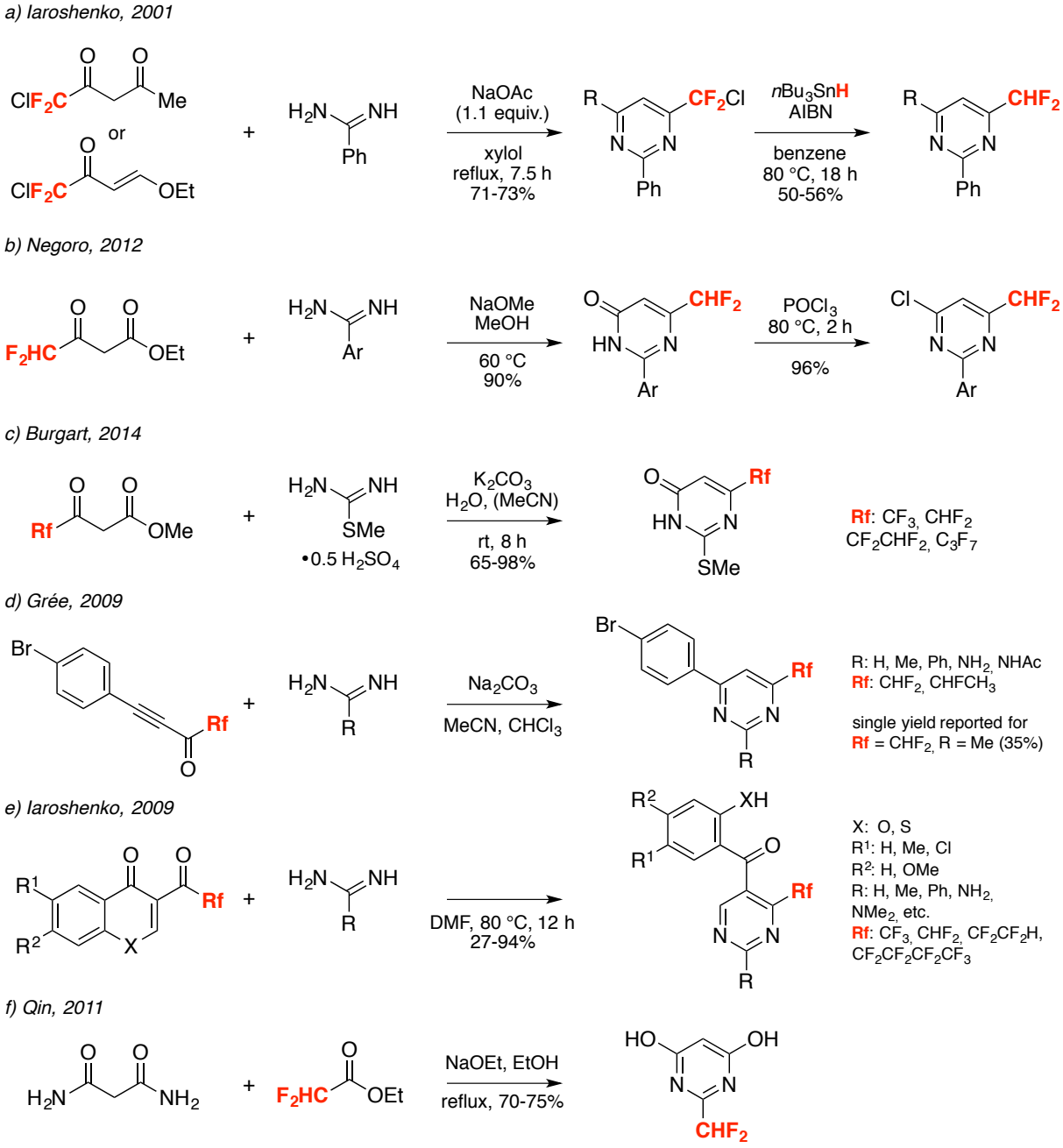


Figure III.4: Reported syntheses of fluoroalkyl pyrimidines from fluorinated substrates

In 2012, Baran *et al.* reported the use of a toolkit of zinc sulphinate salts used as (fluoro)alkyl radical transfer reagents for various heterocycles. In this report, the direct and operationally simple C-H difluoromethylation of a single pyrimidine under mild conditions was included. This innovative transition-metal-free mode of radical generation provided excellent results using analogues of Baran's reagent. In addition with regioselectivity issues, the scope of this strategy is not known.[16]

Very recently (2016), a single example of 2-CHF_2-pyrimidine was included into a report describing the first copper-catalysed difluoromethylation of aryl iodides with zinc reagents.[17]

2. Pyrimidines bearing other EFSs

CHFCl

In 1979 was reported a single example of benzo-fused pyrimidines bearing a CHFCl group, prepared with non activated Yarovenko reagent **1B.**[18] Another example of selective Cl/F exchange was reported in 1982 for the preparation of CHFCl-pyrimidine, without any given yield.[19] An example of 2-(CHFCl)-pyrimidine-4,7-dione was reported similarly to the example of its CHF_2 analogue, probably using malonamide and ethyl chlorofluoroacetate (little experimental details are provided).[15]

CF_2Cl

In 1997 was reported by Hu *et al*. the use of 1-fluoroalkyl-2-iodoalkenes (as 1,3-dielectrophile) and amidines in the preparation of fluoroalkyl heterocycles. In this report were included four examples of CF_2Cl-pyrimidines, but the access to the substrate being difficult, and the scope being limited, this strategy cannot be further exploited.[20] The same year, one example of CF_2Cl-pyrimidine was included in a report describing the one-pot reaction between α-fluoroalkyl carbonyl compounds, orthoesters and ammonium carbonates. The scope of substituents offered by this method is small even though several fluoroalkyl groups can be introduced, and the access to the corresponding carbonyl compounds can be tedious.[21]
Several CF_2Cl-pyrimidines (with pyrazoles and heteroannulated pyridines) were reported in Iaroshenko's report[9] using CF_2Cl-1,3-diketones or enones, usually difficult to prepare. This method has not been further explored.

CF_2Br

Two examples of CF_2Br-pyrimidines were included in the article describing the condensation of α-fluoroalkyl carbonyl compounds, orthoesters and ammonium carbonates in 1997.[21] No other examples can be found in literature reports.

$CHFCF_3$

No pyrimidine bearing the $CHFCF_3$ group was reported in the literature; a single quinazolinone was reported in 1977, resulting from the condensation of perfluoropropene and 2-aminobenzamide, and isolated as a mixture.[22]

The general observation is that there are available strategies to prepare pyrimidines containing a single fluoroalkyl group, but they are not always reliable, and the introduction of other EFS remains a big challenge in the context of pyrimidines.

3. Bis(fluoroalkyl) Pyrimidines

The preparation of mono-fluoroalkyl substituted pyrimidine is a challenge, but not as much as the preparation of bis(fluoroalkyl) pyrimidines. The examples reported in the literature for the synthesis of pyrimidines bearing two EFSs are extremely rare. Baran *et al*. reported in their recent report very few bis-fluoroalkylated diazines containing two difluoromethyl groups, but no pyrimidine was prepared (only a purine analogue).[23]

We can conclude that there is a real need for new methods for the efficient preparation of pyrimidines bearing EFSs, with potential industrial applications, high atom efficiency and easy procedure. This will be further discussed in the next part with the use of FARs (similarly to the previous chapter) but employing other types of substrates.

B. Development of a new method to access innovative 4,6-bis(fluoroalkyl)-5-pyrimidine carboxylates and carboxylic acids

After the successful synthesis of 5-membered-*N*-based heterocycles, with many examples of mono- and bis-fluoroalkyl pyrazoles (and isoxazoles), we investigated the preparation of similar compounds in the context of pyrimidine synthesis.
Inspired by a previous report from our group, the focus was placed on the preparation of key fluorinated building blocks starting from fluorinated acetoacetates. Ethyl 4,4,4-trifluoroacetoacetate **III.1a** was provided in large quantity from Bayer CropScience in the course of the PhD project of F. Giornal, and was used for this purpose. The starting point was the known formation of the key intermediate **II.7** in the preparation of 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates **II.8-11** (Scheme II.7).

Bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2** were efficiently formed *in situ* in presence of excess of pyridine and cyclized with hydrazines to access bis(fluoroalkyl)-4-pyrazole carboxylates **II.8-11**. These valuable building blocks **III.2** are potential 1,3-dielectrophiles, which could react with other dinucleophiles than hydrazines or hydroxylamines; the use of amidines could provide the desired pyrimidine after a modified Pinner-type pyrimidine synthesis (bottom, Figure III.5).

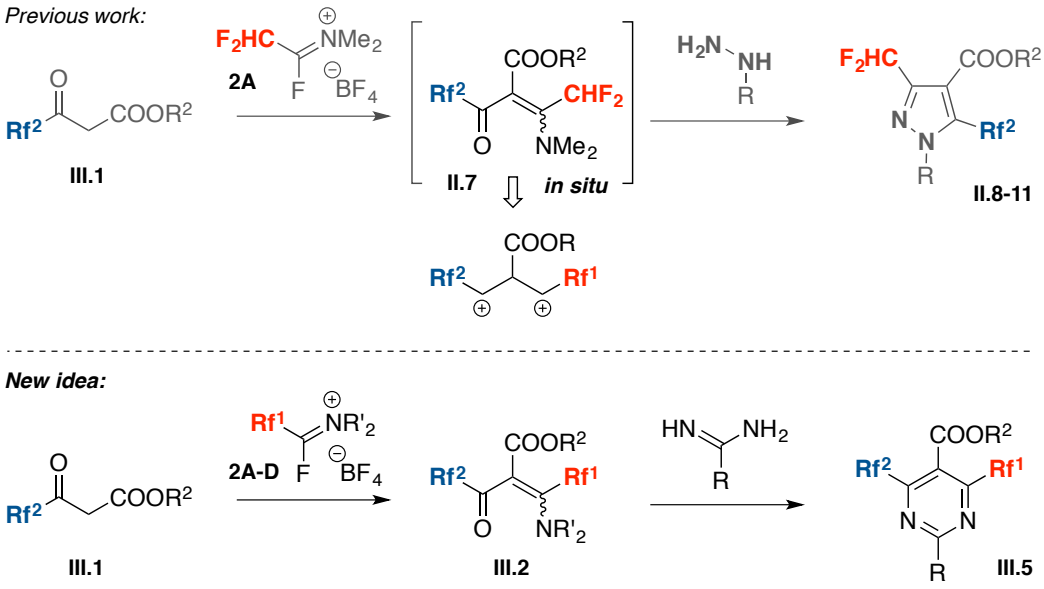


Figure III.5: Initial strategy for the preparation of 4,6-bis(fluoroalkyl)-5-pyrimidine carboxylates

In the previous PhD project (F. Giornal), the corresponding pyrazole carboxylates **II.8-11** were formed after a one-pot sequence: in the first step, fluoro iminium salt **2A** and fluorinated acetoacetates **III.1** are reacted overnight in presence of an excess of pyridine to generate the intermediate **II.7**. The second step is a cyclization towards the pyrazole carboxylates after addition of hydrazines and overnight stirring.

This strategy was time and energy consuming, in addition with the use of many consumables for each reaction. The objective was to isolate the intermediates **III.2** in order to prepare the corresponding products in a divergent way.
For this purpose, a new strategy was targeted, but several attempts to isolate these intermediates **III.2** have failed using standard procedures (aqueous work-up, silica gel chromatography, etc.). Due to the high sensitivity of intermediates **III.2**, the use of inert work up conditions was required, and the presence or use of nucleophilic solvents was prohibited.

In the previous PhD project, many reactions were performed to determine the optimum conditions for the preparation of bis(fluoroalkyl)-pyrazole-4-carboxylates (with **II.9b** as a model candidate). Varying parameters were modified (solvent, temperature, etc.). The best compromise was found to be -30 °C with potassium fluoride (KF) as a base in MeCN, the conversion observed for the intermediate **III.2** reached 75% *in situ*.

At this time, a (2:1) mixture of the intermediate **III.2A.d** with the side-product **III.4A.d** was characterized *in situ* using $^{1}H/^{19}F$ NMR analyses. This side-product resulted from the elimination of the fluoroacyl group (Figure III.6). The elimination of trifluoroacyl group from a reaction of condensation of CF_3-acetoacetate **III.1a** with aldehydes was previously reported in the literature.[24] The use of pyridine finally provided better results for the preparation of the model candidate **II.9b**. The addition of Lewis acids was also investigated without success.

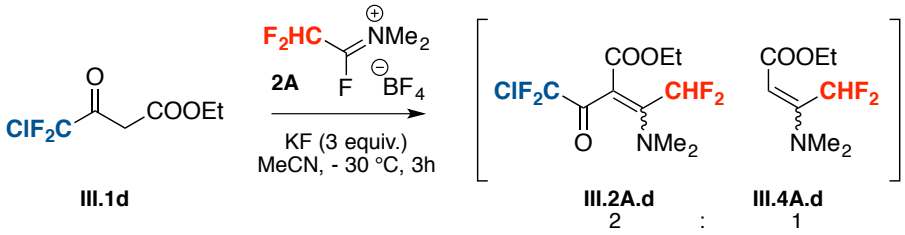


Figure III.6: Characterization of an *in situ* desired intermediate III.2

After the optimization of the reaction conditions for the *in situ* formation of the desired pyrazoles, the scope was extended with *in situ* prepared intermediates **III.2**. No further analysis was attempted, as the priority was the preparation of the innovative and unprecedented pyrazoles **II.8-11**.

After the completion of this PhD project, a post-doctoral fellow (G. Landelle) completed this work by preparing isoxazole carboxylates **II.19** and carboxylic acid **II.20** analogues (bottom, Scheme II.7), using the same strategy with the replacement of hydrazines by hydroxylamine. These results were an important breakthrough in the preparation of fluorinated pyrazoles and isoxazoles.
The preparation of bis(fluoroalkyl)pyrimidine carboxylates was attempted following the same strategy. However, reactions were attempted in protic solvents in presence of water and sometimes of inorganic bases

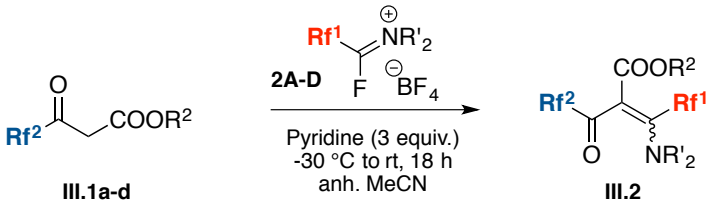
In the following part, the recent results concerning the preparation of bis(fluoroalkyl)pyrimidine carboxylates will be described. Further unexpected developments will be included afterwards.

1. Preparation of key bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters

In order to isolate bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2**, the use of aqueous work-up was prohibited as they can be easily hydrolysed. The high yields observed for some examples of bis(fluoroalkyl)pyrazole carboxylates **II.8-11** demonstrated the efficacy of the developed reaction conditions. The objective was to develop a suitable procedure to remove the side-products (fluorinated boron salts, pyridinium salts, excess pyridine) from the mixture without degrading the desired intermediate **III.2**. After several unsuccessful attempts using silica-gel chromatography, filtrations were investigated.

The evaporation of MeCN followed by an addition of DCM allowed the precipitation of the salts formed during the reaction. A filtration through Celite® was efficient in the removal of these salts. The remaining pyridine was eliminated by means of azeotropic distillation with toluene. The residual insoluble salts were filtered a second time through Celite®, and a second azeotropic distillation was achieved (< 20 mbar, 55-60 °C). This procedure was highly efficient and provided the first example of bis(fluoroalkyl)-α-aminoalkylidene-β-ketoester **III.2A.a**. This demonstrated the robustness of intermediates **III.2** during this non-aqueous work up

Table III.1: Preparation of key bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters III.2



Rf^1 = CHF_2 (**A**), CHFCl (**B**), $CHFCF_3$ (**C**), $CHFOCF_3$ (**D**)
Rf^2 = CF_3 (**a**), CHF_2 (**b**), C_2F_5 (**c**), CF_2Cl (**d**)

Entry	R^2	R'	Rf^1	Rf^2	Cpd.	Yield	Purity (wt.%)
1	Et	Me	CHF_2	CF_3	**III.2A.a**	92%	95%
2	-	-	-	CHF_2	**III.2A.b**	72%	60%[a]
3	-	-	-	C_2F_5	**III.2A.c**	89%	95%
4	*t*Bu	-	-	CF_2Cl	**III.2A.d**	99%	93%
5	Et	-	$CHFOCF_3$	CF_3	**III.2D.a**	80%	95%
6	-	Et	CHFCl	CF_3	**III.2B.a**	93%	75%
7	-	Et	$CHFCF_3$	CF_3	**III.3C.a**[b]	*Cyclobutene rearrangement*	

a: used as such without characterization. b: spontaneous rearrangement (discussed later in the manuscript).

Other fluorinated acetoacetates and FARs were used to extend the scope of this reaction. Fluorinated acetoacetates **III.1a-d** were available in stock, but can be prepared from Claisen condensation using literature conditions.[25-27] The acetoacetate **III.1a** was reacted with activated FARs **2A-D** to provide the bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2A.a-d** (entries 1 and 5-7, Table III.1), while the acetoacetates **III.1b-d** were reacted with **2A** only, as they were available in lower quantities.

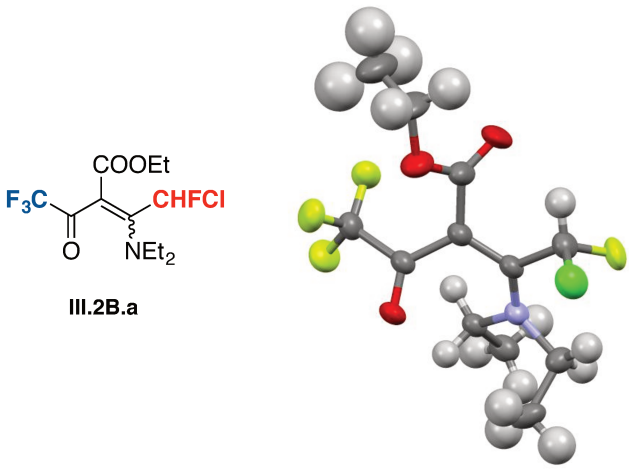


Figure III.7: Crystallographic analysis of a single crystal of compound III.2B.a

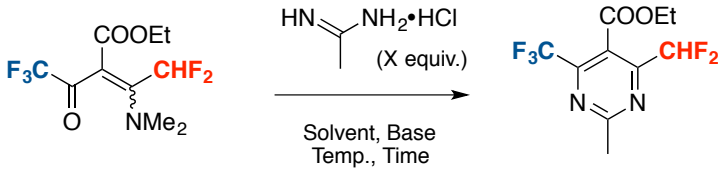
All desired bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters intermediates **III.2** prepared from activated FARs **2A** and **2D** (*N*,*N*-dimethyl iminiums) were isolated with high yields (80-99%) and purities (93-95wt.%) (entries 1, 3-5, Table III.1). One exception is the CHF_2 example (entry 2), which possesses an acidic hydrogen in α-position of the carbonyl involved in the condensation. This may generate side-reactions in disfavour of the desired product formation. The compound **III.2A.b** was used as such (with a low purity in comparison with other examples) for the next step. The activated Yarovenko reagent **2B** was also efficient in this reaction (entries 6, Table III.1) and the compound **III.2B.a** provided a single crystal suitable for X-ray diffraction analysis, confirming the structure and showing a *E*-configuration (Figure III.7). One example (**III.3C.a**, entry 7) did not provide the desired intermediate, but an unexpected rearrangement occurred and will be discussed later in the chapter. Bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2** are shelf-stable under inert atmosphere (preferably stored at -4 °C) and can be prepared in large amount (up to 25 g). These valuable building blocks have been further exploited to prepared pyrimidine products, and the results are discussed in the next part.

2. Synthesis of 4,6-bis(fluoroalkyl)-5-pyrimidine carboxylates

Once bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2** were available, a screening of the optimum reaction conditions was achieved for the preparation of the model pyrimidine **III.5A.a** using the most high yielding intermediate **III.2A.a** with acetamidine hydrochloride.

A protic solvent was initially chosen (EtOH), as proton transfers are probably involved in the ring formation step. After a first attempt using standard thermal conditions with sodium methoxide as a base (entry 1 microwave irradiation showed great influence in the desired transformation (entry 2, Table III.2). Changing the ratio of amidine/base showed no positive influence, and the best ratio was 2 equivalents of amidine hydrochloride for 3 equivalents of triethylamine. The further addition of reagents or a longer reaction time did not improve the conversion (entries 2 and 5, Table III.2). Additives such as molecular sieves or cationic resin had little or negative effect on the reaction (entries 6-7, Table III.2). Several organic bases were tested, and unlike pyridine, which fully inhibited the reaction (entry 8, Table III.2) Hünig's base and even more triethylamine improved dramatically the result. Other protic solvents were tested and afforded rather good results; MeCN was also very efficient as the reaction reached 91% of desired conversion (entries 9-16, Table III.2). Both EtOH and MeCN were suitable for this synthesis.

Table III.2: Optimization of the reaction conditions for the preparation of 4,6-bis(fluoroalkyl)-5-pyrimidine carboxylate III.5A.a

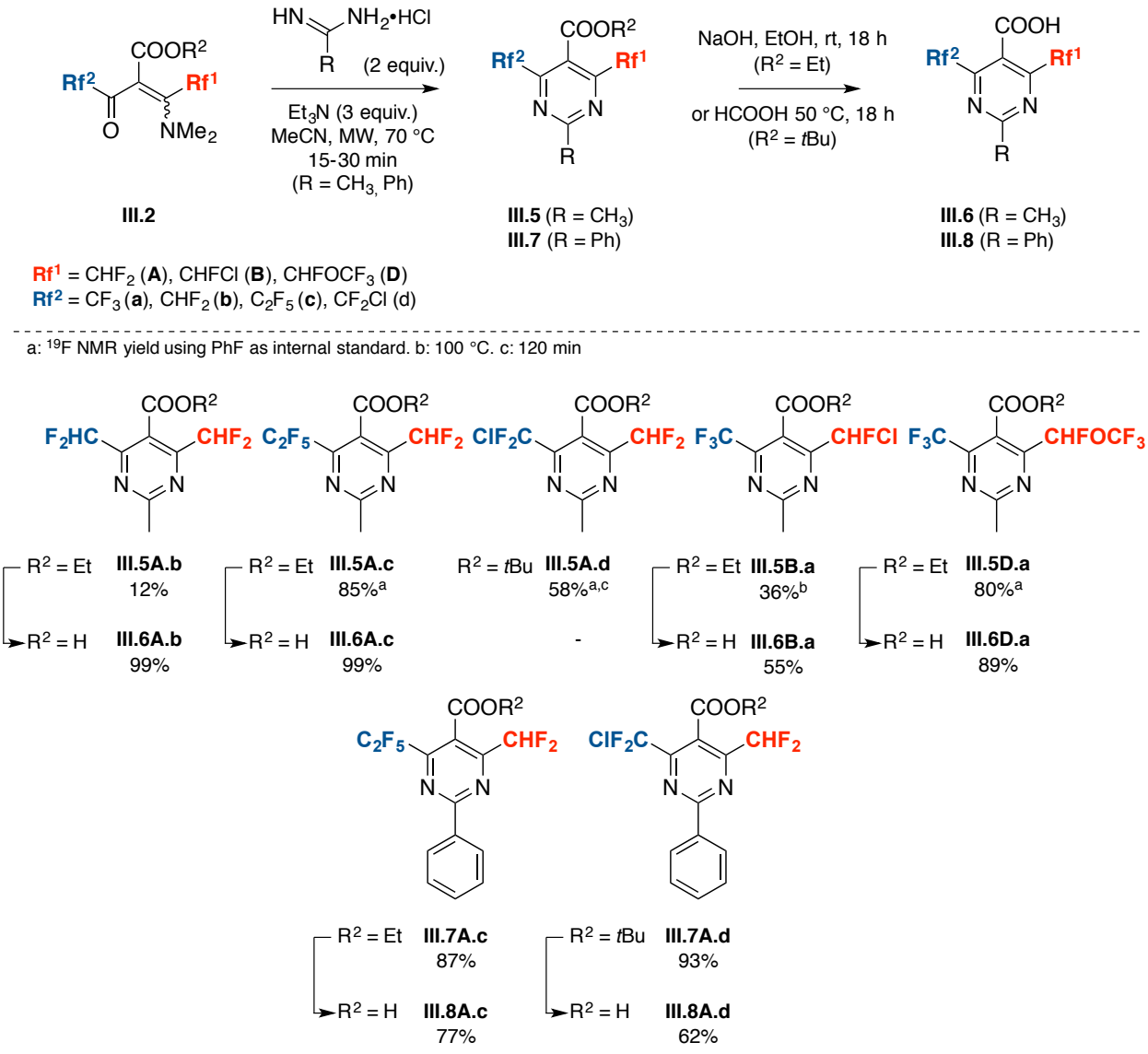


III.2A.a **III.5A.a**

Entry	Solvent	X (equiv.)	Base, equiv.	Temp. (°C)	MW	Time	Yield
1	EtOH	1.5	NaOMe, 3	80	x	18h	33%
2	-	2	3	70	√	30min	57%
3	-	1 + (1)	1.5 + (1.5)[b]	80	√	30 + 30 + (60)min	44%[a]
4	-	4	6	-	√	15min	40%[a]
5	-	2	3	-	√	60min	51%[a]
6	-	1.5	-	-	√	75min[c]	50%[a]
7	-	-	-	-	√	15min[d]	0%[a]
8	-	2	Pyridine, 3	70	√	30min	0%[a]
9	-	4	DIPEA, 6	-	√	30min	60%[a]
10	-	2.5	3	-	√	-	64%[a]
11	-	1.2	1.5	-	√	-	55%[a]
12	-	2 + (2)	3 + (3)	-	√	30 + (30)min	75%[a]
13	EtOH	2	Et_3N, 3	70	√	30min	86%[a]
14	*t*BuOH	-	-	-	√	-	58%[a]
15	*i*PrOH	-	-	-	√	-	87%[a]
16	MeCN	2	Et_3N, 3	70	√	-	91%[a]

a: ^{19}F NMR yield using PhF as internal standard. b: further additions of amidine and base after 60min. c: Excess of molecular sieves 4Å as additive. d: Amberlyst H15 resin as additive. Values in brackets: further additions or reagents and following microwave irradiation.

After having optimized conditions in hand, all bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2** were reacted with acetamidine hydrochloride and/or benzamidine using the optimized reaction conditions previously developed. The first series of bis(fluoroalkyl)pyrimidine carboxylates **III.5** and **III.7** was synthesized with variable results. The symmetrical bis-CHF_2 pyrimidine **III.5A.b** afforded a poor yield, certainly due to the very low quality of the intermediate **III.2A.b**. The example resulting from the Yarovenko reagent also showed lower yield (36% for **III.5B.a** after heating at 100 °C), due to the lower purity of the intermediate **III.2B.a** (even after providing single crystals) and its lower reactivity as a *N*,*N*-diethyl analogue. Other examples from the methyl series provided good to very good yields, especially the example resulting from the new FAR **2D** (80%), consistent with the purity of intermediate **III.2D.a** (Table III.1). Finally, 2-phenyl pyrimidines **III.7A** were prepared in excellent yields (Scheme III.1). Generally, the purification step only required to adsorb the reaction mixture into a silica cake and to directly load it onto a preconditioned silica column using a Biotage® automated system, rendering this step very efficient and straightforward.

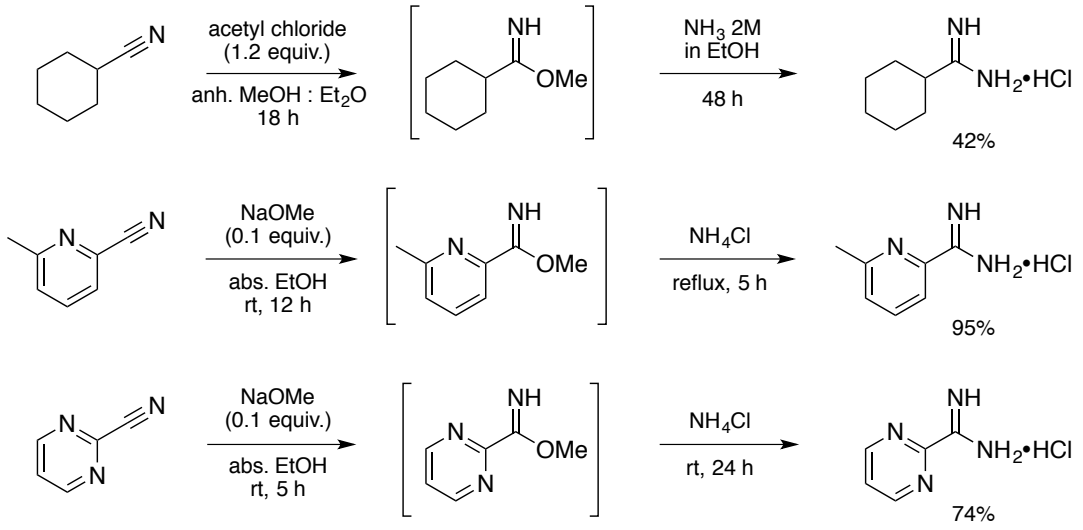


Scheme III.1: Preparation of various (bis)fluoroalkyl pyrimidine carboxylates and carboxylic acids

The saponification of the difficult-to-prepare bis-CHF_2 pyrimidine carboxylate **III.5A.b** was quantitative to give the corresponding carboxylic acid **III.6A.b**. Similarly, the 2-methyl pyrimidine carboxylates **III.5A.c**, **III.5B.a**, **III.5D.a** and 2-phenyl analogue **III.7A.c** were saponified under basic conditions with yields from 55 to 99%. The pyrimidine **III.7A.d** was efficiently saponified after reflux in formic acid overnight. All corresponding carboxylic acids were isolated after acidification using aqueous hydrochloric acid solution and extraction with DCM.

The product **III.6A.c** provided a single crystal, which allowed the confirmation of structure of these pyrimidine carboxylic acids (left, Figure III.8). The scope of this reaction has been further explored, and many other amidines were considered, in order to introduce other groups instead of methyl or phenyl groups in position 2.

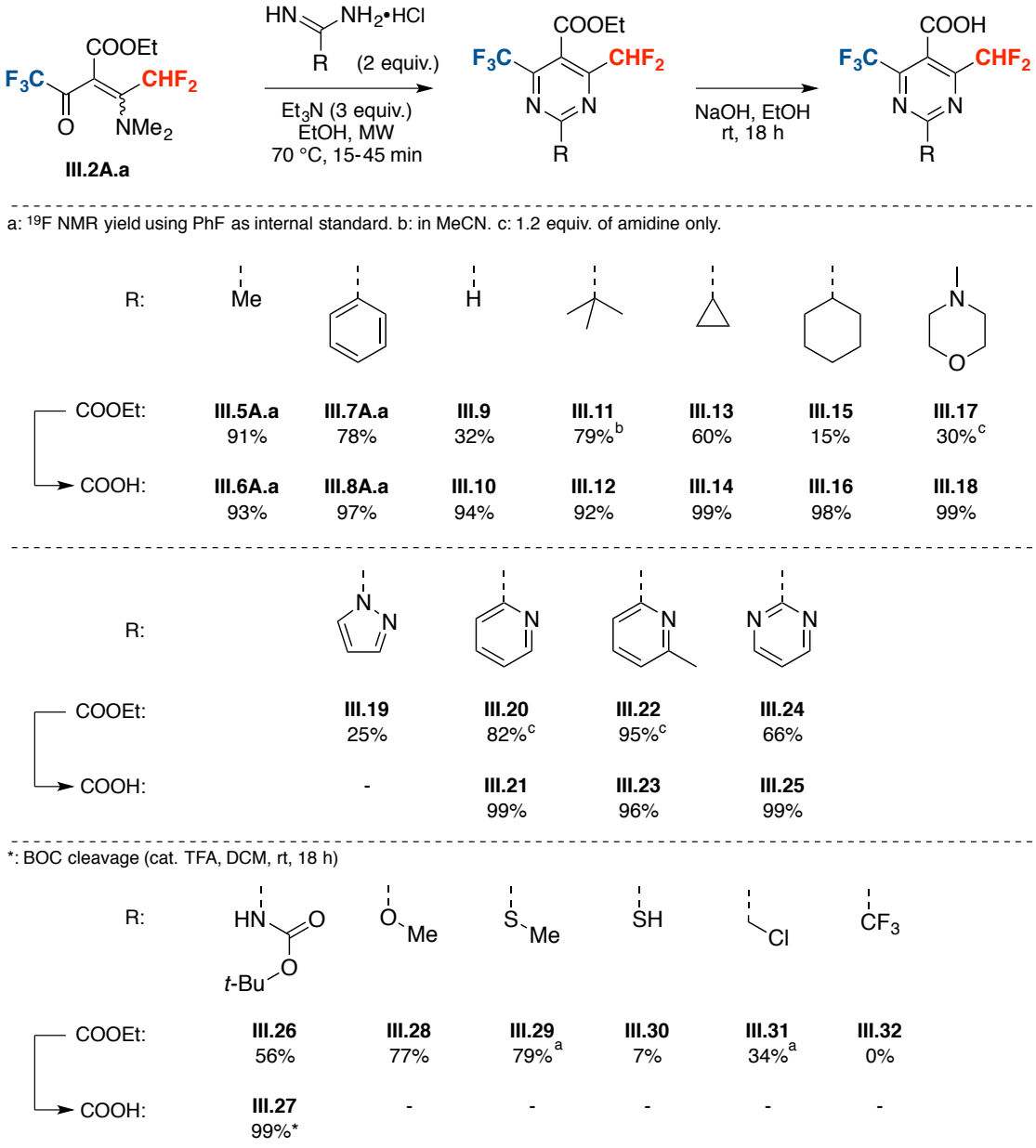
Many amidines or related carbonitriles were commercially available, such as acetamidine hydrochloride, benzamidine, formamidine hydrochloride, *tert*-butyl carbamidine hydrochloride, cyclopropane-1-carboximidamide hydrochloride, 4-morpholinecarboximidamide hydroiodide (1:1), pyridine-2-carboximidamide hydrochloride, pyrazole-1-carboxamidine hydrochloride, BOC-guanidine, guanidine hydrochloride, *O*-methylisourea hydrochloride, 2-methyl-2-thiopseudourea sulphate, urea, thiourea, 2-chloroethanimidamide hydrochloride and trifluoroethanimidamide.
The cyclohexyl-, 2-pyridinyl and 2-pyrimidinyl amidines have been prepared from their carbonitrile analogues. For the cyclohexyl amidine preparation, a Pinner reaction was achieved using acetyl chloride in MeOH with further addition of ethanolic solution of ammonia to convert the corresponding imidate into the desired amidine salt. A poor yield was obtained with an ethanolic solution of ammonia, and the purity of this amidinium salt was low; the use of gaseous ammonia in the second step is preferable and could increase the yield.[28] For the 6-methylpyridinyl or 2-pyrimidinyl amidines, very efficient conditions were reproduced providing high yields and purities.[29]



Scheme III.2: Preparation of three non-commercially available amidine hydrochlorides

With efficient reaction conditions in hand and large variety of amidines, various 4,6-bis(fluoroalkyl)-5-pyrimidine carboxylates were prepared (Scheme III.3). Their purification was easy to achieve using flash chromatography. The formation of both model product **III.5A.a** and its phenyl analogue **III.7A.a** provided very good yields, whereas the use of highly hygroscopic formamidine hydrochloride led to a low result for **III.9**, probably due to the prior degradation of the substrate before the reaction could occur. The use of formamidine acetate salt did not improve the result (24%). 2-(*t*Bu)- and 2-(cyclopropyl)-pyrimidine carboxylates **III.11** and **III.13** were efficiently prepared, but much less in the case of 2-cyclohexyl- and 2-*N*-morpholinyl analogues **III.15** and **III.17**. This can be explained by the low purity of the self-prepared cyclohexanecarboximidamide hydrochloride or the deleterious effect of the iodide counter anion from 4-morpholinecarboximidamide hydroiodide (1:1).

This first series of products was very efficiently saponified to give access to the corresponding carboxylic acids **III.10**, **.12**, **.14**, **.16**, and **.18** with nearly quantitative yields. The introduction of heteroaromatic substituents was globally very efficient (except for the pyrazole example), with excellent isolated yields for esters **III.20, .22** and **.24** and carboxylic acids **III.21**, **.23** and **.25**. In the case of the pyrazole **III.19**, the presence of a weak bond in alpha of the second nitrogen can explain the poor result. The introduction of a methyl group can possibly avoid the degradation of the formed product. The saponification attempted from this product led to complete degradation (Scheme III.3).



Scheme III.3: Extension of the scope for diversity of substituents in position 2

The introduction of heteroatoms and related functional groups directly in position 2 of the pyrimidine carboxylates was attempted. Interestingly, the synthesis of the 2-amino product using guanidine hydrochloride yielded no product at all (further commented in the next part), whereas the use of or BOC-guanidine in EtOH yielded the desired BOC-protected product **III.26** in 56% yield. The protection of potential trinucleophiles (like guanidine) seems favourable to have a more controlled cyclization.

The saponification of **III.26** under basic conditions afforded a highly hygroscopic product (rapidly turning into a gum). However, the deprotection of the BOC group led to the 2-amino pyrimidine carboxylate **III.27** with 99% yield. The 2-amino pyrimidine motif is of great importance in bioactive molecules research, *e.g.* in anti-malarial drug research,[30, 31] or cancer research.[32]
Methoxy- and thiomethoxy-pyrimidine carboxylates **III.28-29** could not be saponified due to the presence of reactive substituents, which can act as leaving groups in nucleophilic aromatic substitution reactions. Degradation was consequently observed mostly. Pyrimidines **III.30-31** were difficult to prepare (discussed in Scheme III.6), and the last example **III.32** was not formed at all. An optimisation of the synthesis of these specific examples has to be performed.

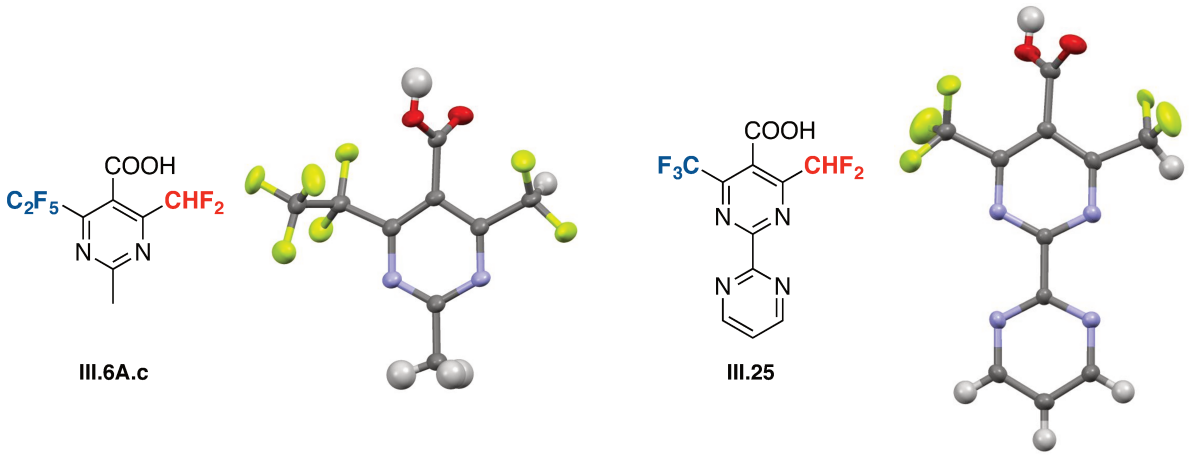
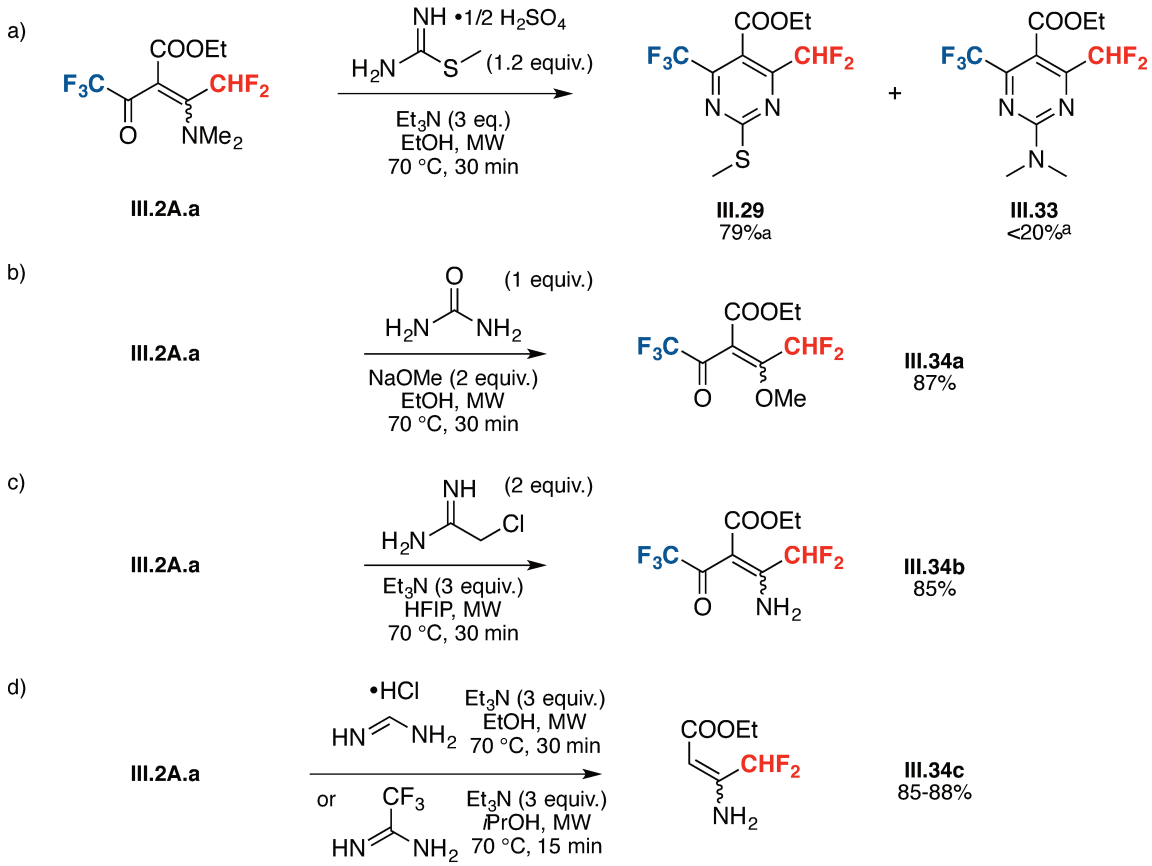


Figure III.8: Crystallographic analysis of a single crystal of compounds III.6A.c (left) and III.25 (right)

Once the desired diversity was accessed using very efficient and straightforward processes, an interest was placed on the various side-reactions. The *N*,*N*-dimethylamino pyrimidine was observed during one attempt to prepare 2-SMe-pyrimidine **III.29**; the *N*,*N*-dimethylamino analogue **III.33** was formed. This probably occurred after formation of the desired product and substitution of the thiomethyl group by dimethylamine released from the starting material **III.2A.a** (a, Scheme III.4).

During an attempt to prepare a 2-hydroxy pyrimidine carboxylate (or the pyrimidone analogue), urea was reacted using the optimized conditions, and sodium methoxide was used instead of triethylamine. The corresponding methoxy-substituted product **III.34a** was isolated in 87% yield as colourless oil (b, Scheme III.4). In another attempt to optimize the result for the preparation of the 2-chloromethyl pyrimidine **III.9n**, HFIP was tested as an alternative solvent for specific cases. Interestingly, the compound **III.11b** was isolated in 85% yield as a stable colourless solid (c, Scheme III.4). After the preparation of a suitable single crystal, its structure was confirmed by crystallographic analysis. In this analysis, the ester group can be seen not included in the plan of the vinamide due to H-bonding between carbonyl oxygen and the amino group (Figure III.9).

In several examples, another structure was often observed as a side-product of the pyrimidine synthesis. When protic solvents (EtOH, *i*PrOH, etc.) were used in poorly efficient cyclizations, the deacylated product **III.34c** was isolated as colourless oil (two selected examples: d, Scheme III.4). All side-products **III.34** led us to propose a potential mechanism for the pyrimidine formation (Figure III.10).



Scheme III.4: Notable side-products isolated in specific cases during the scope extension stage

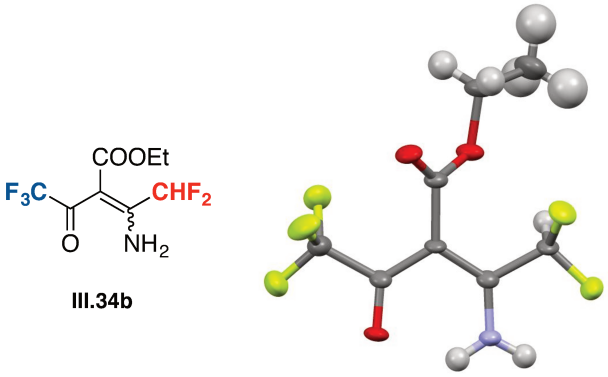


Figure III.9: Crystallographic analysis of a single crystal of compound III.34b

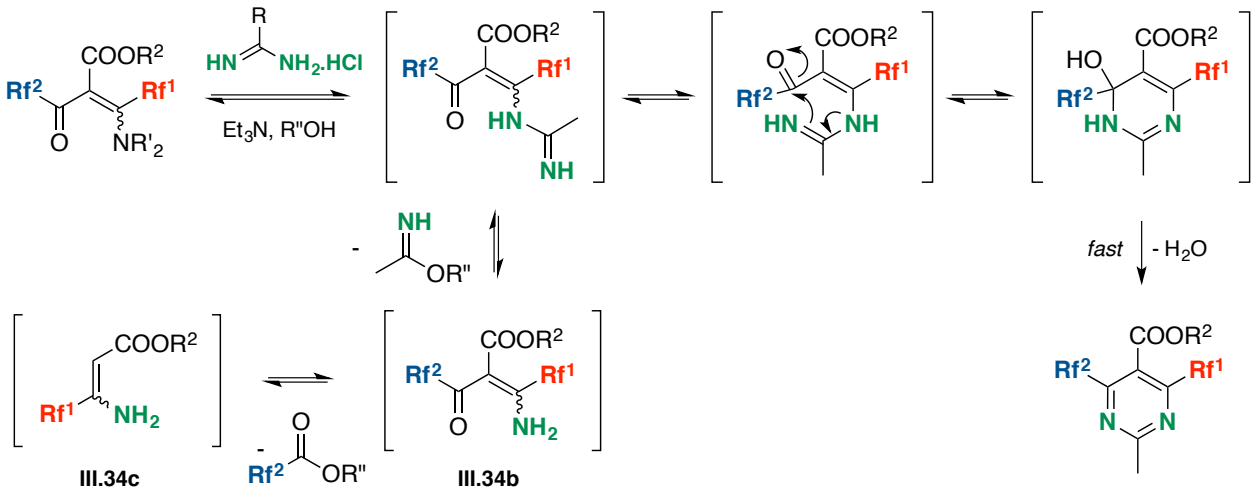
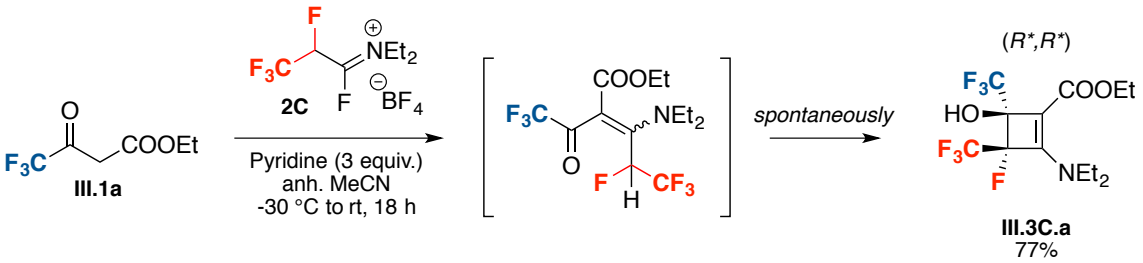


Figure III.10: Proposed pathway for the formation of the pyrimidine core

Under basic conditions, the amidine attacks the most electrophilic position, which is as previously discussed the fluoro iminium group present in solution. After a Michael-type addition, a β-(imidamido)-enone intermediate is formed. At this stage, if the cyclization is favoured, the desired pyrimidine product is rapidly formed after aromatization. If the cyclization is not sufficiently favoured, a polar protic solvent (*e.g.* HFIP) can achieve a nucleophilic attack on the imidamide moiety to release an intermediate **III.34b** (Figure III.10). Under certain conditions (with more nucleophilic protic polar solvents, *e.g.* EtOH, *i*PrOH), a further deacylation can be observed, similarly to observations made by F. Giornal in her early studies concerning the synthesis of bis(fluoroalkyl) pyrazole carboxylates (Figure III.6). The side-product **III.34c** was isolated with high yield in certain cases (d, Scheme III.4). All these observations are interesting to access other valuable building blocks, which could lead to more discoveries. But another side-reaction caught our attention at this stage, as discussed in Table III.1, entry 7. The outcome of this unexpected rearrangement will be discussed in the coming part.

3. Cyclobutene rearrangement

An unexpected outcome was observed during the preparation of key intermediates **III.2A-D** (Table III.1). For the last example, the Ishikawa reagent was reacted with ethyl CF_3-acetoacetate, but the characterization of the resulting product could not be completed; the NMR analyses were not consistent with the expected structure. A large sample was prepared and after filtration and azeotropic distillation procedures an orange oil was isolated. After more than one week of storage at room temperature, a large crystal appeared in the flask. The next crystallographic analysis proved a different outcome (Scheme III.5). In fact, the rearrangement product **III.3C.a** was formed, with a central cyclobutene ring substituted with an ester group and a tertiary amino group in positions 1 and 2 respectively, and 4 more substituents in the remaining positions (one hydroxyl group, one fluorine and two trifluoromethyl groups with a specific anti configuration). Only *R*,*R* or *S*,*S* isomers were included in the crystal structure.
This stereoselective rearrangement can occur *via* various types of mechanisms, including an electrocyclization. To verify the influence of light in this rearrangement, the reaction has been achieved protected from light during all steps of the reactions. The NMR spectrum was exactly the same after isolation of the product. We suppose, that this rearrangement could be thermally driven, involving a possible conrotatory 4Π electrocyclization step, which is symmetrically allowed according to the Woodward-Hoffmann rules of electrocyclization (Figure III.11).



Scheme III.5: Serendipitous discovery of the cyclobutene product III.3C.a

In the presence of an excess of base, the *in situ* formed bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters **III.2C.a** can be readily deprotonated at its most acidic position, forming a fluorinated diene. This diene can be present as different configurational isomers and all possible electrocyclization pathways were considered.

Two configurations provide the wrong cyclobutene products after electrocyclization, and are discarded. For the remaining cases, two very different dienes are observed, one being sterically more favourable with opposite CF_3 groups, the second sterically disfavoured due to neighbouring CF_3 groups. It is difficult to determine which diene could be involved in the process between a more stable (and less reactive?) diene and a less stable (and more reactive) diene (Figure III.11).

Other mechanisms can be considered. In presence of an excess of base, the activated Ishikawa reagent **2C** could be converted into a ketene iminium salt, and a [2+2] cycloaddition could form the observed cyclobutene. Radical or anionic processes are less probably occurring as the stereoselectivity observed would be difficult to rationalize.

To observe the possible influence of ethyl chains in the stereochemistry observed in the final cyclobutene **III.3C.a**, a *N*,*N*-dimethyl analogue of **2C** was prepared using an already described process and reacted similarly with ethyl CF_3-acetoacetate **III.1a**. The resulting cyclobutene was formed in 68% and provided a single crystal, even though its full characterization could not be completed due to low purity.
The crystallographic analysis proved a similar configuration of the CF_3 groups. Consequently, the *N*-alkyl chains do not influence the stereochemistry observed in the final cyclobutenes, but it does influence the conformation of the ester group; an opposed orientation of the carbonyl function can be observed between the *N*,*N*-diethyl and *N*,*N*-dimethyl analogues (Figure III.12). More theoretical work has to be achieved to elucidate the reaction mechanism of this cyclobutene rearrangement

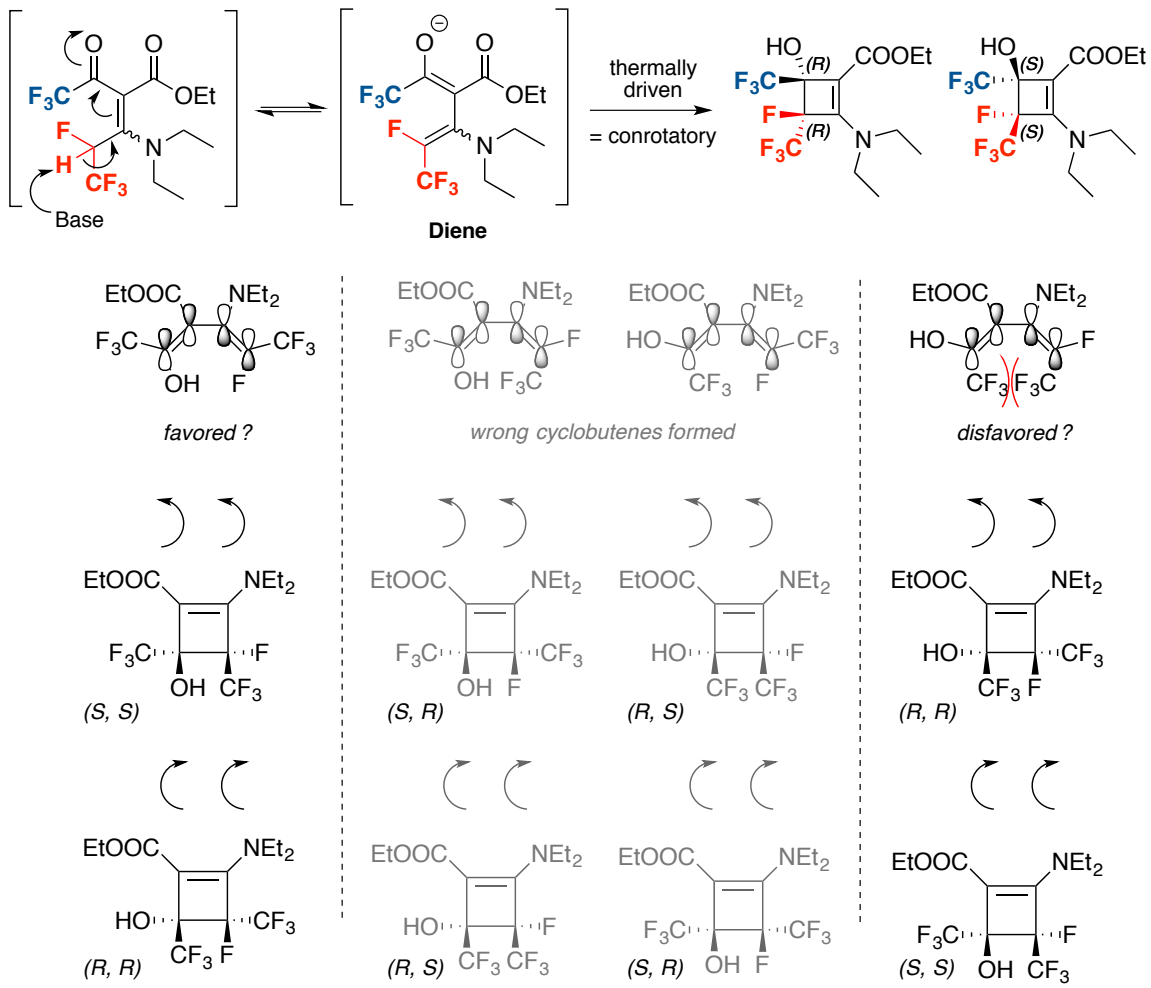
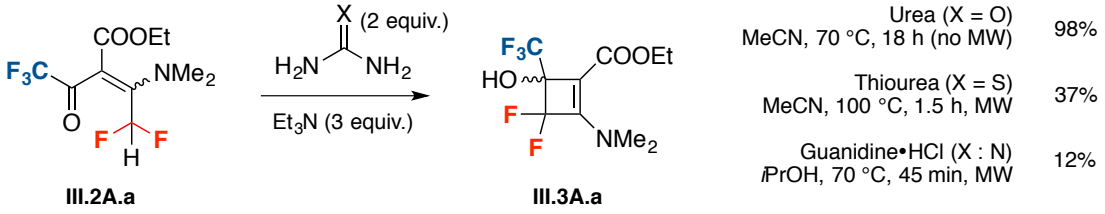


Figure III.11: Possible thermally driven conrotatory 4Π electrocyclization mechanism

More interestingly, the use of urea and analogues (thiourea, guanidine hydrochloride) was attempted in the conditions optimized for the synthesis of the corresponding pyrimidines bearing OH, SH or NH_2 groups in position 2 (as previously mentioned). However, the use of these bis-amino reagents led to the product **III.3A.a** with varying efficiency. The absence of microwave irradiation seems to favour the formation of the corresponding cyclobutene (98%), similarly to the use of non-protic solvent (MeCN). These results could demonstrate the hypothetical assistance of urea-type reagents in this rearrangement, in the case of bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters not undergoing spontaneous rearrangement like **III.2A.a**.



Scheme III.6: Stable cyclobutene III.3A.a prepared from key intermediate III.2A.a in presence of urea-type additives

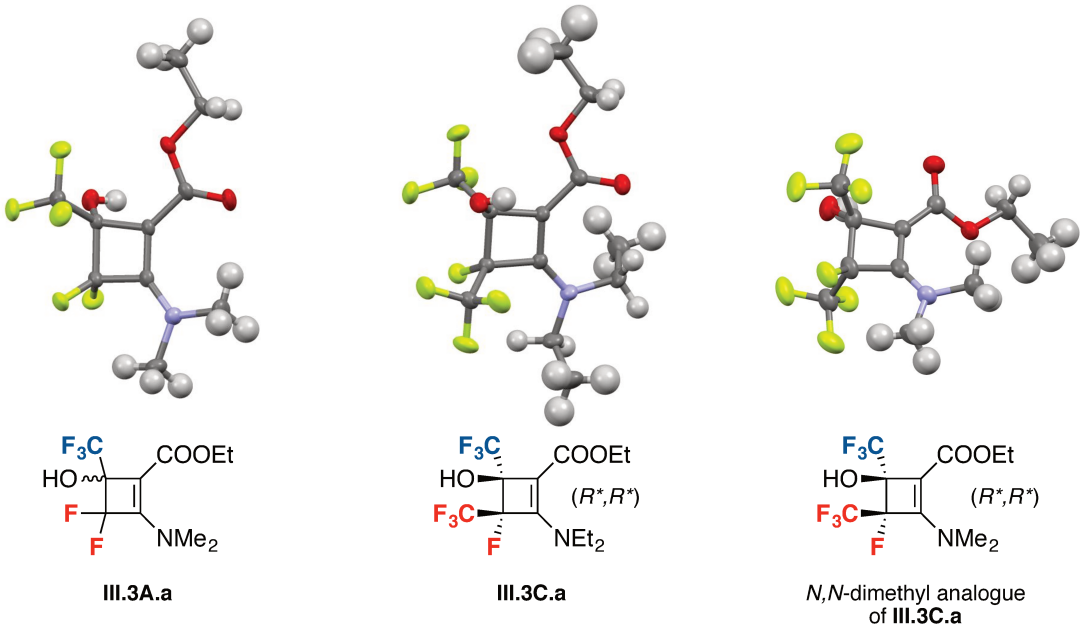


Figure III.12: Crystallographic analysis of a single crystal of compounds III.3A.a (left), III.3C.a (centre), and its *N,N*-dimethyl analogue (right)

The first example of cyclobutene isolated (**III.3C.a**) was rather sensitive and no purification by silica gel chromatography was even attempted. However, the other analogue prepared from TFEDMA (**III.3A.a**) was easily purified by flash chromatography with a quantitative yield, proving its robustness. This product is an ideal candidate for further studies (functionalization, transformations, etc.). Furthermore, a single crystal of this compound provided structural confirmation by means of crystallographic analysis (right, Figure III.12).

The NMR spectrum of the cyclobutene **III.3C.a** was very peculiar, and we decided to performed variable temperature NMR analysis (gradually from -50 °C to +58 °C) in order to attempt a calculation of the rotational barrier of each rotating functional groups (diethyl amino group and ester group). However, this calculation was very complex and was not performed. At low temperature, all CH_2 groups were differentiated, and each six protons from CH_2 groups (from diethylamino and ester groups) were non-equivalent. Between 35 °C and 55 °C, all signals from the CH_2 of the diethylamino group started to coalesce. This clearly indicates that below 25 °C the diethylamino group cannot rotate freely around the C-N bond attached to the cyclobutene. The signal for CH_2 of the ester group remains almost constant between -30 and +58 °C, showing that the ester group is less influenced by the variation of temperature (Figure III.13).

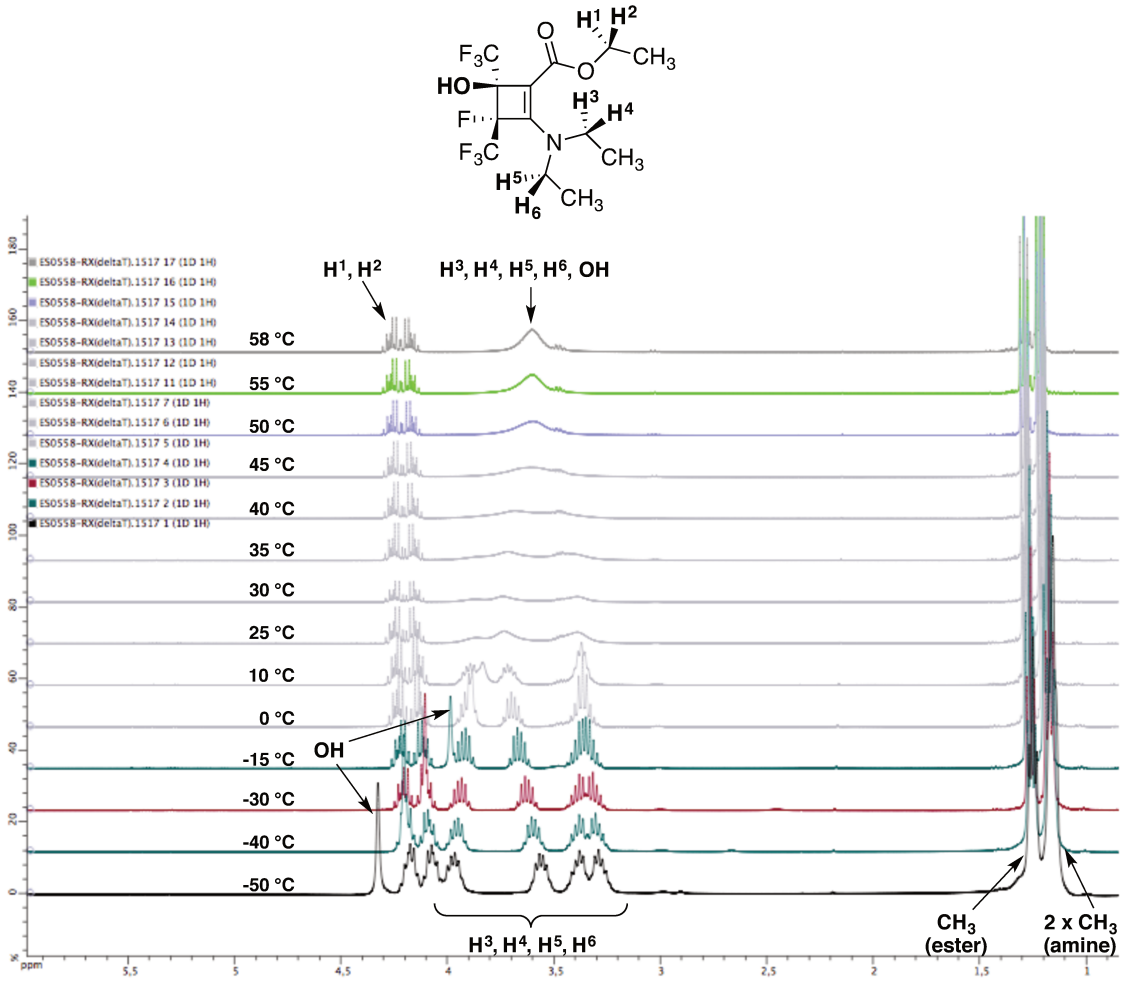


Figure III.13: Variable temperature NMR experiment of cyclobutene III.3C.a

This project allowed the preparation of a large series of unprecedented bis(fluoroalkyl)pyrimidine carboxylates and their corresponding carboxylic acids. These bis(fluoroalkyl) building blocks could be used in the discovery of new bioactive entities.

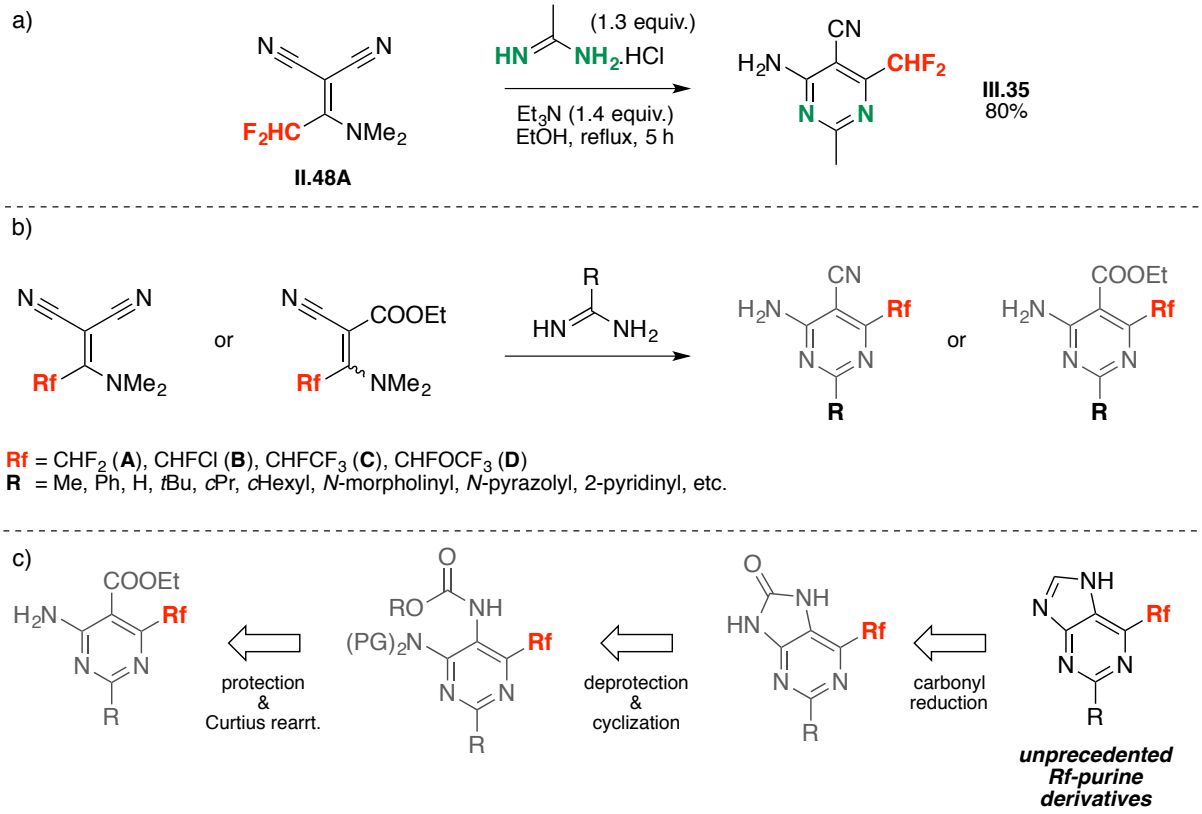
In the same project, an unexpected rearrangement was also observed during the preparation of bis(fluoroalkyl)-α-aminoalkylidene-β-ketoester **III.2C.a** (unstable); this highly reactive compound spontaneously rearranged to an unprecedented cyclobutene **III.3C.a**, whereas the product **III.2A.a** was quantitatively converted into the cyclobutene product **III.3A.a** (much easier to handle).

The experience from both projects is highly valuable, and other structures are potentially accessible using this type of chemistry. In the next part, the first attempts to access mono-fluoroalkyl pyrimidine building blocks will be discussed.

4. Opening the route to mono-fluoroalkyl pyrimidines

In the previous part, the use of activated FARs in combination with fluorinated substrates allowed the preparation of bis(fluoroalkyl) pyrimidines, and consequently the reaction of activated FARs with non-fluorinated substrates was thought to enable access to mono(fluoroalkyl) pyrimidine products.

As the use of CH-acidic substrates has previously allowed the access to mono(fluoroalkyl)-5-amino-4-pyrazole carbonitriles and carboxylates (Scheme II.13), this strategy was considered in the possible preparation of pyrimidine analogues. An initial reaction provided very promising results (a, Scheme III.7):



Scheme III.7: First access to 4-amino-6-(difluoromethyl)-2-methyl-5-pyrimidine carbonitrile III.12 (top); potential scope of application for this new synthesis (middle); possible access to very scarcely described purine derivatives bearing EFSs (bottom)

This building block opens the route to an extension of the scope, which will be achieved by a post-doctoral fellow (B. Commare) in due course. Several examples have already been prepared from TFEDMA, but more interestingly from the intermediate **II.59** prepared from the new FAR **2D** (b, Scheme III.7). Another interest of this building block **III.12** is the further transformation of the nitrogen-based functional groups in position 4 and 5. Considering the acylation/carbamylation of the 4-amino group, followed by a reduction of the carbonitrile group could provide very valuable intermediate, which could be further cyclized *via* nucleophilic attack of the primary amine on the activated carbonyl group. The resulting purinone could be efficiently reduced to purines (c, Scheme III.7).

C. Synthesis of Perfluoroalkylated Pyridines

In the context of the development of new *N*-based heterocycles, the chemistry of FARs has shown great potential and many examples have been prepared. So far, pyrazoles, isoxazoles and pyrimidines bearing one or two EFSs have been accessed, and these new innovative building blocks can be used in the research for new bioactive entities in agrochemical research, or in pharmaceutical research. Another class of *N*-based heterocycles is very broadly represented in life science oriented research. The pyridine core is commonly found in bioactive molecules, as previously shown in this manuscript.

Classical methods for the synthesis of pyridines are based on formal [5+1] cyclocondensations of 1,5-dicarbonyl compounds with ammonia or related nitrogen sources, on Diels–Alder reactions of dienophiles with azines, or on cyclocondensations of enamine derivatives with dielectrophiles.[33]

CF_3-pyridines are of special relevance in medicinal and agricultural chemistry. Several commercialized agrochemicals contain a pyridine core, and selected examples bear fluoroalkyl substituents, especially trifluoromethyl group (Diflufenicanil, Fionicamid, Haloxyfop, Figure I.8; Fluazinam, Figure I.9; Picoxystrobin, Figure I.10). In some examples, a new mode of action (MoA) was demonstrated, which is a real challenge in agrochemistry, in order to avoid resistance phenomenon by various strategies (Figure III.14). Even examples of bis-fluoroalkyl pyridines demonstrated efficiency in marketed herbicides (Dithiopyr, Thiazopyr, Figure I.18). In pharmaceutical research, 2,6-diaryl-4-CF_3-pyridines are considered as promising mGluR2 antagonists[34] and anti-cancer agents.[35]

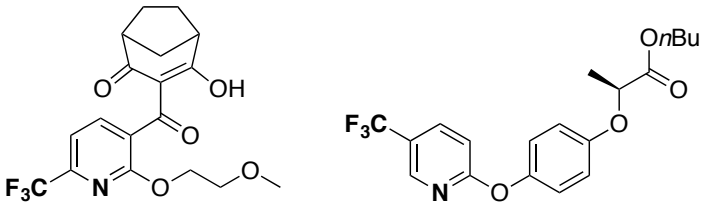


Figure III.14: Marketed CF_3-pyridines with new or known modes of action

The presence of emergent fluorinated substituents in pyridines is very challenging, but the synthetic strategies for their introduction are limited. Marketed herbicides contain pyridines bearing such EFSs (Trifloxysulfuron-methyl-sodium, Prosulfuron, Figure I.13).

One completely unexplored strategy is the introduction of perfluoroalkyl chains into pyridines. Consequently, the potential beneficial effect of such substitution into pyridines is unknown in the research of new bioactive molecules. As the pyridine core is widespread, we decided to attempt the introduction of perfluoroalkyl chains into pyridine cores. No examples are reported in the literature for such innovative pyridine building blocks bearing perfluoroalkylated chains.

1. Initial idea - Concept of Vinylogous FAR

Inspired by a very old reaction reported in 1986,[36] the idea of a vinylogous FAR was considered. As the activation of FARs occurs *via* a difluoromethyl group in *alpha* of the tertiary amine, we were interested in placing an unsaturation in between, to possibly conjugate the phenomenon of activation of FARs. This would provide a vinylogous FAR with new synthetic applications.

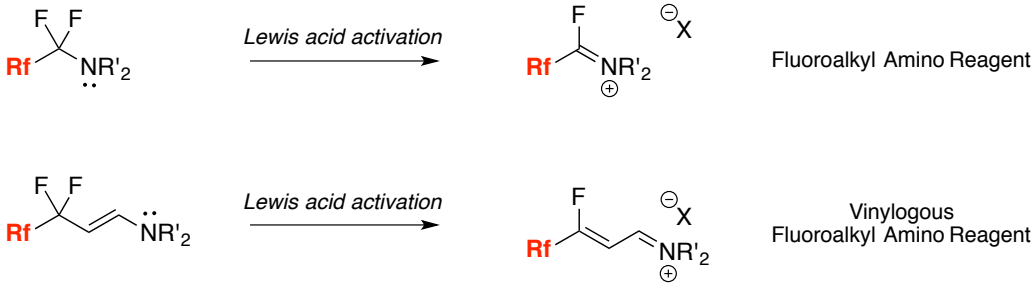
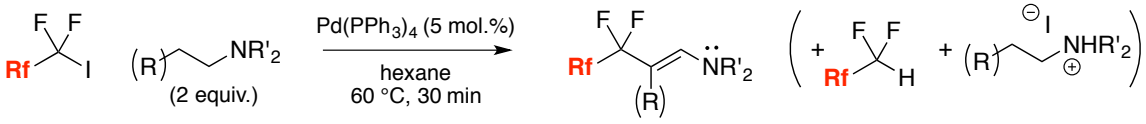


Figure III.15: Concept of Vinylogous FAR

For this purpose, we used an old report on the preparation of perfluoroalkyl alkenyl amines published by Huang *et al.* in 1986.[36] All results included the article were determined by ^{19}F NMR analysis and it appeared that the isolated yields after micro-distillation were generally much lower. The instability of perfluoroalkyl enamines was invoked to explain the low isolated yields.

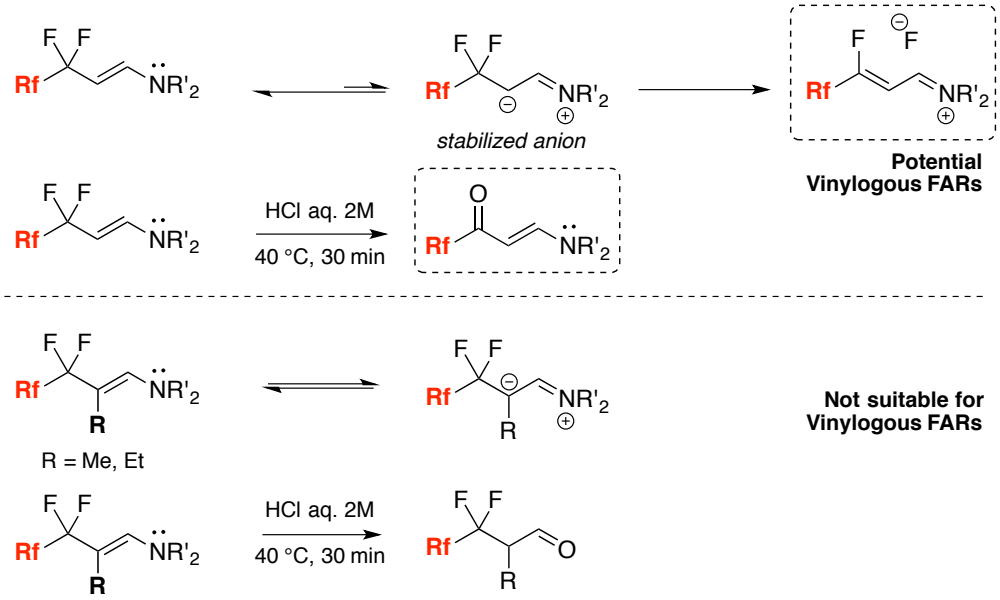


Iodide	Amine	Product	Yield (%) (^{19}F NMR)
$CF_3(CF_2)_2CF_2I$	NEt_3	$CF_3(CF_2)_2CF_2CH{=}CHNEt_2$	45
$CF_3(CF_2)_4CF_2I$	NEt_3	$CF_3(CF_2)_4CF_2CH{=}CHNEt_2$	50
$Cl(CF_2)CF_2I$	NEt_3	$Cl(CF_2)CF_2CH{=}CHNEt_2$	45
$Cl(CF_2)_3CF_2I$	NEt_3	$Cl(CF_2)_3CF_2CH{=}CHNEt_2$	48
$Cl(CF_2)_5CF_2I$	NEt_3	$Cl(CF_2)_5CF_2CH{=}CHNEt_2$	50
$Cl(CF_2)_7CF_2I$	NEt_3	$Cl(CF_2)_7CF_2CH{=}CHNEt_2$	40
$Cl(CF_2)_5CF_2I$	$N(n\text{Pr})_3$	$Cl(CF_2)_3CF_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H{=}CHNEt_2$	50
$Cl(CF_2)_5CF_2I$	$N(n\text{Bu})_3$	$Cl(CF_2)_3CF_2\underset{\displaystyle C_2H_5}{\underset{\vert}{C}}H{=}CHNEt_2$	46

Table III.3: Reported results for the preparation of perfluoroalkyl enamines in 1986

Surprisingly, this supposedly free radical reaction was limited to 50% of desired enamine formed from 2 equivalents of triethylamine, whichever perfluoroalkyl iodide was used. The mechanism initially evoked involved 2 equivalents of Et_3N, but was reviewed to 3 equivalents in a further report from the same group a year later.[37] This could suggest that the reaction might require different ratios of reagents to reach completion (Table III.3).

An interesting description of the reactivity of such perfluoroalkyl enamines was given, and strengthened us in the idea to use these perfluoroalkyl enamines as vinylogous FARs. Due to a conjugation of the electron pair at the *N*-atom with the Π-electrons, the enamine/iminium equilibrium (observed with FARs) is also present in the vinylogous system. As an illustration, most of the perfluoroalkyl enamines reported were efficiently hydrolysed and purified by chromatography (and recrystallization) as perfluoroalkyl enaminones (proving an enhanced stability towards acidic medias).



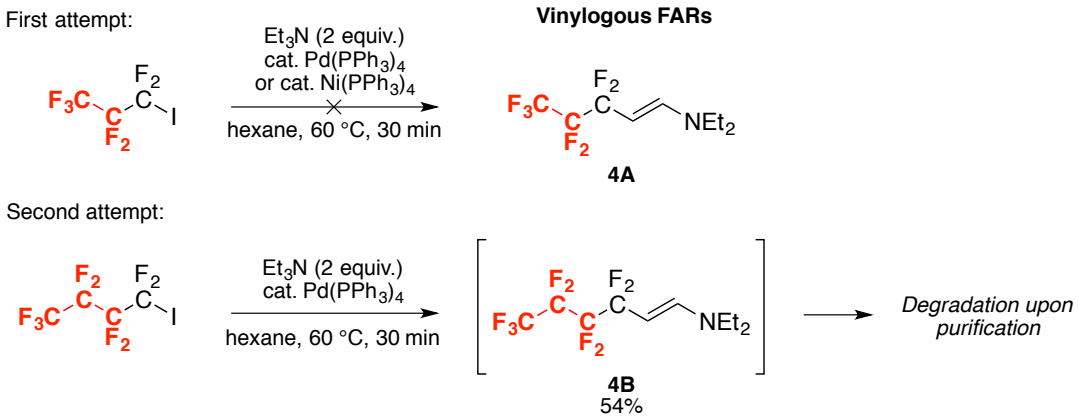
Reagent	Product	Yield (%) (^{19}F NMR)	m.p. or b.p. (° C)
$CF_3(CF_2)_2CF_2CH{=}CHNEt_2$	$CF_3(CF_2)_2COCH{=}CHNEt_2$	92	30-32
$CF_3(CF_2)_4CF_2CH{=}CHNEt_2$	$CF_3(CF_2)_4COCH{=}CHNEt_2$	86	45-47
$ClCF_2CF_2CH{=}CHNEt_2$	$ClCF_2COCH{=}CHNEt_2$	95	20-21
$Cl(CF_2)_3CF_2CH{=}CHNEt_2$	$Cl(CF_2)_3COCH{=}CHNEt_2$	83	42-43
$Cl(CF_2)_5CF_2CH{=}CHNEt_2$	$Cl(CF_2)_5COCH{=}CHNEt_2$	95	50-52
$Cl(CF_2)_7CF_2CH{=}CHNEt_2$	$Cl(CF_2)_7COCH{=}CHNEt_2$	93	53-54
$Cl(CF_2)_3CF_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H{=}CHNEt_2$	$Cl(CF_2)_3CF_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCHO$	69 (91)	70-72 / 15 mmHg
$Cl(CF_2)_3CF_2\underset{\displaystyle C_2H_5}{\underset{\vert}{C}}H{=}CHNEt_2$	$Cl(CF_2)_3CF_2\underset{\displaystyle C_2H_5}{\underset{\vert}{C}}HCHO$	46 (67)	68-70 / 15 mmHg

Figure III.16: Reported reactivity of perfluoroalkyl enamines (and α-alkyl enamines) under hydrolysis conditions (top); Possible vinylogous FAR and related enaminoketones products (possible perfluoroalkyl chains in red)

These products resulted from the nucleophilic attack of water at the β-position of the vinylogous fluoro iminium, which is the desired reactivity to develop the concept of vinylogous FAR. In the case of a perfluoroalkyl enamine with alkyl substituents in the α-position, the behaviour of this entity is modified, and the conjugation of the non-bonding nitrogen pair with Π-electrons is lower. The hydrolysis occurs at the iminium centre and provides an aldehyde product with lower yields (Figure III.16).

2. Early results

Perfluoroalkyl enamines with unsubstituted alkene are suitable candidates to be used as vinylogous FARs, and several attempts were achieved to prepare such compounds according to the reported conditions. Initial attempts were made with commercially available perfluoropropyl iodide, but the resulting enamine **4A** was highly sensitive, and any attempt to isolate it failed. Furthermore, the only example reported from a perfluoropropyl chain was with a terminal chlorine atom. All other examples were prepared from longer chains.



Scheme III.8: Initial attempts to isolate potential vinylogous FARs

Perfluorobutyl iodide was employed and the vinylogous FAR **4B** was formed in 54% yield according to ^{19}F NMR analysis (coherent with the literature report). Any attempt to purify the compound by distillation under reduced pressure failed (Scheme III.8). Next, we have tried to prepare a solution of the desired perfluorobutyl enamine **4B** and to activate it *in situ* using BF_3•Et_2O, similarly to FARs **1A-D**. The resulting activated vinylogous FAR **5B** would be reacted in solution directly with *N*,*N*-dimethylaminoacrylate after prior filtration of the insoluble ammonium iodide salts. MeCN was added before the activation by BF_3•Et_2O to allow this reaction to proceed.

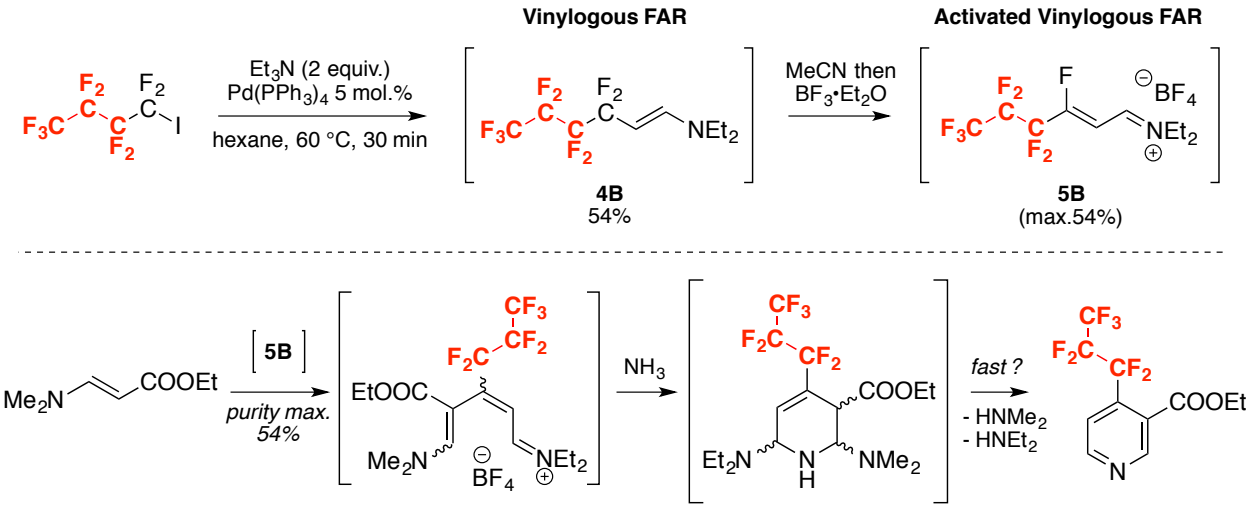
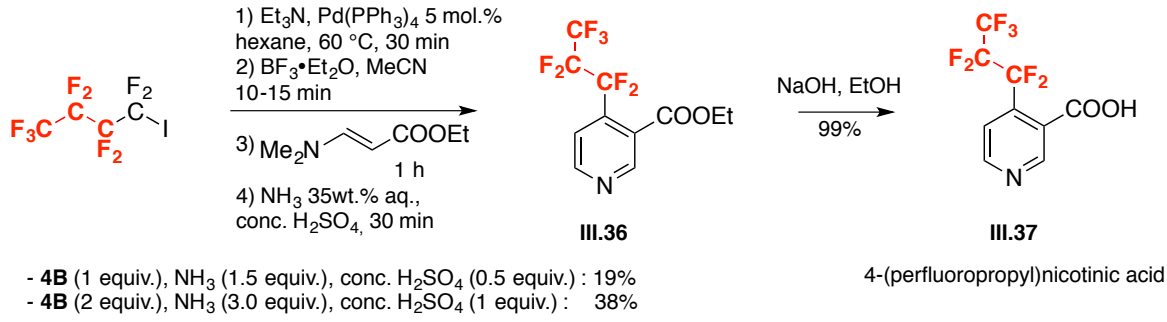


Figure III.17: New strategy to prepare the activated vinylogous FAR (top); expected sequence to access a first example of perfluoroalkylated product (bottom)



Scheme III.9: Early results for the preparation of an unprecedented perfluoroalkylated analogue of nicotinic acid.

A one-pot sequence was attempted with
1) Preparation of the vinylogous FAR **4B** (45% in the literature, max. 54% from earlier experiment);
2) Activation of the vinylogous FAR **4B** in solution after addition of MeCN to obtain activated vinylogous FAR **5B** (max. 54%);
3) Addition of one equivalent of *N,N*-dimethylaminoacrylate to form the desired cationic intermediate;
4) Addition of ammonia to allow the formation of the pyridinyl core;
5) Aromatization step (under acidic assistance).

After the addition of ammonia in the fourth step, concentrated sulphuric acid was added (similarly to the ketimine route) to favour the aromatization step after precipitation of ammonium salts resulting from aromatization. Two experiments were attempted, and by modifying the ratio of some reagents, the yield was multiplied by two (19% to 38%). Importantly, in the current method of preparation, the vinylogous FAR **4B** is formed in maximum 50% (due to the formation of a reduced perfluoroalkyl chain). The saponification of the 4-perfluoropropyl-nicotinic acid ethyl ester **III.12** was quantitative and provided the first reported 4-perfluoropropyl-nicotinic acid **III.13**.

D. Conclusion

The introduction of emergent fluorinated substituents into pyrimidine derivatives remains scarcely described.
In this context, we decided to develop a strategy involving FARs for the preparation of new bis(fluoroalkyl)pyrimidine carboxylates, using a strategy inspired by our previous results (see Chapter II).

For this purpose, we decided to isolate the key intermediates **III.2** (prepared from FARs and fluorinated acetoacetates **III.1**) involved in a procedure for the preparation of 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates **II.8-11** recently reported in our group.

Six key intermediates were isolated after a procedure using two repeated sequences of filtration through Celite followed by azeotropic distillation in toluene. Bis(fluoroalkyl)-α-aminoalkylidene-β-ketoesters intermediates **III.2** were isolated with excellent yields and purities (except one specific example from CHF_2-acetoacetate **III.1b**) (Figure III.18). The product formed from FAR **2C** and acetoacetate **III.1a** provided a different result.

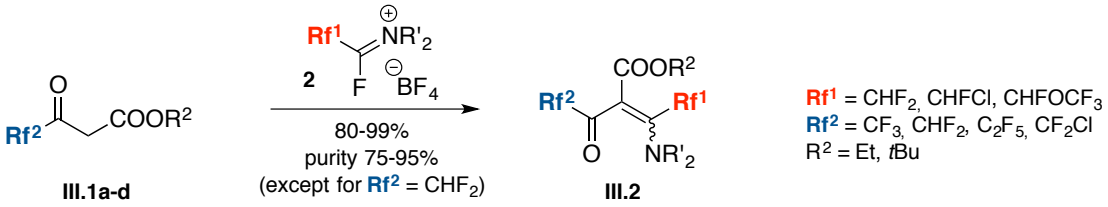


Figure III.18: Efficient preparation of key intermediates III.2

The intermediates **III.2** were used in the preparation of the corresponding 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates after an optimisation of the reaction conditions (solvent, base, stoichiometry, temperature, time, microwave irradiation). A broad scope of amidines was used (either from commercial sources or prepared from commercial carbonitriles by Pinner reaction). All key intermediates **III.2** were successfully converted into the desired products. Consequently, a large variety of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates was prepared, and their corresponding carboxylic acids analogues were accessed *via* saponification reactions. Symmetrical or unsymmetrical pyrimidine carboxylates were prepared with moderate to excellent yields. Seventeen carboxylic acid analogues were isolated with good to excellent yields, usually as stable solid compounds.

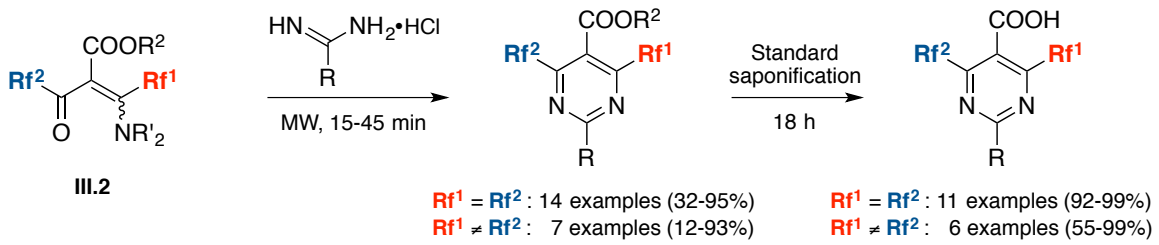


Figure III.19: Summary of the preparation of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates and carboxylic acid analogues

Two examples of carboxylic acid analogues provided crystallographic analyses confirming the observed structures. In the course of this project, interesting side-products were isolated and led us to propose a mechanistic pathway (Figure III.10). These side-products could be used as valuable building blocks (Figure III.20).

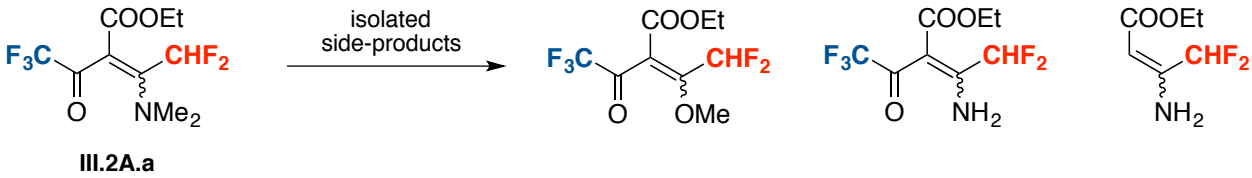


Figure III.20: Side-products isolated during the preparation of bis(fluoroalkyl)pyrimidine carboxylates

A first example of mono(fluoroalkyl)pyrimidine was also prepared from the condensation of the key adduct **II.48A** with acetamidine hydrochloride. The extension of the scope of this reaction is currently under investigation in our group (Figure III.21).

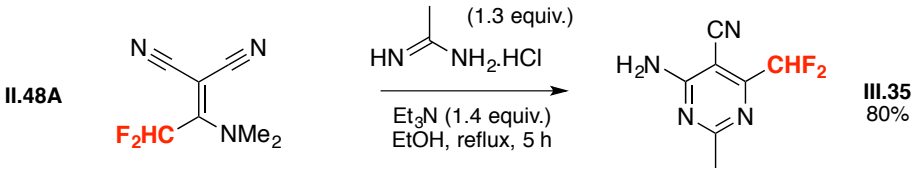


Figure III.21: Preparation of the first example of mono(fluoroalkyl)pyrimidine III.35

One attempt to prepare an key intermediate **III.2** using the activated Ishikawa reagent **2C** led to a very unexpected outcome, with a spontaneous rearrangement leading to a fully substituted cyclobutene product. The first example provided a product relatively sensitive. Further studies demonstrated that the resulting cyclobutene side-products could be quantitatively prepared from the model intermediate **III.2A.a** in presence of urea. The resulting cyclobutene **III.3A.a** was stable and could be purified by flash chromatography. The mechanism of the formation of these cyclobutenes was investigated; the absence of light provided the same NMR analysis, suggesting a thermal pathway. Under basic conditions, the acidic proton of the fluoroalkyl group could be deprotonated and the resulting diene could cyclize following a conrotatory pathway. Other hypotheses were proposed, and additional work has to be done to elucidate this point completely (Figure III.22).

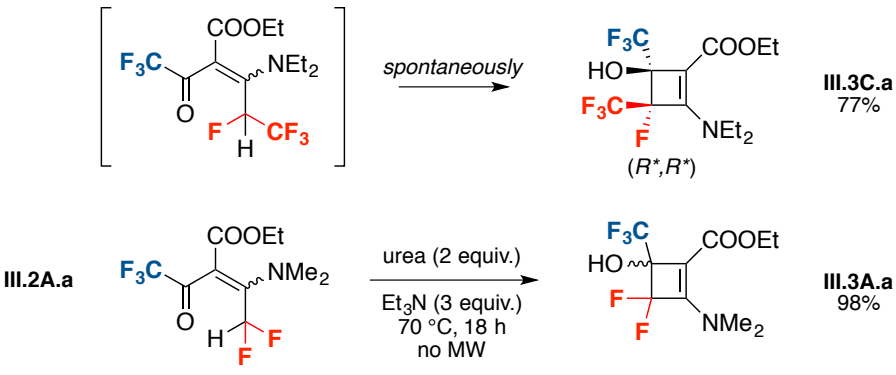


Figure III.22: Formation of cyclobutene products from two intermediates III.2, including one unstable example

Finally, the concept of vinylogous FAR was studied. The perfluoroalkyl enamine was prepared according to a procedure reported in 1986,[36] and activated *in situ* with BF_3•Et_2O, similarly to FARs **1A-D**. The resulting activated vinylogous FAR was reacted with ethyl *N*,*N*-dimethylaminoacrylate and the resulting intermediate was treated with ammonia. This reaction conditions were modified and the yield reached 38%. The resulting perfluoropropyl nicotinic ester was easily saponified, to provide the 4-perfluoropropyl analogue of nicotinic acid **III.13** (Figure III.23).

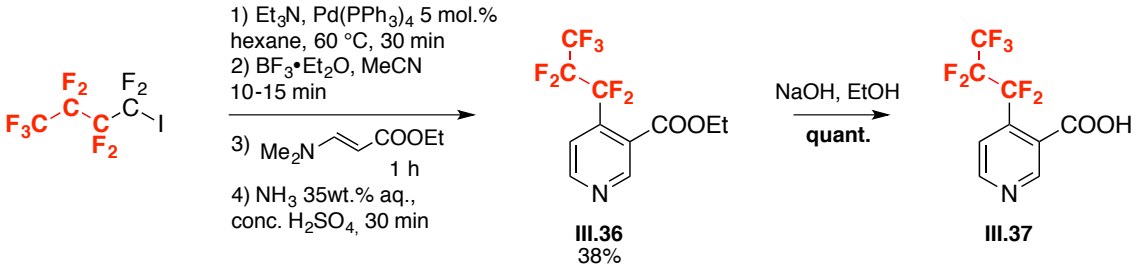


Figure III.23: Preparation of 4-perfluoropropyl nicotinic acid using the vinylogous FAR 4B prepared *in situ*

The results described in this chapter will be submitted for publication in due course, and several topics could be investigated in more details.

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Chapter IV

Fluoroalkyl Amino Reagents And OCF_3-Synthons For the Synthesis of Challenging OCF_3-Substituted *N*-based Heterocycles

Table of contents

In the previous chapters, the use of FARs provided a large series of unprecedented fluorinated building blocks, such as difluoromethylated pyrazoles and isoxazoles, in addition with difluoroacylated (het)arenes (Chapter I), bis(fluoroalkyl) pyrazoles (Chapter II), or bis(fluoroalkyl)pyrimidine carboxylates and cyclobutenes (Chapter III).

In many cases, the use of a suitable nucleophilic substrate with a fluoro iminium salt allowed for the formation of a reactive 1,3-dielectrophile intermediate. The further ring formation occurred after addition of the desired 1,2- or 1,3-dinucleophile (hydrazine, hydroxylamine, amidine). Using this strategy, many EFSs have been introduced, opening the way to new possibilities in either the discovery of new hits, or in the fine-tuning stage of lead optimization.

One type of EFS is not included in the previous chapters, but deserves some attention. The α-fluoroethers (and α-fluorothioethers), which are not a first priority topic in this PhD project, represent an important part in the expanding field of fluorinated bioactive molecules. The question of the introduction of such groups into heterocycles using the chemistry developed in this manuscript was opened, as it is currently a real synthetic challenge when considering *N*-based heterocycles. But what would be the interest of introducing α-fluoroethers or α-fluorothioethers into building blocks or fine molecules, in the perspective of the discovery of new bioactive compounds?

A. α-Fluoroethers – "Exotic" functional groups

The introduction of α-fluoroethers and α-fluorothioethers into aromatics has become another common strategy to tune the physico-chemical properties of a bioactive candidate, due to the very specific features of such groups. Both *O*- and *S*-ethers groups can impart increased lipophilicity, in addition with high electronegative parameters (Figure IV.1). It has also been shown that groups like OCF_3 can induce particular conformational changes.

The trifluoromethoxy group – the most represented example of this class, was considered as difficult-to-make and anecdotic not long ago, until the synthetic tools to prepare trifluoromethoxylated aromatic building blocks were developed (summarized later in the chapter). Due to the specific effects induced by the introduction of this group, several OCF_3-drugs and -agrochemicals are now marketed.

The agrochemicals bearing OCF_3 motif possess various possible MoAs (Figure I.13, bottom, and Figure IV.2, top), and the introduction of this group in pharmaceuticals led to major breakthrough, with the examples of Riluzole (the first drug approved for amylotropic lateral sclerosis) or Delamanid [included in the World Health Organization (WHO) List for Essential Medicines] (Figure IV.2).

Substituent	σ_m	σ_p
$OCHF_2$	0.31	0.18
OCF_3	0.38	0.35
$SCHF_2$	0.33	0.36
SCF_3	0.40	0.50
SO_2CHF_2	0.75	0.86
SO_2CF_3	0.79	0.93

Figure IV.1: Hammett constants of several *O*- and S-based fluorinated substituents.[1]

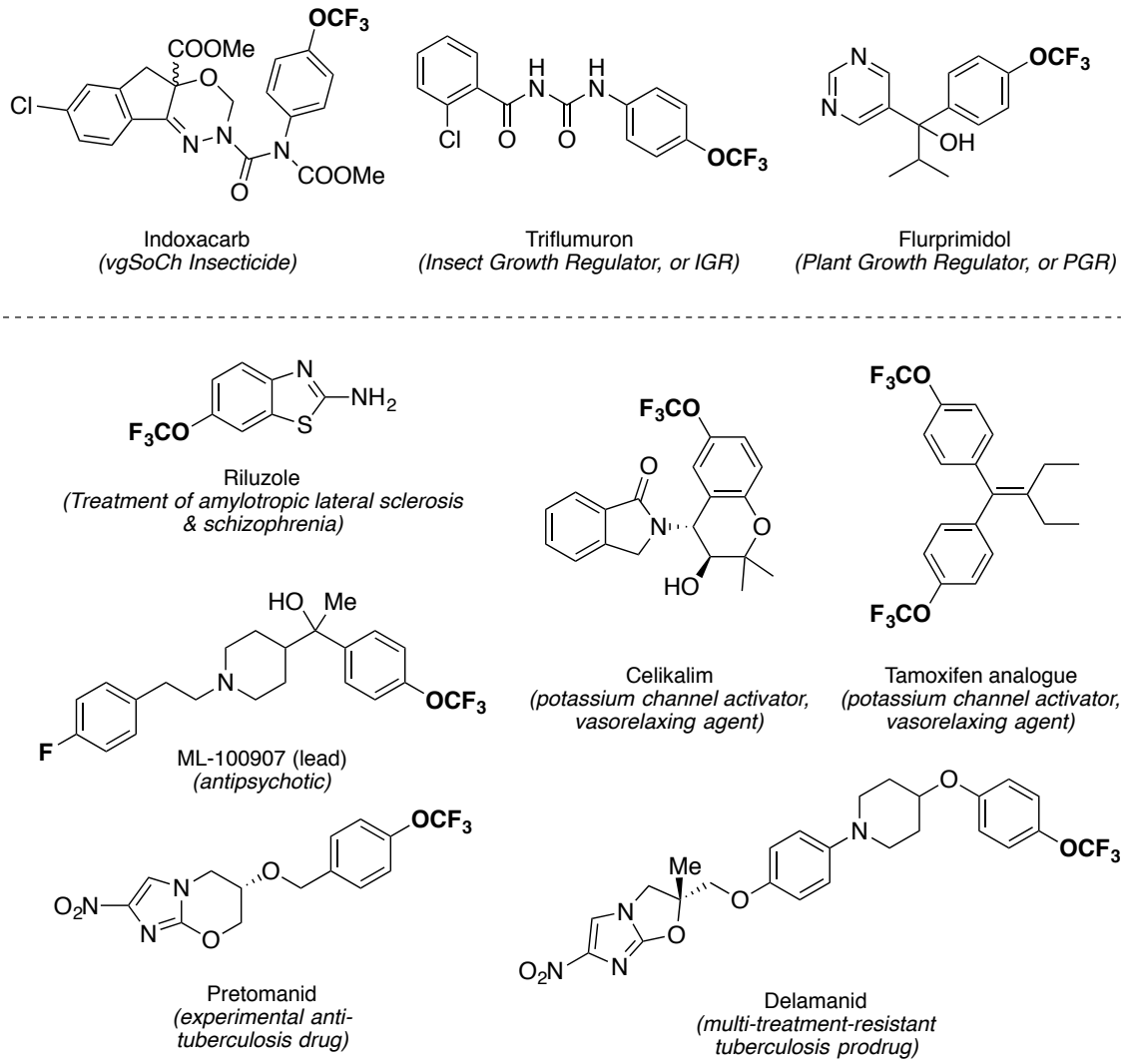


Figure IV.2: Pharmaceuticals and agrochemicals bearing OCF_3 group(s) with various applications

One can notice that the OCF_3 motif is preferentially introduced on phenyl rings, due to current technical limitations concerning its introduction into heteroaromatics. A great advance could be to develop new strategies allowing for the introduction of the OCF_3 motif into various types of heterocycles (especially nitrogen-based).

Nowadays, more and more examples of marketed compounds or lead candidates bearing other α-fluoroethers can be found in a vast array of research fields, either in agrochemistry or pharmaceutical research, proving the great potential of such EFS for modern drug design and agrochemicals development (Figure IV.3). The introduction of these groups does not face the same synthetic challenges than OCF_3, as they can be prepared differently. Still, their presence in bioactive compounds is limited. In agrochemical research, these α-fluoroethers are present in molecules displaying various MoAs, and can be used in all research fields (fungicides, herbicides, insecticides, etc.). In pharmaceuticals, the $OCHF_2$ motif is almost the exclusive alternative to OCF_3, due to an "easier" introduction of the motif into aromatics.

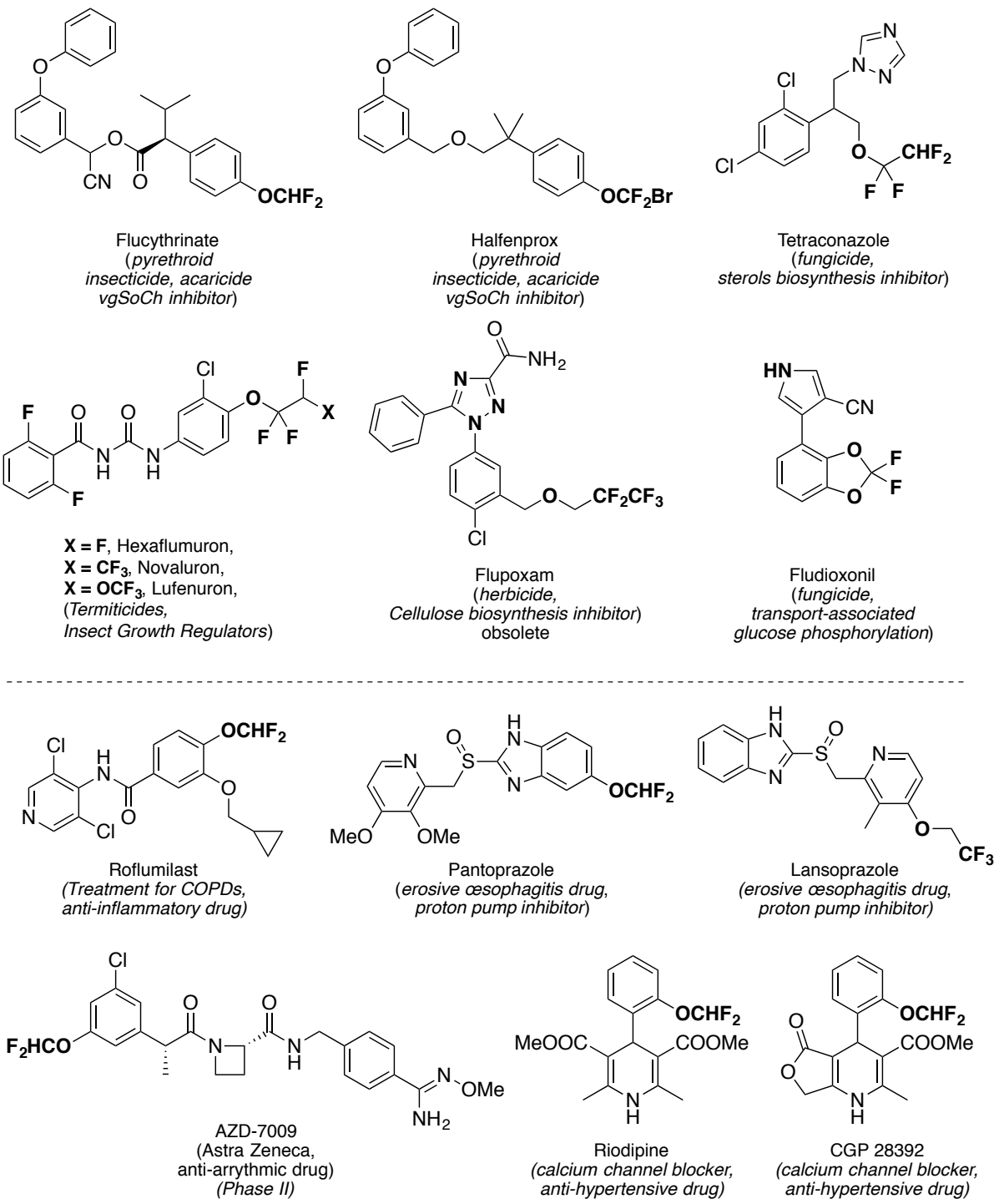


Figure IV.3: Pharmaceuticals and agrochemicals bearing other α-fluoroethers with various applications

The α-fluoroethers are excessively potent groups for the fine-tuning of bioactive candidates physico-chemical properties. A summary of their own characteristics will illustrate the possibilities they offer in lead optimization stage.

1. Properties of α-fluoroethers

OCF_3

One of the most electronegative groups [$\chi(OCF_3)$ = 3.7] with excellent lipophilicity [$\pi_x(OCF_3)$ = +1.04, $\pi_x(OCH_3)$ = 0.02], due to the fluorinated carbon adjacent to the oxygen atom. It can replace advantageously a fluorine atom (π_X = +0.14) with a beneficial lipophilicity increase.

In aryl trifluoromethyl ethers, the O-CF_3 bond is preferentially orthogonal to the plane of the arene ring, as shown in several reports and reviews.[2-5] This is due to the very low electron density of the oxygen's non-bonding p-orbitals, highly delocalized into the C-F antibonding orbitals in CF_3. Thus, the oxygen lone pairs are not conjugated with the aromatic ring system, and the rotational barrier is significantly lower than for the OCH_3 analogue (Figure IV.4).

Studies have shown that this unusual orientation may provide additional binding affinity in drug–target complexes; for example, OCF_3 showed positive effect in the inhibition of pulmonary adenocarcinoma cells,[6] but also in tuberculosis treatment (*e.g.*: Pretomanid, with very complex MoA, acting on both genes responsive to cell wall inhibition and respiratory poisoning, Figure IV.2)[7]. However, 2-trifluoromethoxypyridine shows in-plane conformation due to a weaker electronic repulsion from the π-system. The conformational flexibility of OCF_3 group could be used for altering binding affinity parameters.[3]

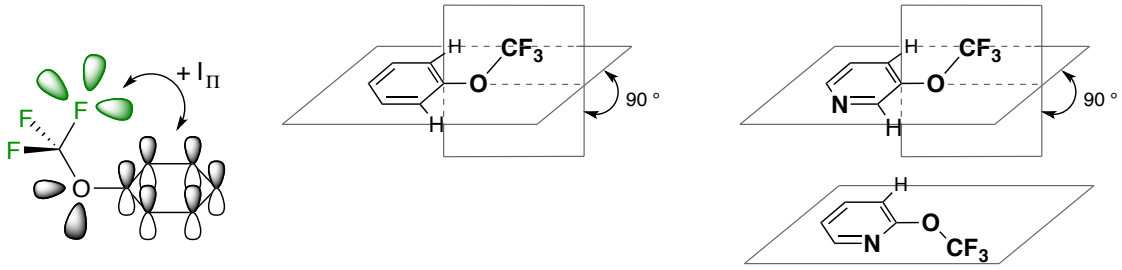


Figure IV.4: Illustration of the specific conformational behaviour of (het)aryl-OCF_3 substituents

The introduction of OCF_3 into relevant bioactive compounds is also intriguing due to its unique electron distribution. The geminal alkoxy/aryloxy lone pairs and fluorine atoms enable bonding/non-bonding resonance, formally expressible as the superimposed covalent and ionic limiting structures (Figure IV.5).[3]

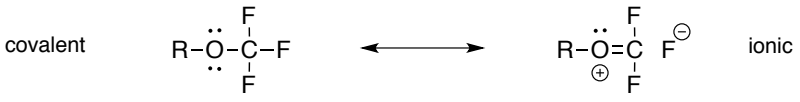


Figure IV.5: Specific electronic distribution of OCF_3 group possessing mixed covalent/ionic character

In addition with high electronegativity, high lipophilicity, specific conformational behaviour and electronic distribution, the OCF_3 substituent is thermally and chemically resistant to attack by acids, bases, organometallic reagents and oxidizing/reducing agents.[8, 9]

Other types of α-fluoroethers have been utilized to develop compounds currently marketed (Figure IV.3). If the OCF_3 group suffers from a lack of theoretical studies, it is still more common than these groups, which are extremely scarcely used and studied. A quick description of the other possible α-fluoroether will be made, without going into further details concerning the synthetic strategies for their introduction.

$OCHF_2$

This α-fluoroether is more and more represented in marketed compounds, proving its great characteristics. It shows similar physico-chemical properties compared with OCF_3, with an additional H-bonding capacity. The $OCHF_2$ group seems to have a more flexible orientation than OCF_3 regarding the aromatic ring system ($1° < \theta < 90°$). $OCHF_2$-compounds are little described in marketed agrochemicals (top, Figure IV.3), with the exception of bis-$OCHF_2$-sulfonyl urea Primisulfuron-methyl (Figure I.13) or Pyroxasulfone (Figure I.18) herbicides, but are found in medicinally relevant compounds that include enzyme inhibitors,[10] anti-HIV agents[11] and antimicrobial agents.[12] Pantoprazole [13] is another nice example of $OCHF_2$-containing drug (bottom, Figure IV.3, top 100 selling drugs in 2013), as well as Roflumilast (Merck & Co, Ltd.) a selective and long-acting phosphodiesterase-4 inhibitor (PDE-4), a member of the highly studied family of PDE inhibitors.

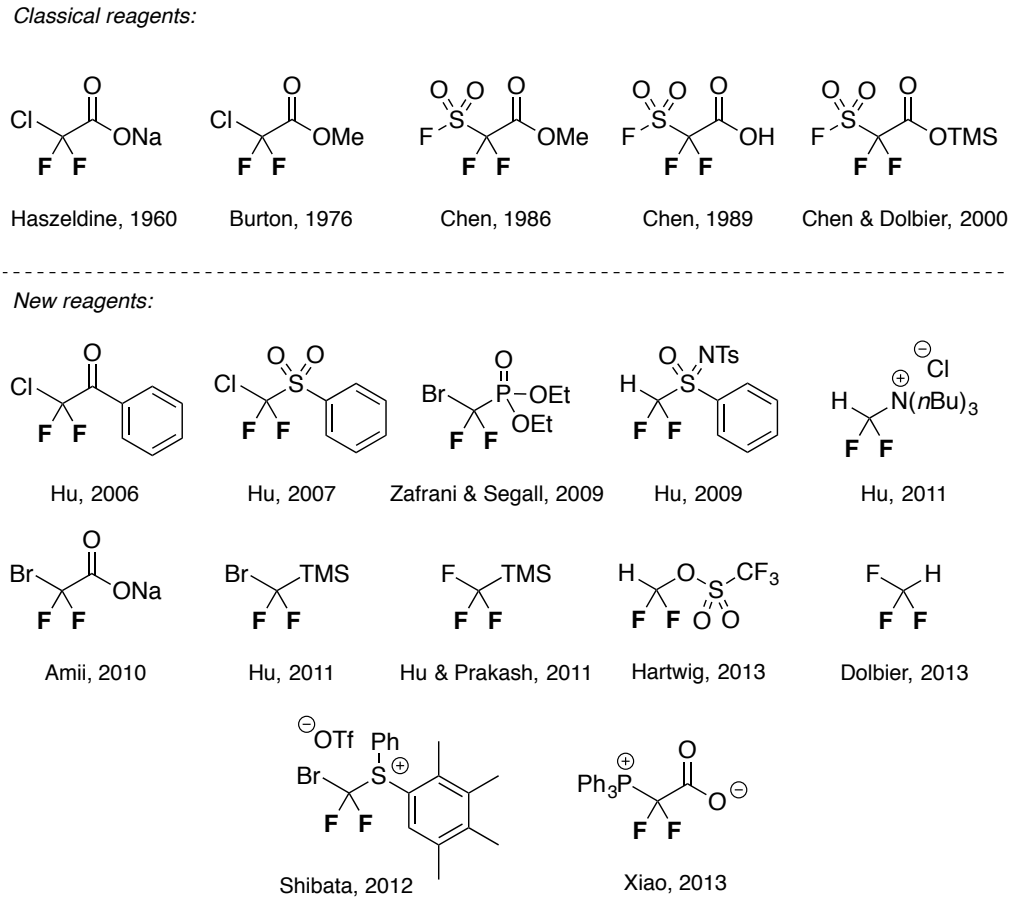


Figure IV.6: Difluorocarbene sources (ozone-depleting reagents such as HCF_2Cl are not listed) reported in Hu's review

The synthesis of $OCHF_2$-compounds was reported either by the use of ozone-depleting CHF_2Cl gas, difluoromethyl triflate, or many other difluorocarbene precursors (Figure IV.6). The generated difluorocarbene reacts with an alkoxide/phenoxide to provide the corresponding $OCHF_2$ product. An excellent review from Hu *et al*. recently covered the numerous applications of the use of difluorocarbene, including the preparation of $OCHF_2$ aromatic compounds.[14] At the opposite, even though the preparation of 3- and 5-$OCHF_2$-pyrazoles are described in several patents,[15, 16,] $OCHF_2$-pyrazoles remain very rare compounds.

α-Fluoroethers are known for their presence in several agrochemicals or drugs, but physico-chemical properties induced by their introduction are very difficult to find.

OCH_2F

No data for this fluorinated ether, neither could we find any example in the literature for active compounds bearing this moiety. The preparation of aryl fluoromethyl ethers was however reported by cleavage of aryl *O*,*S*-acetals with Xenon difluoride or more recently by photo-fluorodecarboxylation of phenoxy acetic acid derivatives with Selectfluor.[17-19] Very few *N*-based heterocycles are reported with this motif, but much more in patent applications (very few pyridines, pyrimidines, but no pyrazoles), usually prepared by nucleophilic substitution reactions of phenols/phenolates on fluoromethyl tosylate.

OCH_2CH_2F

This motif is used in [^{18}F] PET imaging in the well-established ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) radiotracer.[20-22] The preparation of such fluorinated ether can be achieved *via* an S_N2-type reaction (using ^{18}F-ethyl tosylate, etc.) or *via* nucleophilic fluorination of the corresponding alcohol (*e.g.*: DAST).

OCH_2CF_3

This group is broadly described in various arenes and *N*-based heterocycles (except in 3-pyrazoles, and limitedly in 4-pyrazoles), and are usually prepared by S_N-type reactions of phenols with 2,2,2-trifluoroethyl bromide, nucleophilic aromatic substitution of (het)aryl halides with 2,2,2-trifluoromethyl ethoxide, etc. Trifloxyusulfuron-methyl, Flupyrsulfuron-methyl-sodium, Triflusulfuron-methyl (Figure I.13) are great but rare and related examples of marketed sulfonyl urea herbicides bearing this motif. Lansoprazole (Figure IV.3) is an even more rare example of pharmaceutical (proton-pump inhibitor drug) bearing such EFS.

$OCH_2C_2F_5$

The introduction of this EFS is a little less described in arenes and pyridines than its analogue (see above), but almost not described in pyrimidines and pyrazoles, and is achieved similarly to the previous example, from 2,2,3,3,3-pentafluoropropanol. Flupoxam, a triazolyl herbicide is the only example of marketed bioactive compound bearing this substituent, but it is obsolete (Figure IV.3).[23, 24]

OCF_2Br

This group is generally formed from phenoxide (or silyl ethers) and difluorodibromomethane. Its introduction is reported mostly into arenes, and this group was found (with aryl-OCHFCl and aryl-SCF_2Br) to be an efficient substrate for the preparation of ^{18}F-labeled aryl-$OCHF_2$, -OCF_3 and -SCF_3 derivatives, inclusive of [^{18}F]-riluzole. expanding the scope for PET applications.[25]
However, it is very less reported in pyridines (with much lower yields), and absent in pyrimidines and Halfenprox (insecticide, acaricides, Figure IV.3)

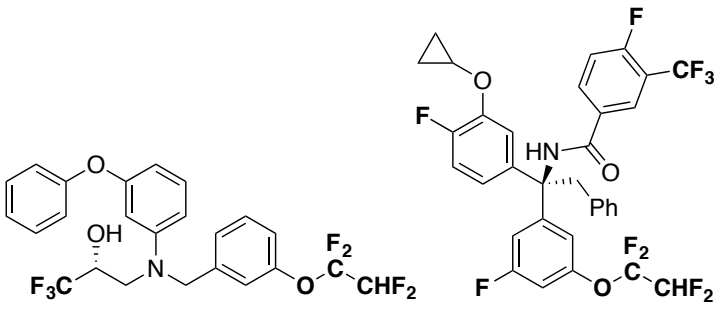


Figure IV.7: Potent Cholesteryl Ester Transfer Protein (CETP) inhibitors[26, 27]

OCF_2CHF_2

This group has shown important bioactivity in insecticides, herbicides [Tetraconazole and Hexaflumuron[28] are two nice but rare examples of marketed fungicide and termiticide bearing this group (Figure IV.3)] but has also demonstrated high potential in anti-tumoral candidates, in cholesteryl ester transfer protein (CETP) inhibitor candidate (for atherosclerosis and coronary heart disease treatments) (Figure IV.7).

It is prepared from phenoxides and either tetrafluoroethylene, phenols and (halo)-1,1,2,2-tetrafluoroethane or alternatively from reduction of an bromo-1,1,2,2-tetrafluoroethyl ether intermediate after its optimized formation from phenoxide and 1,2-bromotetrafluoroethane.[29]. It is broadly reported in arenes, however very less into pyridines, pyrimidines, or pyrazoles (mostly in patents). Yagupolskii's group recently reported two strategies for the preparation of 4-OCF_2CHF_2-pyrazoles, -pyrimidines and -pyrimidin-2-ones using fluoroalkoxylated enaminoketone or malonic aldehyde diacetal substrates and amidines, urea or hydrazines, but only 4-OCF_2CHF_2-building blocks were prepared.[30, 31]

OCF_2CHFCl

This α-fluoroether is much more reported in arenes, due to an easier access and handling of chlorotrifluoroethylene compared with explosive tetrafluoroethylene. However, it is almost not reported in pyridines, pyrimidines and pyrazoles, except in a few patents and in previously cited Yagupolskii's work for several pyrimidines and pyrazoles substituted in position 4. It is most commonly formed by nucleophilic addition of phenoxides onto chlorotrifluoroethylene. Unfortunately, no bioactive compound containing this group was found in the literature.

OCF_2CHFCF_3

This group is very similar to the previous one, formed using similar strategies, with perfluoropropene instead.

Easily introduced into arenes (from phenols/phenoxides), it is similarly almost not reported in pyridines, pyrimidines and pyrazoles. Still, one single marketed termiticide is commercialized (Novaluron, Figure IV.3).

$OCF_2CHFOCF_3$

This group is also formed by nucleophilic attack of phenoxides onto perfluoromethyl perfluorovinyl ether (used for the preparation of the new FAR **2D**). It is reported in several articles and patents into arenes, but is almost absent in heterocycles. Once again, a single termiticide compound bearing this group is marketed (Lufenuron, Figure IV.3).

Concerning the four last α-fluoroethers described, a comment could be made on the stability of such groups. Indeed, similarly to FARs **1A-D**, a possible hyperconjugation can occur between the non-bonding orbitals of oxygen and the anti-bonding bonds of the neighbouring CF_2, possibly enabling the hydrolysis of such highly fluorinated groups (Figure IV.8).

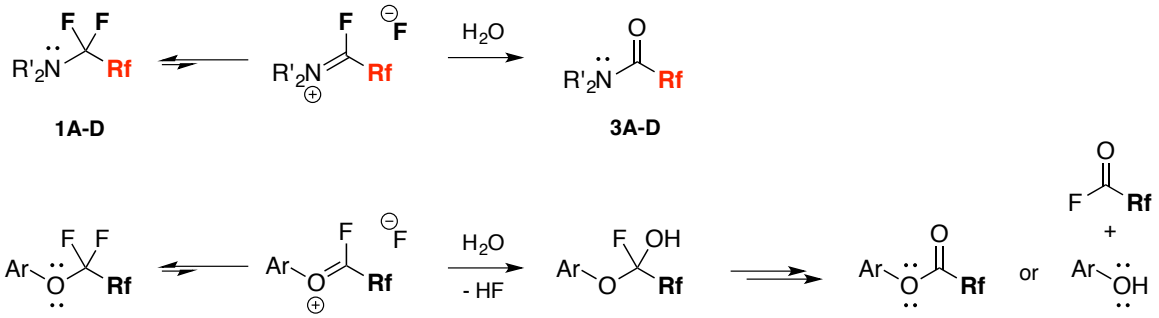


Figure IV.8: possible hydrolysis pathway for α-fluoroethers prepared from perfluoroalkenes, similarly to hydrolysis pathway of FARs 1A-D

OCF_2O

The preparation of difluorobenzodioxoles is broadly reported in the case of arenes, either *via* fluorination of dichlorodioxoles or the fluorination of cyclic thionocarbonates, but also from condensation of dibromodifluoromethane and catechols. Similar strategies are applied to pyridines in a much smaller occurrence,[32] and this group is absent in pyrimidines and pyrazoles. One single example of fungicide is available on the market (Fludioxonil, Figure IV.3).

To summarize concerning this description of α-fluoroethers, they have already contributed to the development of highly potent drug candidates (*e.g.*: Figure IV.7) and of marketed agrochemicals (Figure IV.2, Figure IV.3), and could be meaningful in the future, especially OCF_3 and $OCHF_2$, both largely represented and proving year after year their potential.

As it has been described, the introduction of both groups is achieved according to different strategies. As illustrated in Figure IV.6, many research groups have reported synthetic methods to prepare difluoromethoxylated compounds, based on the generation of difluorocarbene from various precursors. There is no intent in this manuscript to further discuss this part.

In the other hand, the introduction of OCF_3 group into pyrazoles (and other *N*-based heterocycles) remains a challenge, and we became interested in this objective. As illustrated in Figure IV.2, all marketed compounds bearing a OCF_3 motif are restrictively aryl-OCF_3 compounds. There is a real lack of synthetic strategies to access to heteroaryl-OCF_3 analogues, and we decided to use the experience from the FAR's chemistry to prepare a few examples.

2. Trifluoromethoxylation of heterocycles – State-of-the-Art

The introduction of OCF_3 motif has been broadly studied since the first report of trifluoromethyl ethers in 1935, and the first aryl trifluoromethyl ethers in 1955. The currently assumed aspects of the introduction of the OCF_3 group is that it cannot be achieved *via* trifluoromethylation of hard nucleophiles (phenoxides, etc.) with CF_3I through S_N2 type mechanism, regarding (Figure IV.9):

- The strong electron repulsion between three fluorine atoms and an incoming nucleophile
- The required formation of energetically disfavoured CF_3 carbocation transition state
- The reversed electron density inducing competing iodination of nucleophiles

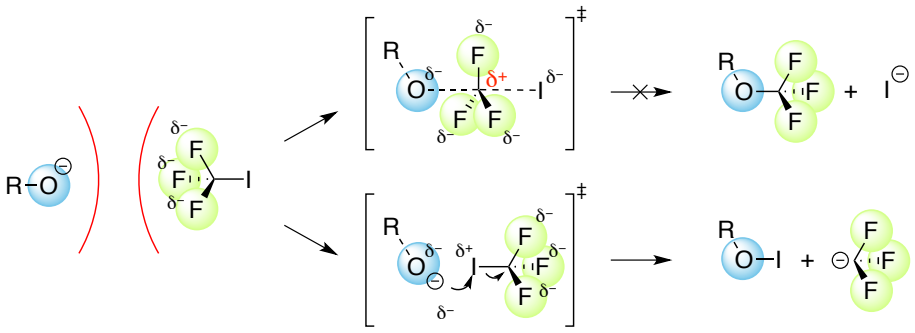


Figure IV.9: Specific behaviour of OCF_3^- anion preventing trifluoromethoxylation *via* S_N2 type reactions[33]

The general methods for the preparation of OCF_3-arenes are (see corresponding references[34]):
(1) The fluorination of CCl_3-precursors (using nucleophilic HF sources)
(2) The deoxofluorination of fluoroformates (Sheppard's method, using toxic COF_2)
(3) The Hiyama's oxidative fluorodesulfurization (from xanthates)
(4) The electrophilic trifluoromethylation of alcohols (using CF_3 electrophilic sources like Togni reagent)
(5) The nucleophilic trifluoromethoxylation (from stabilized trifluoromethanolates $Q^+ OCF_3^-$)
(6) The transition metal-mediated trifluoromethoxylation of aryl borates and stannanes
(7) The radical trifluoromethoxylation
The direct OCF_3 incorporation methods [C-OCF_3 bond formation, (4)-(7)] are the most promising strategies, but are only at an early development stage, due to the specific reactivity of trifluoromethoxide anion (Figure IV.10).

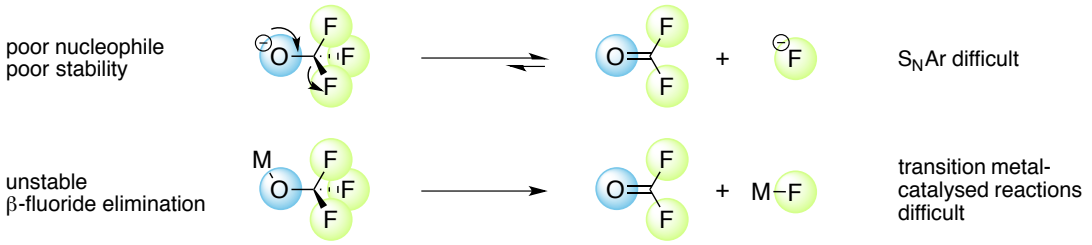


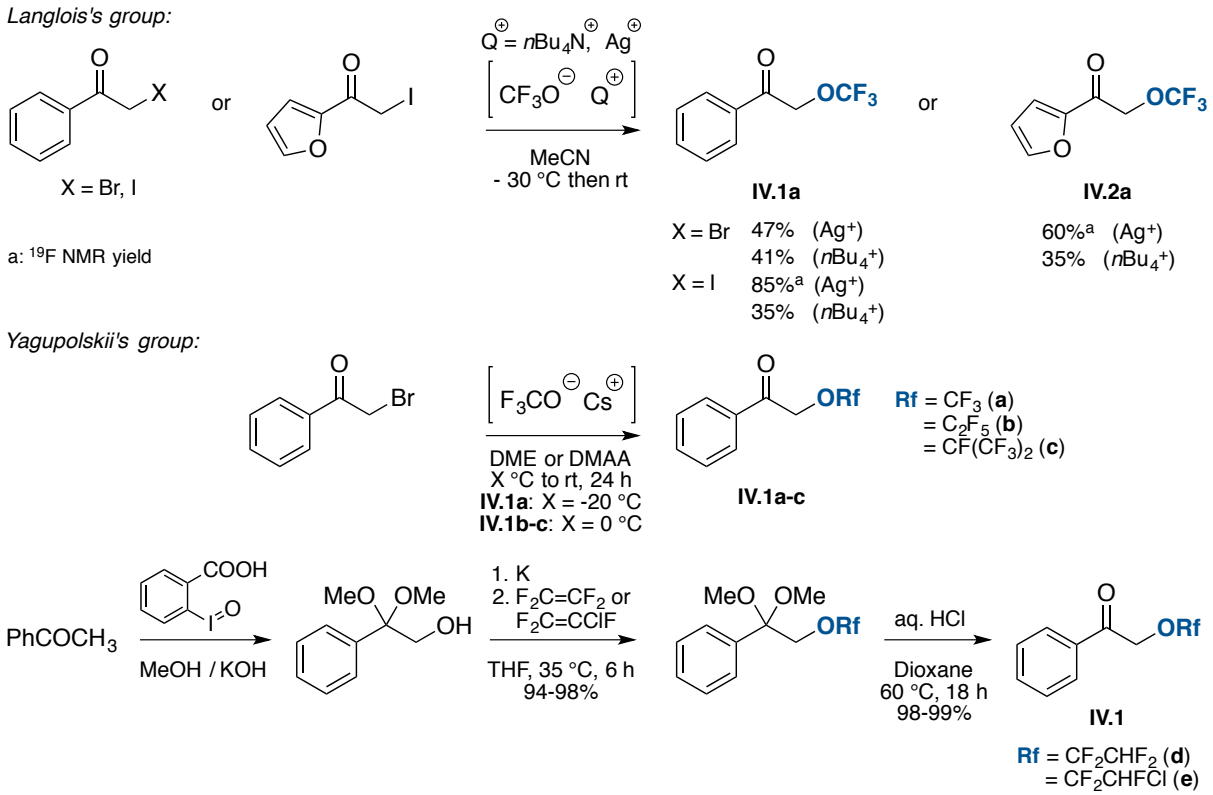
Figure IV.10: Low stability of trifluoromethoxide anion and trifluoromethoxide metal complexes.[33]

Our group published an excellent review covering all recent methods developed for the preparation of OCF_3-arenes, and recent articles have been published to complement its content (*O*-trifluoromethoxylation of hydroxylamines, silver-mediated direct oxidative trifluoromethylation of phenols, synthesis of *o*-trifluoromethoxy aniline derivatives by OCF_3-migration).[2, 34-36] Concerning *N*-based

heterocycles, it is more difficult to efficiently prepare OCF_3-compounds by direct strategies, but new methods have been frequently reported over the last few years. Our group reported in 2010 the first preparation of OCF_3-pyridines using oxidative fluorodesulfurization of pyridine xanthogenates and subsequent transformations, but also from fluorination of halodifluoromethoxy pyridines. This multi-step strategy requires the use of toxic fluorinating reagents and displays moderate overall yields.[37, 38]

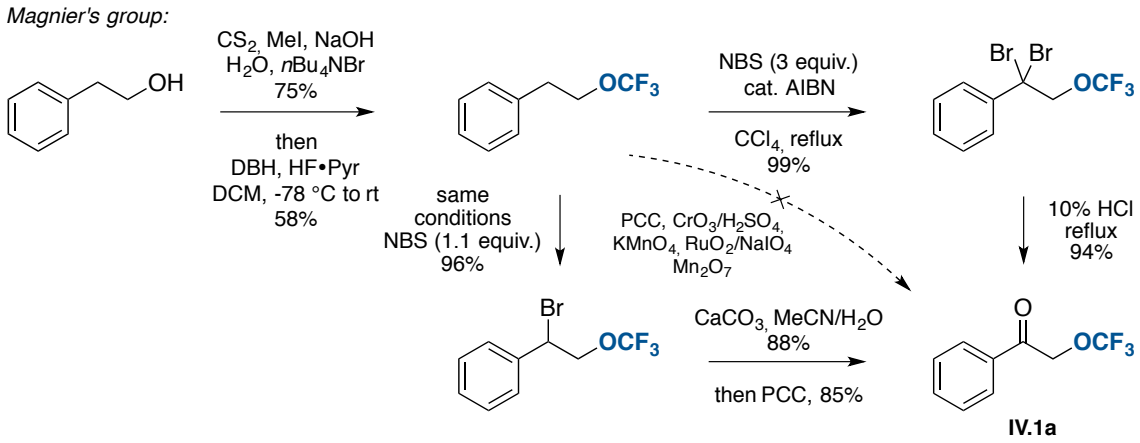
Feng *et al*. have recently applied the migration strategy previously reported for arenes to pyridines, using radical *O*-trifluoromethylation of carbamate-protected (3-pyridinyl)-hydroxylamines and subsequent OCF_3-migration onto the pyridine core. The substrate scope and tolerance to functional groups are broad, in addition with very good yields. Pyrimidines and other *N*-based heterocycles were also compatible. However, this strategy allows only *ortho*-migration and requires the difficult preparation of the substrates, which are important limitations.[33] Liang *et al*. reported very recently the first one-pot *O*-trifluoromethylation of hydroxylated *N*-based heterocycles, including many pyridines and few examples of other heterocycles. The yields were lower but these results are very promising.

The presence of OCF_3-pyrimidines in the literature is limited to the examples reported in the articles discussed above, and a few more examples found in patents, prepared by fluorination of trichloromethyl pyrimidine substrates using harsh conditions. There is still a lack of general synthetic approaches towards OCF_3-pyrimidines. The synthetic approaches to OCF_3-pyrazoles are extremely scarce, as only a very limited number of examples can be found. The synthesis of 3-OCF_3-pyrazoles has never been reported up to now. Concerning 5-OCF_3 analogues, only one patent described the *O*-trifluoromethylation of a 2-thienyl pyrazol-3-one using bromotrifluoromethane.
The recent results for the direct *O*-trifluoromethylation of aliphatic alcohols initially reported in Langlois's group and later extended in Yagupolskii's group have given access to new OCF_3-building blocks such as OCF_3-acetophenone and analogues (**IV.1-2**, Scheme IV.1).[5, 39-41]



Scheme IV.1: Reported preparation of key OCF_3-aryl ketones

An alternative efficient but stepwise approach was reported from the Magnier's group; they accessed the valuable OCF_3-acetophenone **IV.1a** starting from 2-OCF_3-ethyl-benzene (prepared from 2-phenylethan-1-ol using oxidative fluorodesulfurization strategy) after mono- or bis-bromination of the benzylic position under radical conditions. Both mono- and bis-brominated products were converted into the ketone **IV.1a** with a maximal overall yield of *ca.* 40% (Scheme IV.2).[42]
Unfortunately, the direct oxidation of the benzylic position was not possible due to the high deactivating effect of adjacent OCF_3 moiety, whichever oxidizing reagent used. Consequently, several different methods are available for the preparation of the OCF_3-acetophenone **IV.1a**, but none represent an easy and cheap access, which leaves this compound highly expensive to buy.

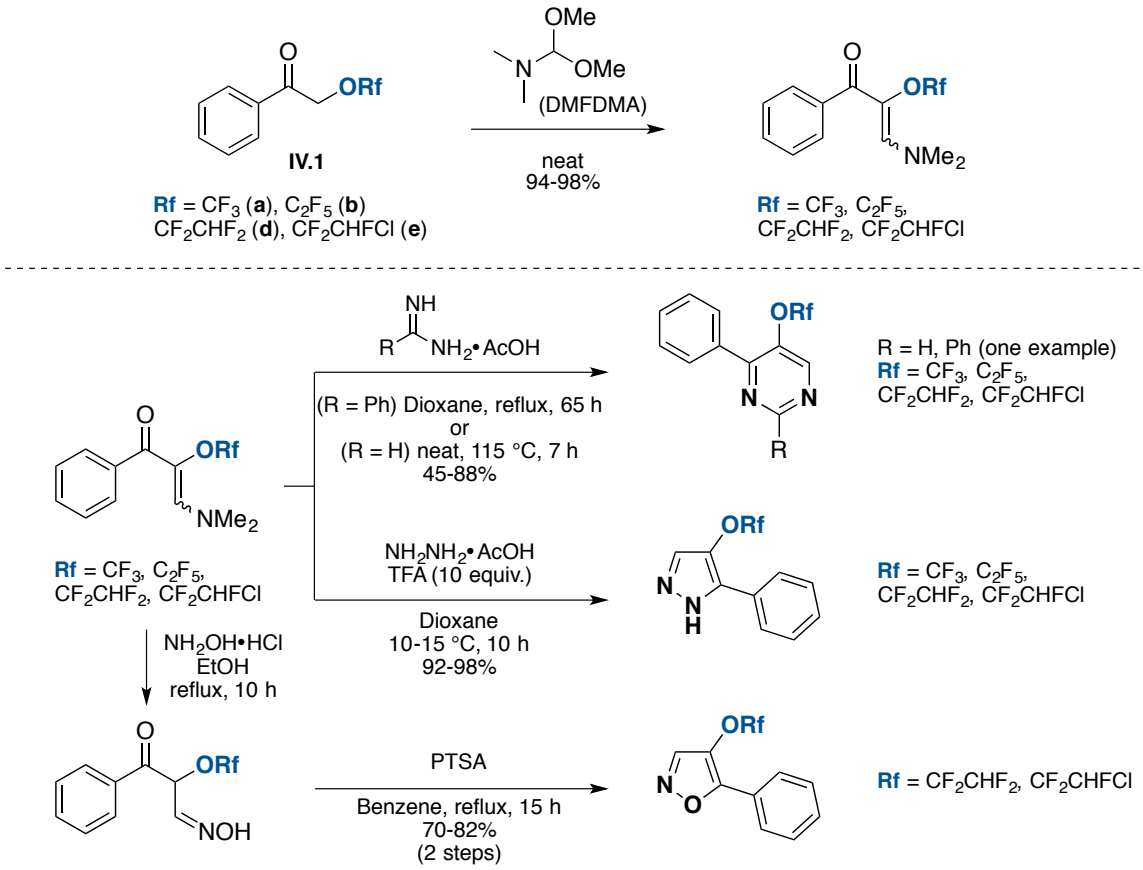


Scheme IV.2: Alternative stepwise approach to OCF_3-acetophenone IV.1a

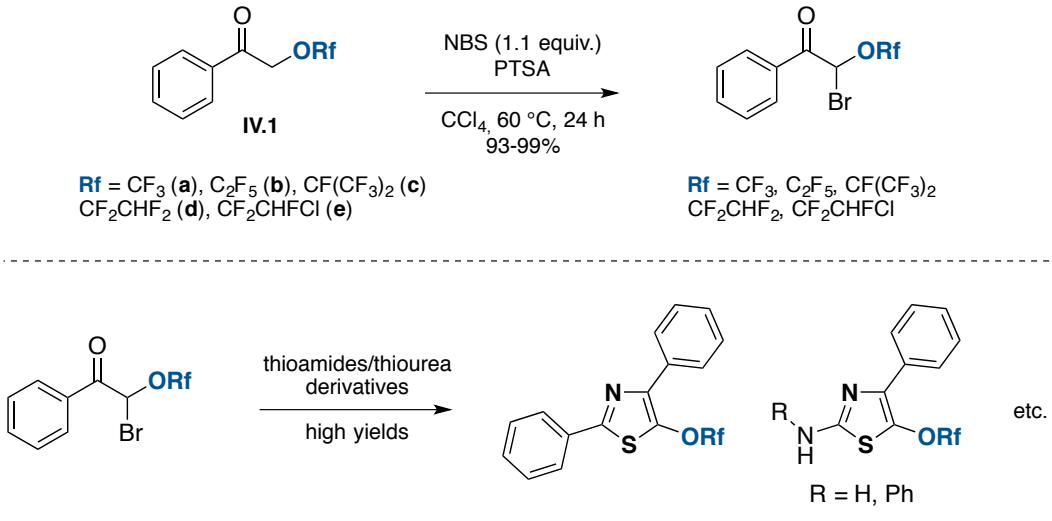
OCF_3-Arylketone **IV.1a** has been employed in the efficient Mannich-type synthesis of the corresponding ORf-enaminoketone using DMFDMA, and this building blocks enabled the preparation of a number of challenging and unprecedented 4-OCF_3-pyrazoles, -isoxazoles and -pyrimidines (Scheme IV.3).[31, 39]

Other ORf-arylketones **IV.1** prepared from hydroxyacetophenone and perfluoroalkenes[41] (used for the preparation of FARs) have been successfully used in the preparation of enaminoketones, and consequently in the corresponding heterocycles (-OC_2F_5, -OCF_2CHF_2, -OCF_2CHFCl, $OCF(CF_3)_2$). These results constitute a nice breakthrough in the introduction of -OCF_3 and -ORf motifs in *N*-based heterocycles (Scheme IV.3).
The bromination of ORf-enaminoketones enabled their use in Hantzsch-type thiazoles syntheses, giving access to unprecedented fluoroalkoxy thiazoles derivatives. This topic will not be further detailed as it is not related enough to the topic of this manuscript, but it deserved to be cited (Scheme IV.4).[41]

The development of novel strategies for the preparation of OCF_3-*N*-based heterocycles is strongly demanded, due to the increasing interest of agrochemical- and pharmaceutical companies for trifluoromethoxylated heteroaromatic compounds.
Inspired by the results recently reported using a building block approach to construct heterocycle cores (Scheme IV.3, Scheme IV.4), we investigated the possibility to apply the high reactivity of FARs for the preparation of valuable bis(fluoro-alkyl/alkoxy) aryl enaminoketones, and perhaps succeed in the preparation of highly challenging bis(fluoro-alkyl/alkoxy) heterocycles.



Scheme IV.3: Synthesis of ORf-heterocycles using ORf-enaminoketones or ORf-ketooximes



Scheme IV.4: Examples of *S,N*-based heterocycles prepared *via* Hantzsch-type reactions from brominated ORf-acetophenones and thioamide/thiourea derivatives

B. Combining OCF_3-synthons and FARs

The use of FARs proved to be compatible with a number of enolizable carbonyl substrates, such as enols ethers, silyl enol ethers, β-ketoesters, etc. In the case of silyl enol ethers, the reaction between the corresponding enolate and the fluoro iminium salt was extremely efficient and fast.

The two commercially available but prohibitively expensive OCF_3-carbonyl compounds **IV.1a** and **IV.2a** were used in combination with FARs. Their preparation was described in Scheme IV.1, and a multi-gram laboratory scale preparation was recently reported.[43] The objective was to develop conditions to access (similarly to the previous projects) key enaminoketone intermediates, which allowed the preparation of a large variety of unprecedented heterocycles in the other projects already discussed.

1. Preparation of key enaminoketone intermediates

Initially, the objective was to develop the optimal conditions for the preparation of the ORf-enaminoketones from the α-trifluoromethoxy acetophenone **IV.1a**. Afterwards, the possibility to apply the developed conditions to the expensive furyl analogue **IV.2a** was considered (Figure IV.11). The further oxidation of the furyl ring could give access to a highly valuable pyrazole carboxylic acid.

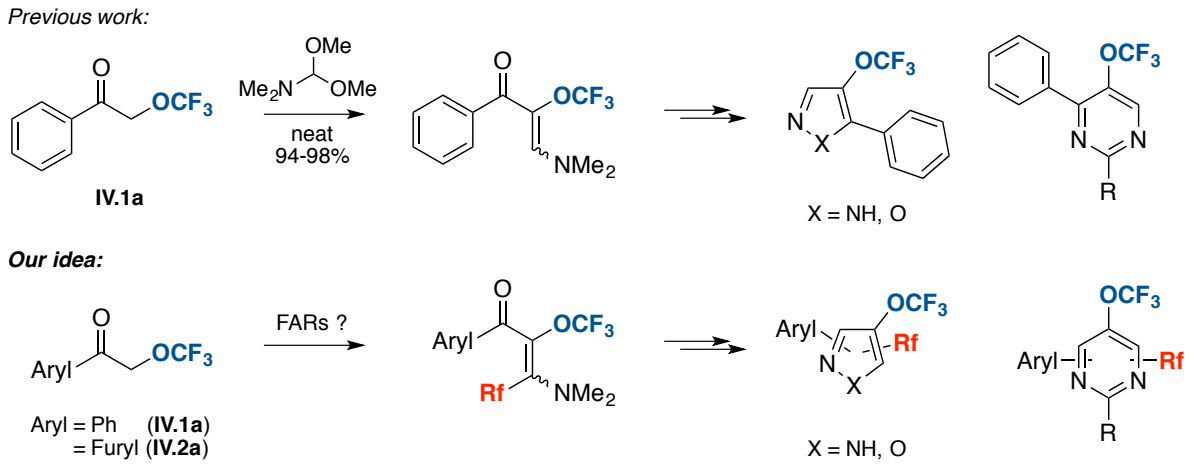
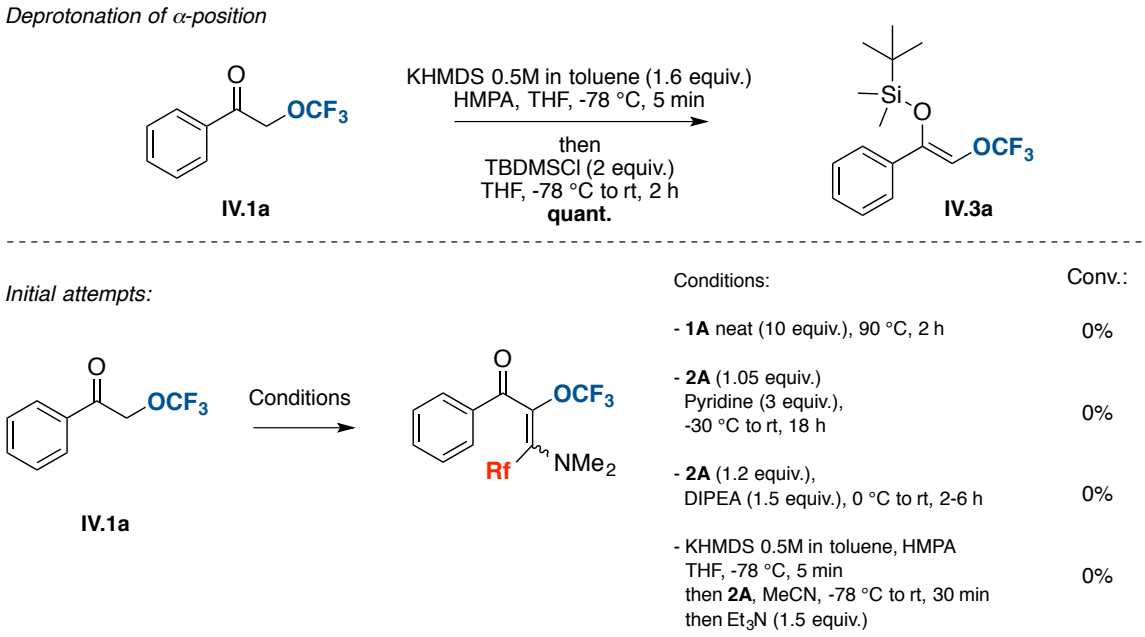


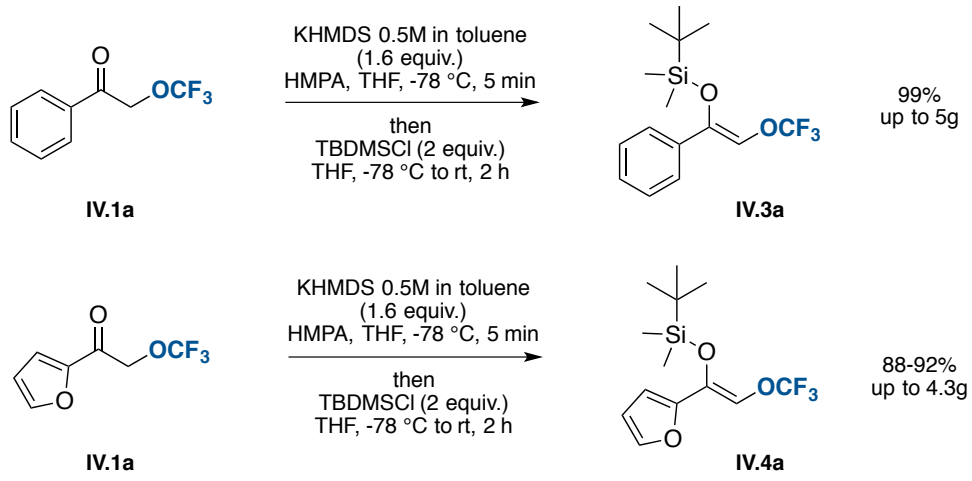
Figure IV.11: Initial project for the preparation of bis(fluoroalkyl) heterocycles

As previously reported by Magnier *et al.*, the OCF_3-acetophenone **IV.1a** possesses a very poorly acidic α-CH_2 position in presence of the OCF_3 group.[42] It was suspected that this substrate would not react similarly to CH-acidic compounds previously used in this manuscript (malonitrile, ethyl cyanoacetate). In the same report, the attempted preparation of the corresponding silyl enol ether using Et_3N as a base failed, whereas the use of KHMDS (and HMPA) followed by enolate trapping with TBDMSCl provided quantitatively the corresponding silyl enol ether (top, Scheme IV.5). To compare these observations with the use of FARs (highly electrophilic species), several experiments were attempted and confirmed the low reactivity of the α-position towards electrophiles. TFEDMA was exclusively used due to the high price of the starting substrate, for reasons previously described (reactivity, purity) (bottom, Scheme IV.5).



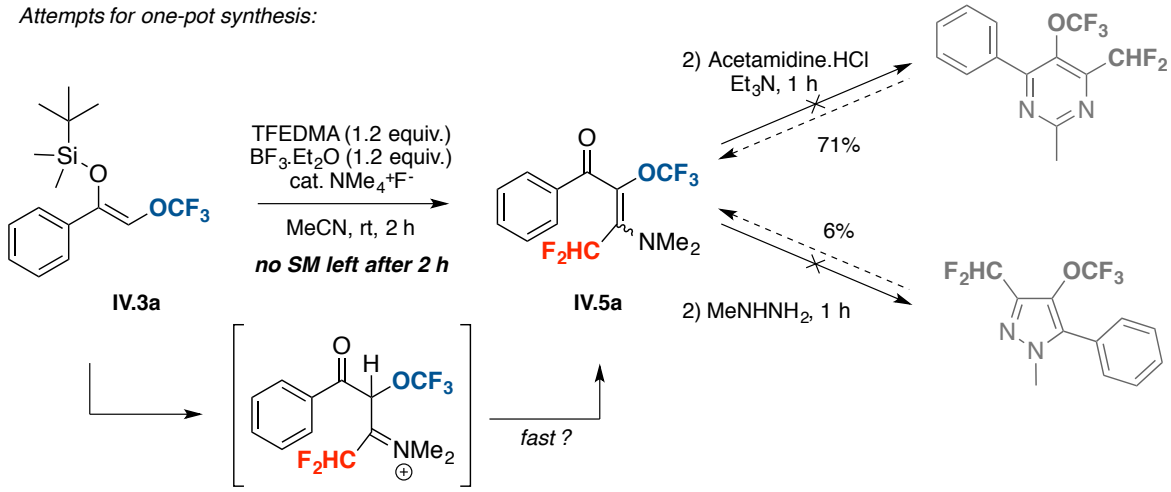
Scheme IV.5: Initial attempt to condense TFEDMA and OCF_3-substrate IV.1a

After these failed attempts, it became clear that the preparation of the known TBS enol ether was a step forward, as the compatibility of TFEDMA with silyl enol ethers was proven in the chapter II. Interestingly, after reproducing the exact same deprotonation conditions, the preparation of the TMS enol ether was not efficient at all, due to the straightforward O-Si bond cleavage observed during silica gel chromatography with the TMS group. We decided to use exclusively the previously described TBS enol ether **IV.3a** as starting substrate for the preparation of the OCF_3-enaminoketone **IV.5a**. The preparation of the furyl analogue **IV.4a** was found to be also very efficient using the same conditions (Scheme IV.6).

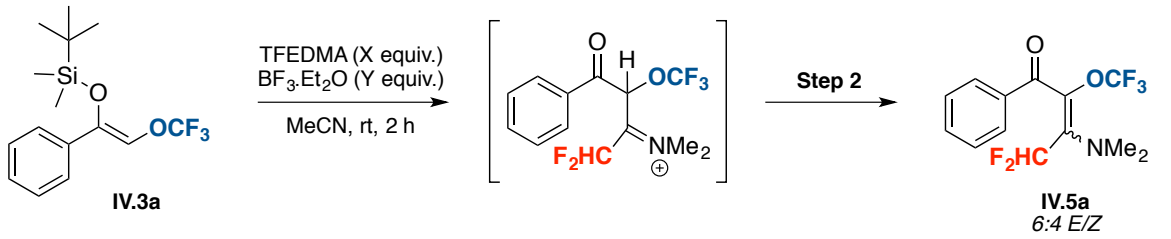


Scheme IV.6: Preparation of phenyl and furyl TBS enol ethers IV.3a and IV.4a

Both silyl enol ethers **IV.3a** and **IV.4a** were usually pure up to 95wt.% after a simple filtration through silica using cyclohexane as a single solvent. As the reactivity study achieved with TFEDMA and silyl enol ethers (Scheme II.11) showed a better outcome after addition of dielectrophiles (hydrazines or hydroxylamine) *in situ* on the preformed keto-fluoroiminium intermediate, this strategy was initially investigated for the preparation of the corresponding pyrazole and pyrimidine. The supposedly *in situ* formed intermediate **IV.5a** was isolated from both experiments with respectively 71% and 6% yields, with no traces of the desired heterocycles (top, Scheme IV.7).



*Conditions' screening for the preparation of **IV.5a**:*



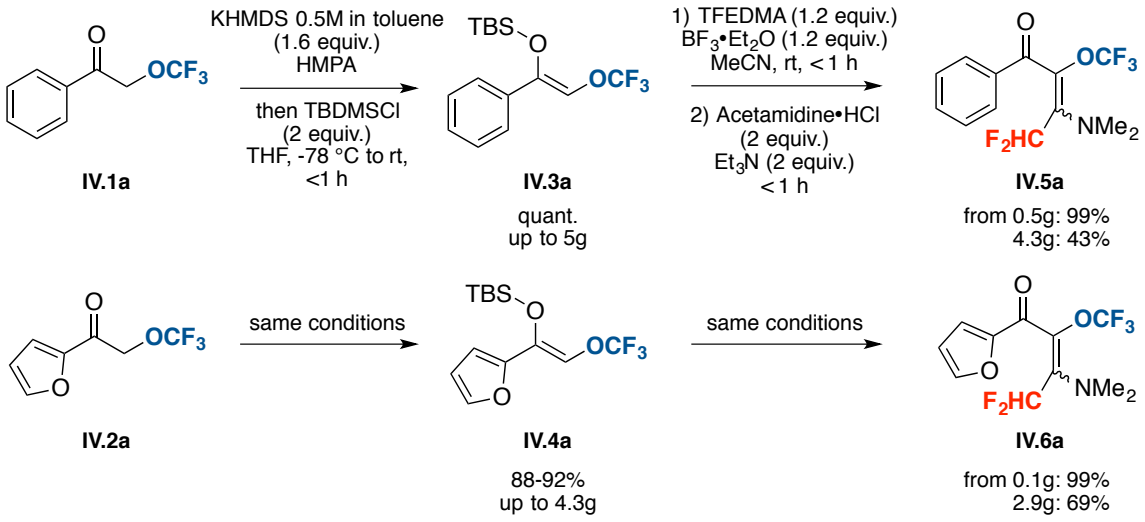
X (equiv.) / Y (equiv.):	Conditions (step 2):	Yield (**IV.5a**):	
1.20 / 1.20	- Acetamidine•HCl (2 equiv.), Et_3N (3 equiv.), rt, 1 h	71%	(300mg scale)
1.25 / 1.25	- $MeNHNH_2$ (1.8 equiv.), rt, 1 h	6%	(400mg scale)
1.25 / 1.25	- Et_3N (1.1 equiv.), rt, 1 h	0%	
1.30 / 1.50	- Acetamidine•HCl (2 equiv.), Et_3N (3 equiv.), rt, 1 h (step 1: 18 h)	98%	(100mg scale)
1.05 / 1.06	- Acetamidine•HCl (2 equiv.), Et_3N (2 equiv.), rt, 1 h (step 1: 18 h)	99%	(500mg scale)
1.05 / 1.05	- Acetamidine•HCl (2 equiv.), Et_3N (2 equiv.), rt, 1 h	56%	(500mg scale)
1.18 / 1.20	- Acetamidine•HCl (2 equiv.), Et_3N (2 equiv.), rt, 1 h	43%	(4.3 g scale)

Scheme IV.7: One-pot reactions providing the intermediate OCF_3-enaminoketone IV.5a (top); screening of conditions for the preparation of the intermediate IV.5a (bottom)

The analysis of the reaction mixture by $^1H/^{19}F$ NMR analyses showed complete consumption of the starting material after the first step. A screening of the optimum conditions was consequently achieved concerning the second step (bottom, Scheme IV.7). Interestingly, no desired product could be isolated in absence of acetamidine hydrochloride (mixed with Et_3N). This combination was suitably providing the product **IV.5a** in excellent yields in some cases.

A general observation is that this reaction depends on several factors, such as the ratio of activated FAR, the ratios of both acetamidine hydrochloride and Et_3N, probably also the temperature, the concentration, etc. One important point is the influence of the scale, as the best yields were obtained with rather small scales, and decreased with larger scale (up to 5g). Another critical aspect is the storage time (less than a few days), which must be short for the use of the silyl enol ether, easily prone to degradation.
Unfortunately, the optimization could not be further developed by lack of time, but it would be interesting to rationalize the effect of each parameter to be able to access quantitatively and reproductively this type of valuable building blocks.

The best conditions were applied to the preparation of the furyl analogue of the OCF_3-enaminoketone **IV.6a**, with similar observations concerning the small storage time required for the TBS enol ether **IV.4a**. Finally, one could access efficiently both enaminoketones **IV.5a** and **IV.6a** with good to excellent yields, with reproducibility issues, especially after modification of the reaction scale. The corresponding products were equally prone to degradation and had to be used rapidly after their preparation (Scheme IV.8).



Scheme IV.8: Summary of results in the preparation of key enaminoketones IV.5a and IV.6a

With these valuable building blocks in hand, the synthesis of heterocycles was attempted, as these yellow oils are unstable upon storage.

2. Synthesis of heterocycles

The synthesis of *N*-based heterocycles was rapidly attempted after the preparation of each enaminoketone. The phenyl analogue **IV.5a** was chosen as model substrate, as its price (*ca.* 700€/g, source: Enamine Ltd.) is lower than the furyl analogue.

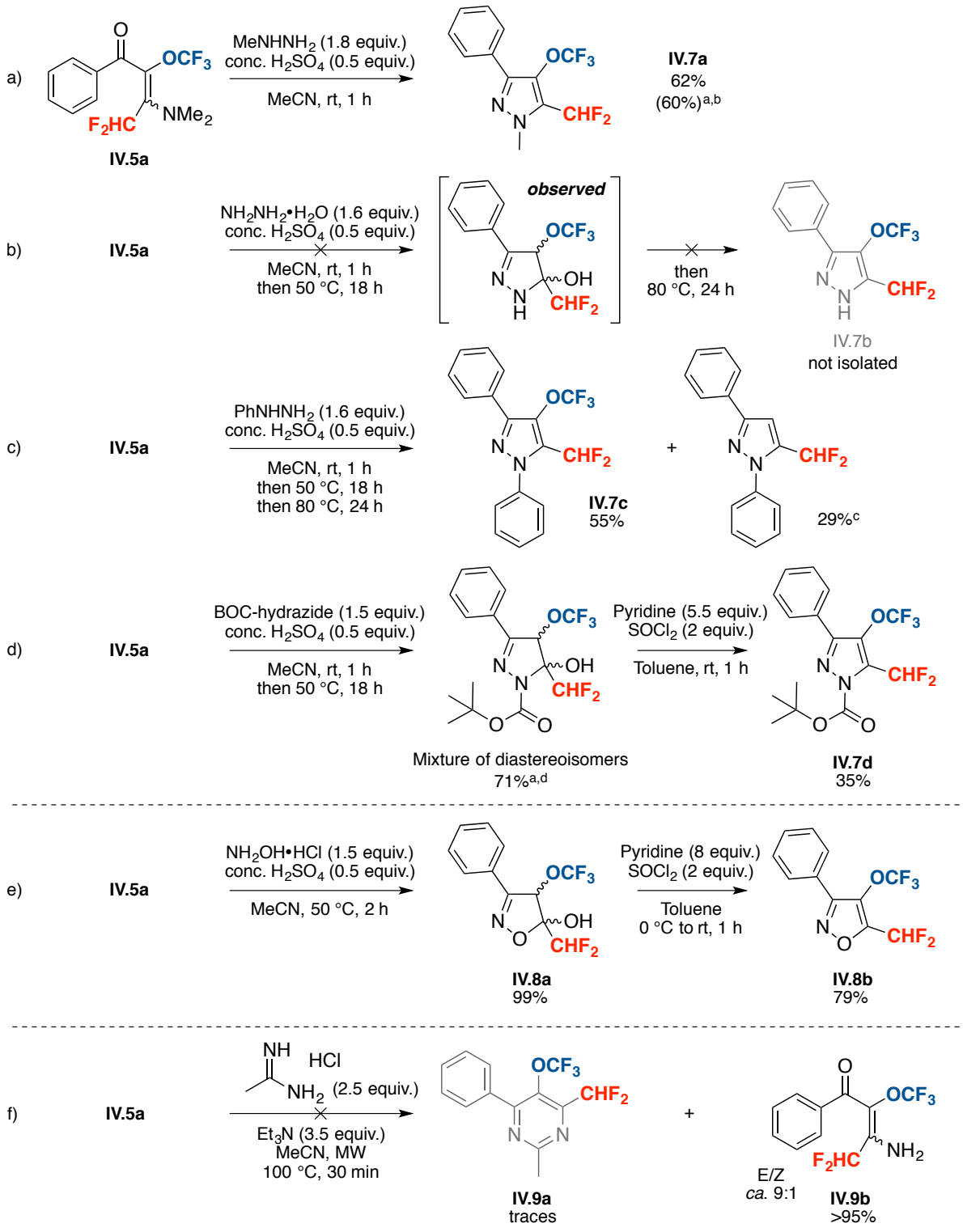
The methyl pyrazole was prepared from enaminoketone **IV.5a** and methyl hydrazine with acidic assistance, to give the methyl pyrazole **IV.7a** with a yield of 62%. A preliminary experiment provided almost equal yield from the silyl enol ether **IV.3a** in a one-pot sequence [a), Scheme IV.9].

However, HMBC experiments showed a reversed regioselectivity compared to the previous results obtained after the addition of methyl hydrazine to bis(fluoroalkyl) enaminoketones (see Chapter II). The electronic and steric influence of a phenyl ring is completely different to the one of a fluoroalkyl group (CF_3, etc.). Consequently, the rationalization of the methyl hydrazine addition is not adapted anymore to this case. The preparation of the *N*H-pyrazole analogue **IV.7b** was attempted but this compound seemed to be quite unstable. The reaction mixture was containing a good proportion of the intermediate pyrazoline, but after 24 h at 80 °C, the product was not isolated [b), Scheme IV.9].
The phenyl pyrazole **IV.7c** was isolated after similar reaction conditions, even though heating was required for the reaction to occur. A non-negligible amount of a side-product resulting from the loss of OCF_3 moiety was isolated. This bis-phenyl difluoromethyl pyrazole is known in the literature [c), Scheme IV.9].[44]

The preparation of *N*-BOC analogue **IV.7d** was slightly more complicated, due to the previously described effect of EWG-groups in the aromatization of 5-fluoroalkyl pyrazoline cores (Figure II.26). Indeed, after complete consumption of the starting enaminoketone, a complex mixture of isomers was isolated (71% measured by ^{19}F NMR analysis) and their separation by silica gel chromatography was very tedious. The different fractions were recombined and the mixture was submitted to dehydration conditions, to access the corresponding *N*-BOC pyrazole **IV.7d** with 35% yield only [d), Scheme IV.9].

The reaction between enaminoketone **IV.5a** and hydroxylamine hydrochloride was very straightforward, and the resulting 5-hydroxy-5-CHF_2-isoxazoline **IV.8a** was isolated quantitatively. Its subsequent treatment with thionyl chloride in toluene in presence of an excess of pyridine (similarly to Scheme II.22) allowed the preparation of an unprecedented bis(fluoroalkyl/alkoxy) isoxazole **IV.8b** with 78% of overall yield. The isoxazolines **IV.8a** provided a single crystal suitable for crystallographic analysis (Figure IV.12) [e), Scheme IV.9].

Finally, the attempts to prepare the bis(fluoroalkyl/alkoxy)pyrimidine **IV.9a** only allowed to observed the desired product as traces, and a side-product similar to previously described examples (Figure III.7) was quantitatively isolated.
One attempt provided an unknown product when using HFIP as the solvent, which was suspected to be the very sensitive desired product. Investigations could be pursued in the challenge of the preparation of such compounds [f), Scheme IV.9]. The side product **IV.9b** has not been fully characterized but its occurrence was consistent with the side-products observed in Figure **III.6-7** in the course of the bis(fluoroalkyl)pyrimidine carboxylate project.



a: ^{19}F NMR yield. b: 1) IV.3a, 2A (1.2 equiv.) cat. $Me_4N^+F^-$, rt, 18 h. 2) $MeNHNH_2$ (1.8 equiv.), rt, 72 h. c: difficult separation by chromatography. d: mixture of diastereoisomers isolated and recombined.

Scheme IV.9: Preparation of unprecedented bis(fluoroalkyl/alkoxy)-3-phenyl pyrazoles IV.7 and isoxazoles IV.8

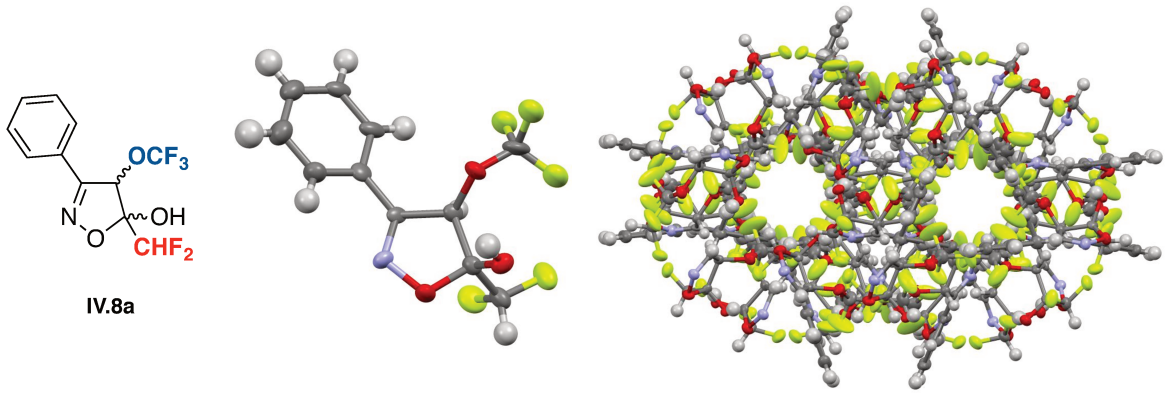


Figure IV.12: Crystallographic analysis of 5-hydroxy-5-CHF_2-isoxazoline IV.8a (left) confirming the regioselectivity observed by HMBC; packing structure along the *c*-axis (right)

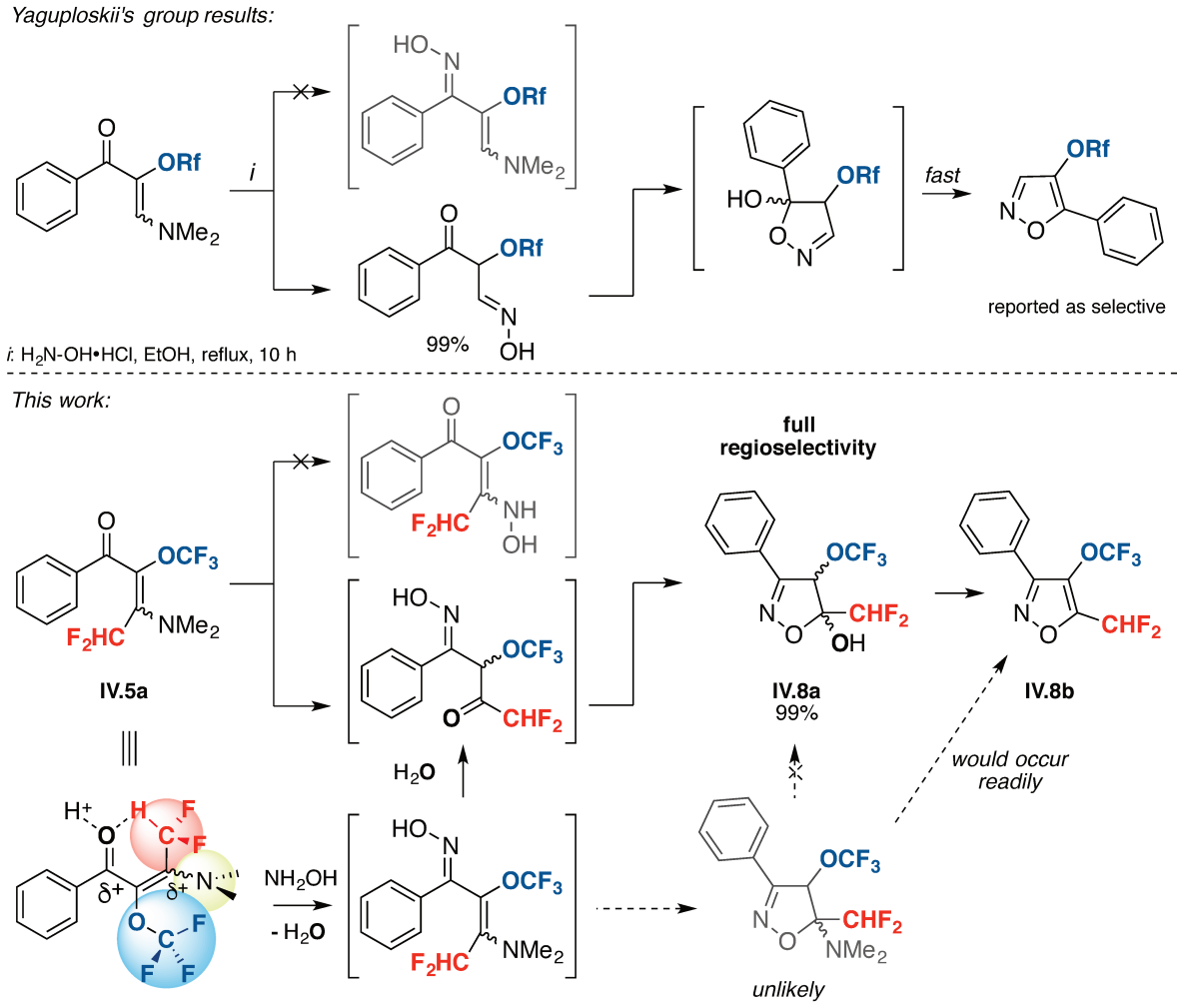


Figure IV.13: Peculiar reactivity of enaminoketone IV.5a

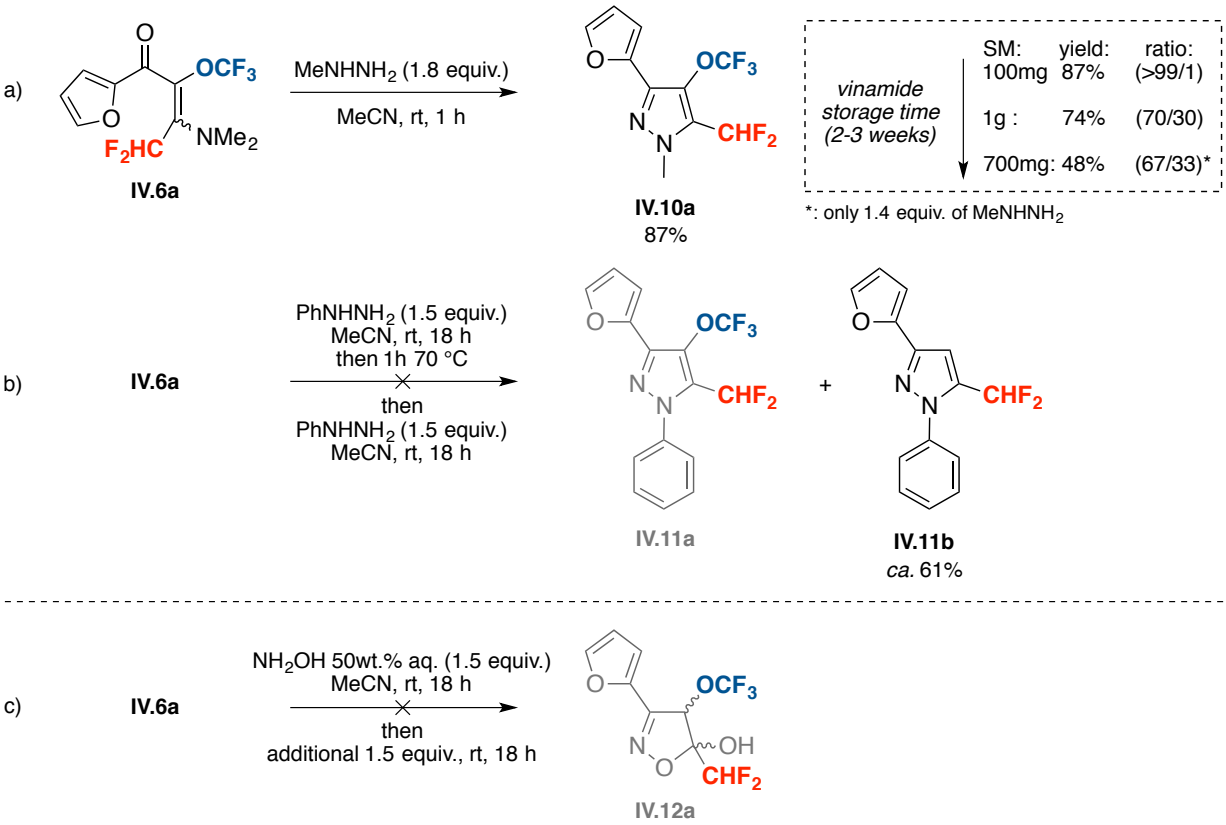
One very confusing point is the regioselectivity observed in the preparation of these unprecedented heterocycles, certified by a structural confirmation by crystallographic analysis.

The only presence of a difluoromethyl group in β-position of the enaminoketone **IV.5a** completely reverses the addition of hydroxylamine, in comparison with the work reported by the Yagupolskii's group. In their report, the controlled oxime synthesis allowed the regioselective preparation of 5-phenyl isoxazole products (Scheme IV.3, Figure IV.13). Their starting enaminoketone only differs from one CHF_2 with the enaminoketone **IV.5a**.
In our case, the presence of the CHF_2 group in addition with OCF_3 and NMe_2 groups in the vicinity of the most electrophilic centre blocks the nucleophilic attack of NH_2 group of hydroxylamine. However, under acidic conditions the aryl carbonyl group can be activated, and its electrophilicity becomes sufficient to undergo the nucleophilic attack. In addition, H-bonding can be considered from the CHF_2 group to increase this activation phenomenon.

The resulting enaminoketone oxime could potentially form the expected isoxazoline core, but this hypothesis is very unlikely occurring as the resulting isoxazoline would convert very readily to the isoxazole **IV.8b**. To illustrate this, the synthesis of bis(fluoroalkyl)pyrazole and isoxazole carboxylates (achieved by G. Landelle and discussed in Scheme II.7) never produced any pyrazoline or isoxazoline compounds, proving their rapid aromatization. The most probable pathway involves the hydrolysis of the fluoroalkyl enamine moiety after the formation of the oxime. The resulting enol can tautomerize to allow the isoxazoline ring formation from the fluoroalkyl ketone moiety, explaining the presence of a stabilizing hydroxyl group in position 5 in absence of water in the media. The configurational stability (demonstrated by the formation of a single crystal of the product **IV.8a**) could also be crucial to shift the equilibrium of this reaction.
An opposite conclusion was made after the attempt to prepare a pyrimidine example [f, Scheme IV.9]. Under basic conditions, the side-product quantitatively isolated was probably formed *via* nucleophilic attack of acetamidine. Indeed, without acidic assistance the reactivity of the aryl carbonyl moiety is not sufficient, and the reaction was forced to occur under microwave irradiation. The resulting enoyl acetimidamide was degraded by solvolysis (similarly to Figure III.7) to yield the side-product **IV.9b**.
All these observations could be complemented by further investigations to understand the properties of such OCF_3-substituted enaminoketones bearing additional fluoroalkyl groups under acidic or basic conditions.

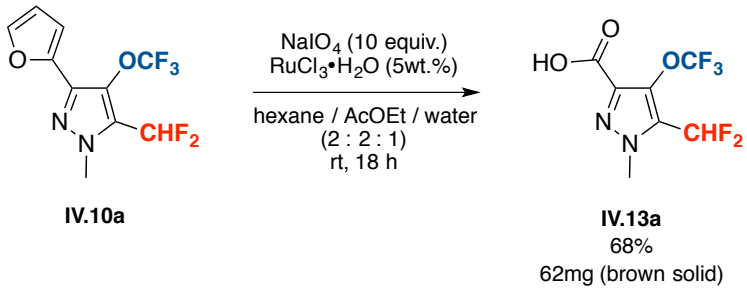
After the successful preparation of these heterocyclic building blocks with an unexpected regioselectivity, an even more challenging objective was to apply this strategy to the preparation of furyl analogues, in the perspective of the oxidation of the furan ring to provide highly attractive carboxylic acid analogues.
The methyl pyrazole **IV.10a** was efficiently prepared in a small-scale reaction (100mg) with an excellent yield of 87%. However, when a larger scale reaction was attempted, the results were lower. Indeed, both reaction scale and storage time of the starting enaminoketone **IV.6a** seems to have a great influence on the outcome of this reaction. The regioselectivity of the hydrazine addition seems equally impacted by these two parameters. This observation would also deserve further investigation in order to achieved reproducible and highly efficient synthesis of such valuable products.
The attempt to prepare the *N*-phenyl analogue **IV.11a** provided a major amount of reduced pyrazole **IV.11b** with *ca.* 61% yield but was difficult to purify from several other minor side-products. This phenomenon was not rationalized so far (Scheme IV.10). The attempt to prepare the isoxazole **IV.12a** showed only traces of the desired compound.

The oxidative degradation of 3-furyl pyrazole **IV.10a** was attempted on small-scale, by reproducing reaction conditions previously reported in a patent from S. Pazenok *et al* (Bayer CropScience, Monheim).[39]

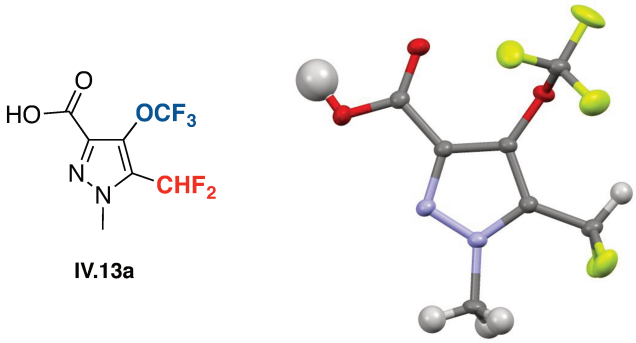


Scheme IV.10: Preparation of 3-furyl analogues using the furyl enaminoketone IV.6a

The small-scale reaction provided the first example of pyrazole carboxylic acid **IV.13a** bearing OCF_3 and CHF_2 substituents, and the compound formed a single crystal suitable for a crystallographic analysis useful in the confirmation of the regioselectivity observed by HMBC NMR experiment (Figure IV.14, Scheme IV.11).



Scheme IV.11: Oxidative degradation of furan ring to access the unprecedented pyrazole-3-carboxylic acid IV.13a



IV.13a

Figure IV.14: Crystallographic analysis of a single crystal of unprecedented 4-OCF_3-5-CHF_2-pyrazole-3-carboxylic acid IV.13a

The outcome from the preparation of furyl analogues (Scheme IV.10) is not comparable to the phenyl series (Scheme IV.9), probably due to a higher sensitivity of the furan ring, and its proximity with the very peculiar OCF_3 group. Interestingly, the use of acidic assistance was not compatible with the preparation of the furyl analogue **IV.10a** and led to degradation. Other precursors of carboxylic acids could be investigated to overcome this difficulty.

These results are completing the work of the Yagupolskii's group with bis-substituted pyrazole products. It would be interesting to improve several results, and to access pyrimidine analogues.

C. Conclusion

The preparation of pyrazoles bearing α-fluoroethers (especially the OCF_3 group) is very scarcely reported in the literature and remains a synthetic challenge. After completing the synthesis of diverse mono- and bis-fluoroalkyl pyrazoles, isoxazoles and pyrimidines in the previous chapters, we decided to attempt the preparation of *N*-based heterocycles bearing this peculiar motif.

For this purpose, we decided to use OCF_3-synthons, whose preparation was well optimized over the last years, even though the starting substrates remain prohibitively expensive. The strategy chosen was to prepare key enamino intermediates (similarly to previous chapters) from the corresponding OCF_3-acetophenones to allow a divergent access to heterocycles. The phenyl analogue was used to develop suitable reaction conditions, but the direct conversion from the OCF_3-acetophenone **IV.1a** to the corresponding enaminoketone **IV.5a** was not possible using our conditions, due to a low acidity of the reactive methylene position (Figure IV.15).
The quantitative conversion to the previously reported TBS-enol ether **IV.3a** (by means of a strong base) was performed to access an equivalent of protected enolate; similar species proved to be compatible with the use of activated FARs in the previous chapters. Fortunately, we could optimize the reaction conditions to isolate the desired intermediate with moderate to excellent yields. This reaction showed a high sensitivity towards the reaction conditions, the purity of all reagents, etc. The yield seemed to be scale-dependant, and more efforts could be achieved to render this step reproducible and robust (Figure IV.15).

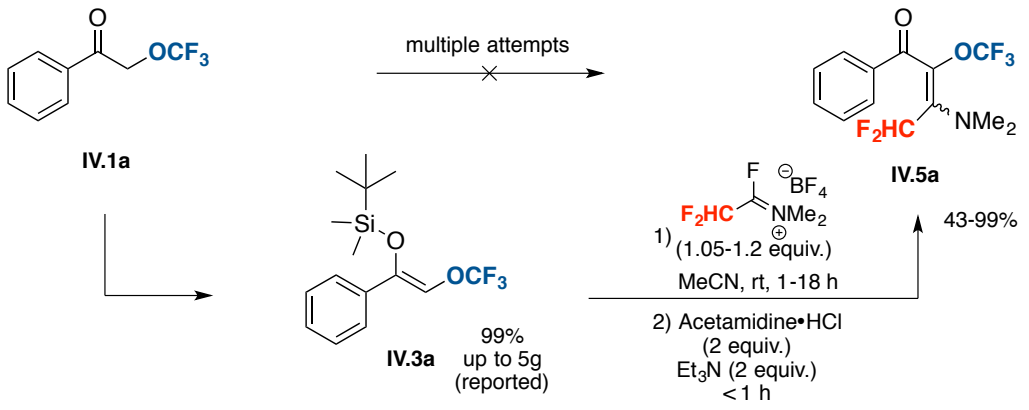


Figure IV.15: Preparation of the key enaminoketone intermediate IV.5a *via* the TBS-enol ether IV.3a

The key intermediate **IV.5a** was used to prepare a series of corresponding heterocycles bearing the OCF_3 group adjacent to the CHF_2 group (from TFEDMA). This can potentially be extended to other FARs (for the introduction of -CHFCl, -$CHFCF_3$, -$CHFOCF_3$).

The preparation of the *N*-methyl pyrazole **IV.7a** and the *N*-phenyl pyrazole **IV.7b** were achieved in one step using acidic assistance. In the case of the phenyl pyrazole, a fraction containing the reduced pyrazole (with hydrogen in position 4) was isolated (29%). The *N*-BOC pyrazole was isolated in two steps; the pyrazole ring formation led initially to a mixture of diastereoisomers of the corresponding pyrazoline (due to the presence of the *N*-BOC group, as discussed in Figure II.26). The subsequent dehydration of this mixture led to the desired *N*-BOC pyrazole, with a moderate overall yield. The *in situ* dehydration could improve this result. Similarly, the isoxazoline **IV.8a** was very rapidly formed and provided crystallographic analysis for the confirmation of the regioselectivity obtained. A dehydration step provided efficiently the desired isoxazole (Figure IV.16).

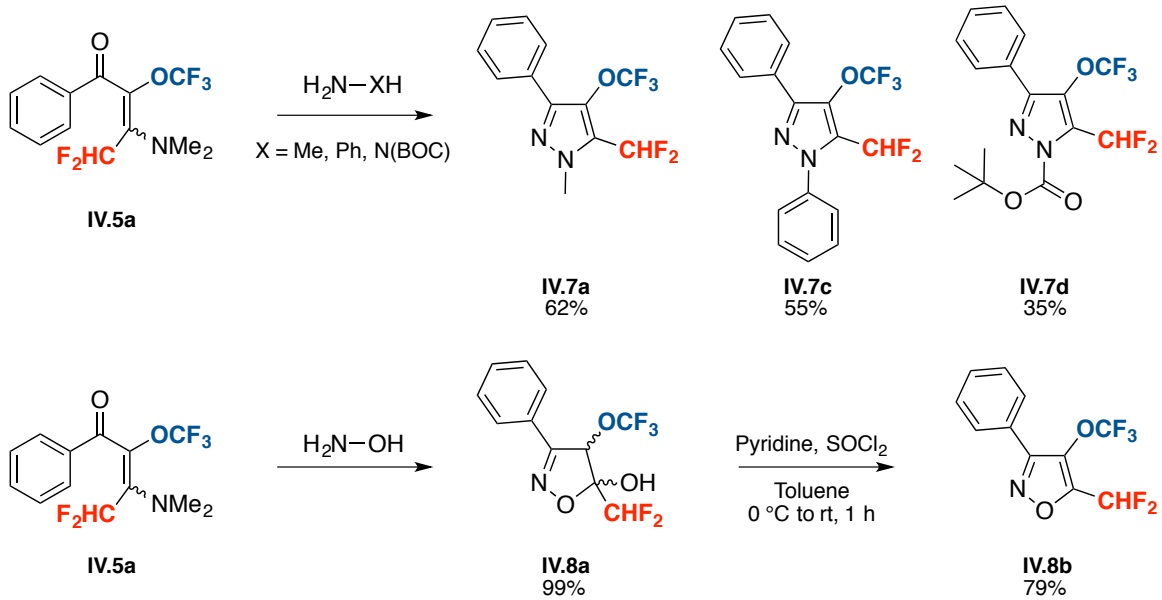
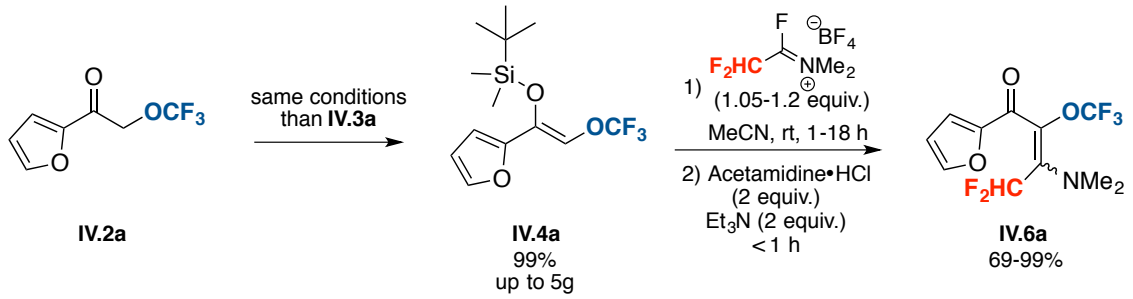


Figure IV.16: Preparation of 4-OCF_3-5-CHF_2-pyrazoles, isoxazoline and isoxazole from the intermediate IV.5a

After having successfully prepared this series of heterocycles bearing two adjacent fluorinated groups, we decided to apply the same strategy to the furyl analogue **IV.2a**, in order to attempt the preparation of a challenging carboxylic acid example.

The preparation of the key intermediate was achieved similarly with comparable results (Figure IV.17).



IV.2a

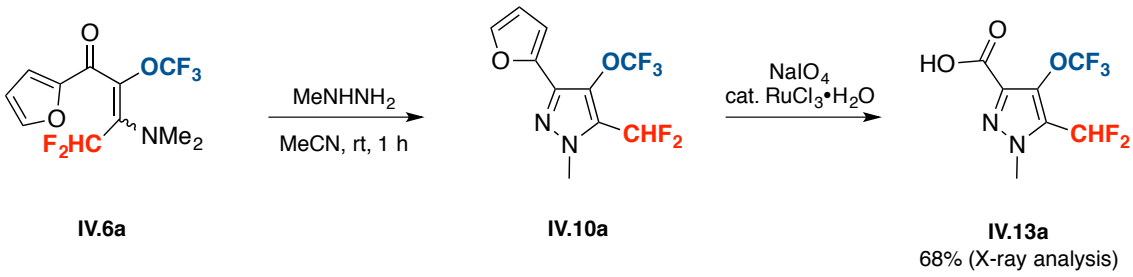
IV.4a
99%
up to 5g

IV.6a
69-99%

Figure IV.17: Preparation of the furyl key intermediate IV.6a from IV.2a *via* the TBS enol ether IV.4a

The intermediate **IV.6a** was used in the preparation of the corresponding 3-furyl heterocycles. The outcome of these experiments was different. The only example isolated was the *N*-methyl pyrazole **IV.10a** in absence of any acidic or basic assistance (Figure IV.18).

The *N*-phenyl analogue could not be isolated and only observed as a trace. The major product from this experiment was the reduced pyrazole (hydrogen in position 4). The attempt to prepare an isoxazole or isoxazoline analogue failed.
Similarly, several attempts to prepare a pyrimidine example in either phenyl or furyl series failed to provide the desired product. The resulting products could not be fully characterized, and this objective remains a challenge.



IV.6a

IV.10a

IV.13a
68% (X-ray analysis)

Figure IV.18: Preparation of the N-methyl pyrazole IV.10a and oxidative degradation of the furan ring to access the carboxylic acid IV.13

The pyrazole-3-carboxylic acid **IV.13a** provided a single crystal confirming the structure after crystallographic analysis (Figure IV.14).

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General Conclusion
&
Perspectives

Organofluorine chemistry has become an important field with numerous applications in the development of new compounds, relevant in pharmaceutical research and more importantly in agrochemistry. Companies have been developing fluorinated agrophores for decades, but the introduction of emergent fluorinated groups into aromatic and heteroaromatic structures led to a new breath in the field.
Up to a half of the most recently marketed agrochemicals contain fluorine, and a non-negligible part of it contain emergent fluorinated substituents. However, the lack of synthetic techniques for the introduction of these new fluorinated groups slows down the process of development of new bioactive molecules (see Chapter I).

In this PhD project, we decided to pursue the previous efforts achieved in our group for the introduction of EFSs into various structures, which led to the innovative synthesis of 3,5-bis(fluoroalkyl)pyrazole carboxylates or trifluoromethoxy pyridines. The objective was to develop new approaches to give an access to novel fluorinated building blocks. *N*-Based heterocycles such as pyrazoles, isoxazoles, pyridines, pyrimidines, etc. were targeted (Figure C.1). For this purpose, we were interested in the use of fluoroalkyl amino reagents (or FARs), a family of reagents prepared from bulk chemicals (perfluorinated alkenes and secondary amines). These reagents have been used previously in our group, but in limited applications. However, they offer an interesting reactivity once activated using a Lewis acid. These reagents are also potentially compatible with industrial applications, as demonstrated by the use of TFEDMA (or Petrov reagent) in the preparation of a key intermediate of Bixafen (a marketed SDHI fungicide from Bayer CropScience).

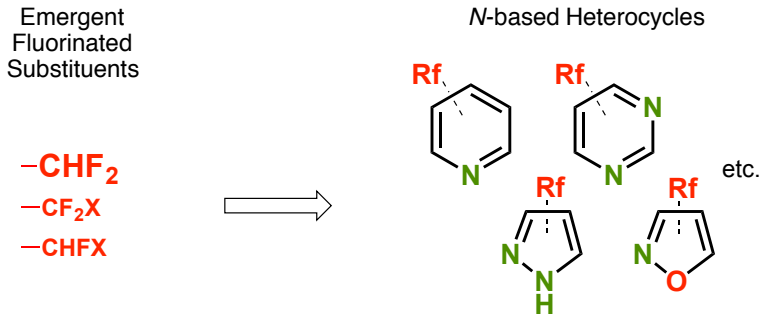


Figure C.1: Introduction of EFSs into *N*-based heterocycles as a general objective of the PhD project

In the Chapter II, the importance of fluoroalkyl pyrazoles has been discussed in the context of SDHI fungicides, a fast-developing area where these fluorinated building blocks have demonstrated a critical impact. After the recent entry on the market of a series of SDHI fungicides containing a 3-CHF_2-pyrazole core, the interest for 3,5-bis(fluoroalkyl)pyrazoles was growing. The currently limited synthetic approaches for the introduction of EFSs into pyrazoles was outlined, and the development of new synthetic strategies to access these innovative structures was consequently defined as a central objective of this PhD project, which could be reached by means of the use of FARs.
In order to achieve this objective, it was important to develop the knowledge concerning the use of FARs in the synthesis of fluorinated heterocycles. A model FAR (the TFEDMA) was defined and a study of its reactivity with various substrates was performed. This FAR enabled the facile preparation of various difluoromethylated heterocycles, but also of difluoroacylated heterocycles and arenes. A regioselective approach was also developed using a halide/metal exchange approach (Figure C.2). This study was recently summarized in an article recently published:

Schmitt, E.; Rugeri, B.; Panossian, A.; Vors, J. P.; Pazenok, S.; Leroux, F. R. *Org. Lett.* **2015,** *17*, 4510-4513.

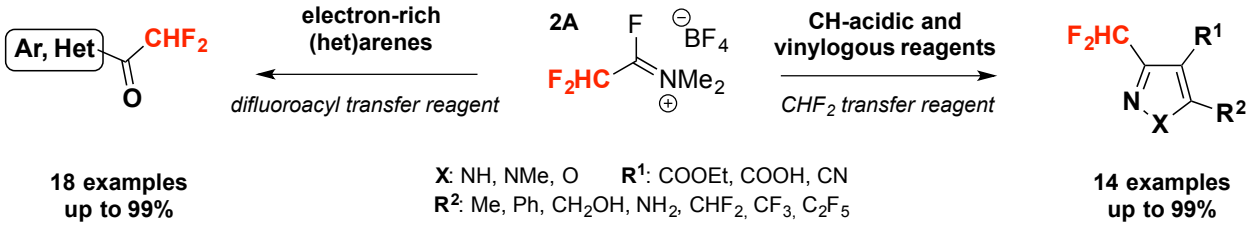


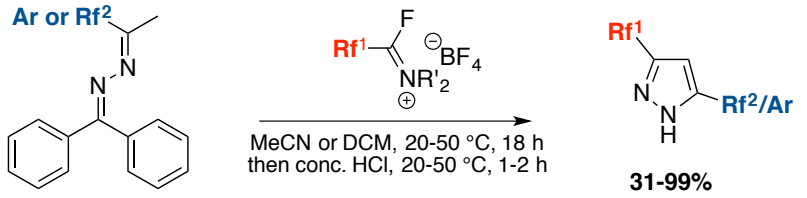
Figure C.2: Use of TFEDMA as a difluoromethylation or difluoroacylation reagent

At this point, we developed a procedure for the preparation of a new FAR *via* hydroamination of liquefied perfluoromethyl perfluorovinyl ether. The *in situ* activation of the resulting FAR allowed the preparation of the corresponding fluoro iminium salt with 85% yield. This procedure was filed into a patent:

F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing substituted pyrazoles containing haloalkoxy-haloalkyl- and haloalkylthio-haloalkyl groups from α,α-dihaloalkylamines and ketimines, *BCS153048* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 24/06/2015).

As previously mentioned, the preparation of 3,5-bis(fluoroalkyl)pyrazole-4-carboxylates was previously reported in our group, but this approach was limited to *N*-functionalized pyrazole-4-carboxylates. The saponification and subsequent decarboxylation of these products was tedious, and the access to decarboxylated *N*H-pyrazoles was not possible. Consequently, we decided to develop a new approach to access 3,5-bis(fluoroalkyl)-pyrazole building blocks *via* a more efficient strategy. We successfully developed a method to access novel 3,5-bis(fluoroalkyl)-N*H*-pyrazoles, based on the use of fluorinated azines. This approach was named the "azine route" and was recently published:

Schmitt, E.; Landelle, G.; Vors, J.-P.; Lui, N.; Pazenok, S.; Leroux, F. R. *Eur. J. Org. Chem.* **2015**, 6052-6060.



Rf1 = CHF_2, CHFCl, $CHFCF_3$
Rf2 = CH_2F, CHF_2, CF_3, CHFCl, C_2F_5 Ar = C_6H_4F, $C_6H_4(CF_3)$, $C_6H_4F_2$, $C_6H_3(CF_3)_2$

Figure C.3: Preparation of novel 3,5-bis(fluoroalkyl)-N*H*-pyrazoles using the azine route

This approach presented drawbacks such as the use of benzophenone, difficult to remove from the sensitive bis(fluoroalkyl)-*N*H-pyrazoles at the end of the synthesis. An alternative approach was developed using fluorinated ketimines and FARs. The developed method provided in a short reaction time highly substituted bis(fluoroalkyl)pyrazole building blocks from simple chemicals; depending on the method, both possible pyrazole regioisomers were accessible either highly regioselectively or with full regioselectivity. The functionalization of the position 4 of bis(CHF_2)-pyrazole (model substrate) derivatives was also studied and a broad scope of functional groups have been introduced (Figure C.4).

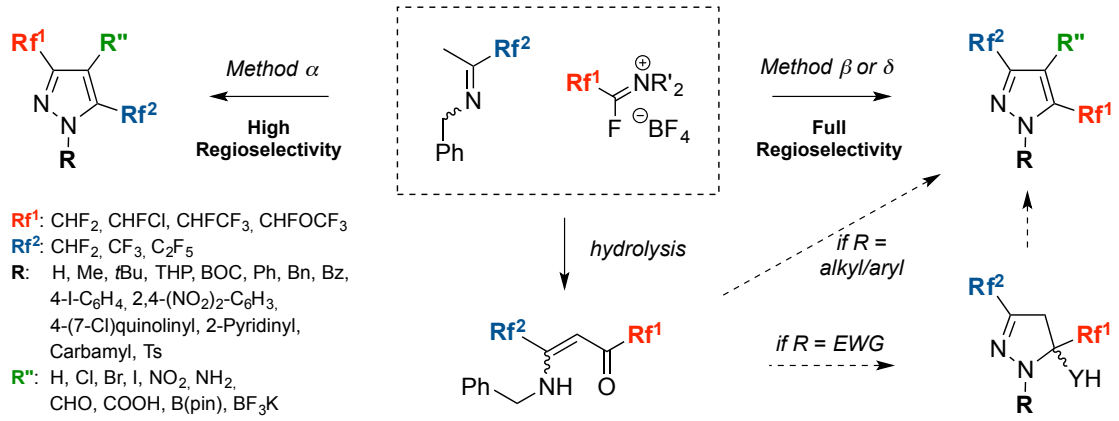


Figure C.4: Summary of the Ketimine route results

The rationalization of the regioselectivity observed was attempted, with the help of computational calculations (Dr. P. Genix, Bayer CropScience, Lyon). The attack of the NH_2 group of methyl hydrazine was favourably considered for both methods, due to energetically more favourable pathways. These results were recently published and the article was accepted as inside back cover in the corresponding issue:

« A Major Advance in the Synthesis of Fluoroalkyl Pyrazoles: Tuneable Regioselectivity and Broad Substitution Patterns », E. Schmitt, A. Panossian, J.-P. Vors, C. Funke, N. Lui, S. Pazenok, F. R. Leroux, *Chem. Eur. J.* **2016**, *22*, 11239-11244.

The new FAR has been employed in a similar study than previously described with TFEDMA. The preparation of the key adducts was less efficient despite a similar reactivity of both FARs. The preparation of the pyrazoles and isoxazoles was almost equally efficient (Figure C.5).

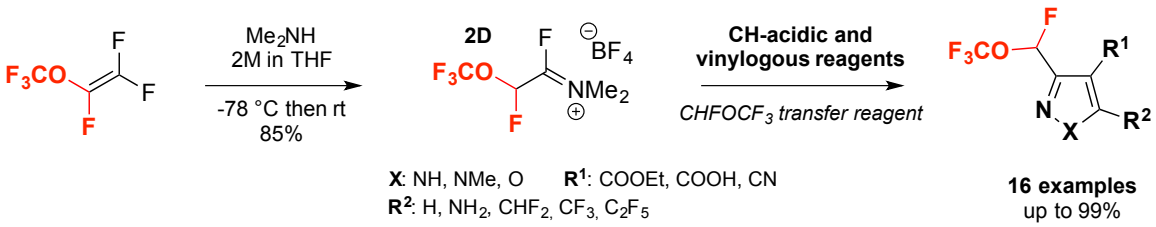


Figure C.5: Preparation of novel 3-CHFOCF3-pyrazoles and isoxazoles derivatives

Finally, the preparation of mono- and bis-fluoroalkyl pyrazoles was achieved using more accessible reagents than FARs (anhydrides, oxoacetates) (Figure C.6). This approach was very efficient for the preparation of bis(fluoroalkyl)-pyrazoles, and the preparation of mono(fluoroalkyl)pyrazole-5-carboxylates was recently filed in a patent:

F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates and 3- fluoroalkyl-5-pyrazolecarboxylic acids, *BCS163094* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 13/09/2016).

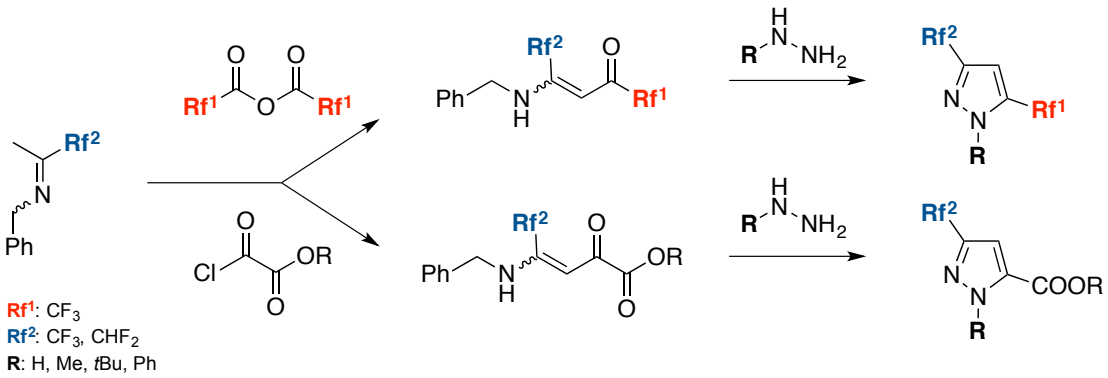


Figure C.6: Preparation of mono- and –bis(fluoroalkyl) pyrazole building blocks without FARs

In the Chapter III, the interest for fluoroalkyl pyrimidines has been detailed, with the recent development of agrophores or pharmacophores based on the fluoroalkyl pyrimidine core. After a summary of the limited approaches for the synthesis of pyrimidines bearing EFSs, the development of a new approach to access fluoroalkyl pyrimidines was defined as an objective of this PhD project. Once again, the use of FARs was considered to complete this objective, regarding the previous results obtained in the synthesis of pyrazoles. As the reports describing the preparation of bis(fluoroalkyl)pyrimidines are almost non-existing, we decided to attempt their preparation using a similar approach than previously described.
The preparation of key bis(fluoroalkyl)-α-aminoalkylidene-β-ketoester intermediates was successfully achieved using fluorinated acetoacetates and FARs. These intermediates were isolated using simple filtration through Celite® followed by an azeotropic distillation in toluene with high yields and purities (Figure C.7).

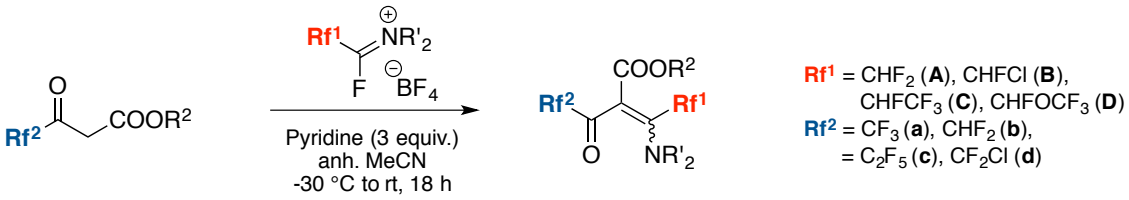


Figure C.7: Preparation of key bis(fluoroalkyl)-α-aminoalkylidene-β-ketoester intermediates

With this set of key intermediates and a variety of amidines, a large variety of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates was prepared, and their corresponding carboxylic acids analogues were accessed *via* saponification reactions. Symmetrical or unsymmetrical pyrimidine carboxylates and carboxylic acids were prepared with moderate to excellent yields (Figure C.8). These results will be submitted for publication in due course.

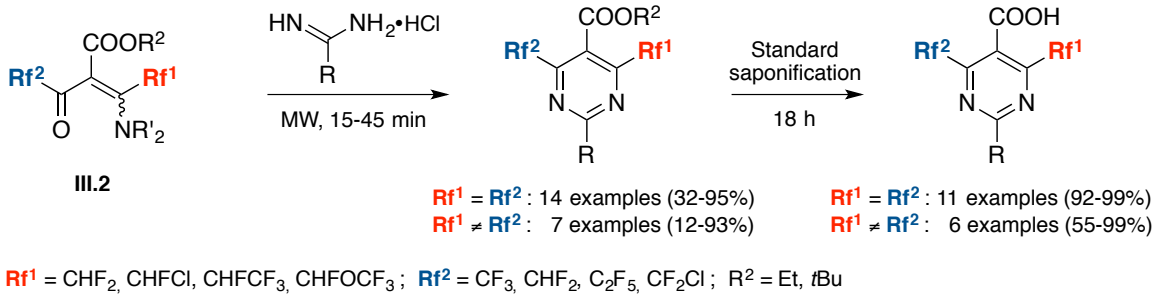


Figure C.8: Summary of the results for the preparation of innovative bis(fluoroalkyl)pyrimidine derivatives

The preparation of mono(fluoroalkyl)pyrimidine derivatives was attempted, and a first example was prepared. This strategy is currently under investigation to determine the possible scope of application and the potential of the resulting pyrimidines in further transfortmations (Figure C.9).

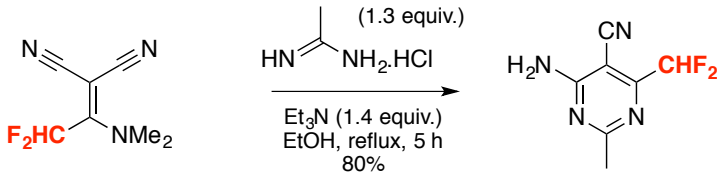


Figure C.9: Preparation of a first example of mono(fluoroalkyl)pyrimidine derivative from FARs

During the course of this project, interesting and unexpected products were isolated, and would deserve more focus. The highly functionalized cyclobutene were isolated in high yields and were surprisingly stable. The structural confirmation was helped by crystallographic analysis. This topic is of high interest in the perspective of developing new pharmacophores and agrophores containing fluorinated substituents (Figure C.10).

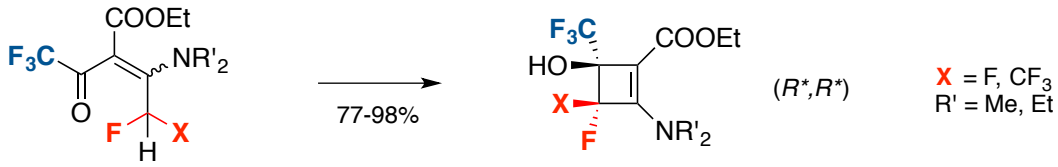


Figure C.10: Preparation of novel highly functionalized cyclobutene products

Finally, the concept of vinylogous FAR was developed, and a procedure was developed for the preparation of perfluorobutyl enamine. The *in situ* preparation of the vinylogous FAR, its activation using a Lewis acid, its condensation with ethyl *N*,*N*-dimethylaminoacrylate and the subsequent cyclisation after addition of ammonia was achieved in one-pot. A novel perfluoropropyl nicotinic ester product was isolated in 38% yield, and the following saponification provided 4-perfluoropropyl nicotinic acid quantitatively (Figure C.11).

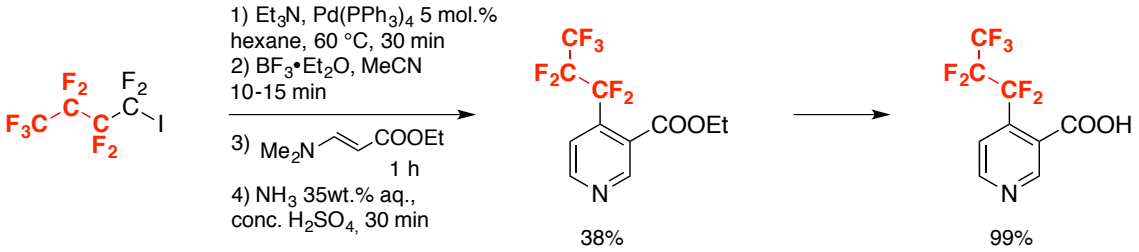


Figure C.11: Innovative one-pot procedure providing 4-perfluoropropyl nicotinic acid

In the Chapter IV, the interest for the preparation of *N*-based heterocycles bearing α-fluoroethers was described, and illustrated by many examples of compounds bearing such groups in pharmaceutical and agrochemical research, which are currently on the market and proved their efficacy in biological systems. The peculiar properties of α-fluoroalkyl groups have been highlighted, especially for the OCF_3 group. The limited strategies for the introduction of the OCF_3 group was also discussed, especially its introduction into heterocycles such as pyrazoles.

Consequently, we were interested in the development of a new approach to prepared new pyrazole products bearing OCF_3 groups. For this purpose, we decided to use available OCF_3-synthons and FARs to prepare novel pyrazole building blocks bearing both OCF_3 and fluoroalkyl substituents.

The preparation of key enaminoketones was achieved *via* the use of silyl enol ethers previously described in the literature, as this type of substrate demonstrated good compatibility with the use of FARs. The corresponding enaminoketones were efficiently prepared but were found to be highly sensitive (Figure C.12).

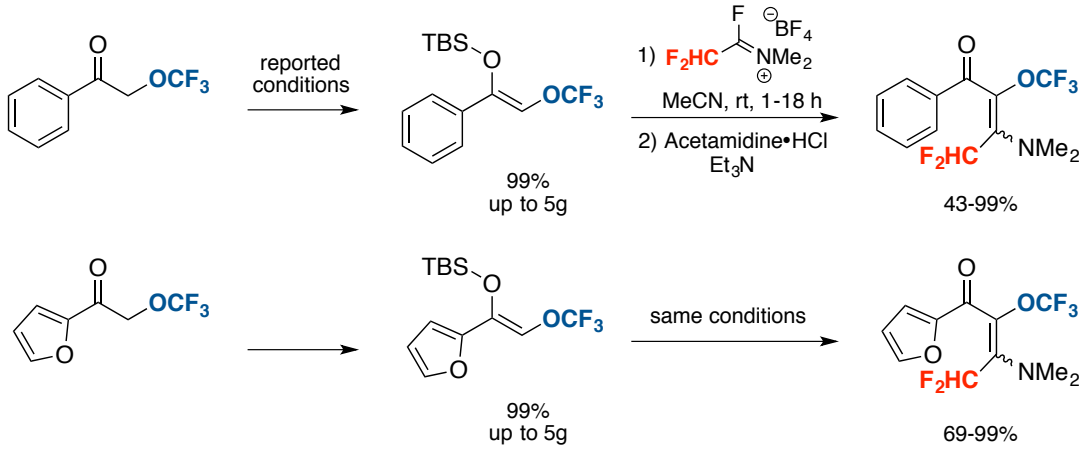


Figure C.12: Preparation of key vinamide intermediates from OCF_3-ketones

These key intermediates were used in the synthesis of OCF_3-heterocycles with a reversed selectivity of the hydrazine addition, in comparison with previously described projects. This aspect was confirmed by crystallographic analysis of one isoxazoline intermediate, but could not be rationalized so far. Several examples of novel OCF_3-substituted heterocycles were prepared in phenyl series. However, the furyl series showed much lower efficiency and only one pyrazole example was prepared (Figure C.13).

This product was converted into the corresponding pyrazole-3-carboxylic acid *via* oxidative degradation of the furan ring, using a reported procedure. The structure of the corresponding product was confirmed by crystallographic analysis (Figure C.14).

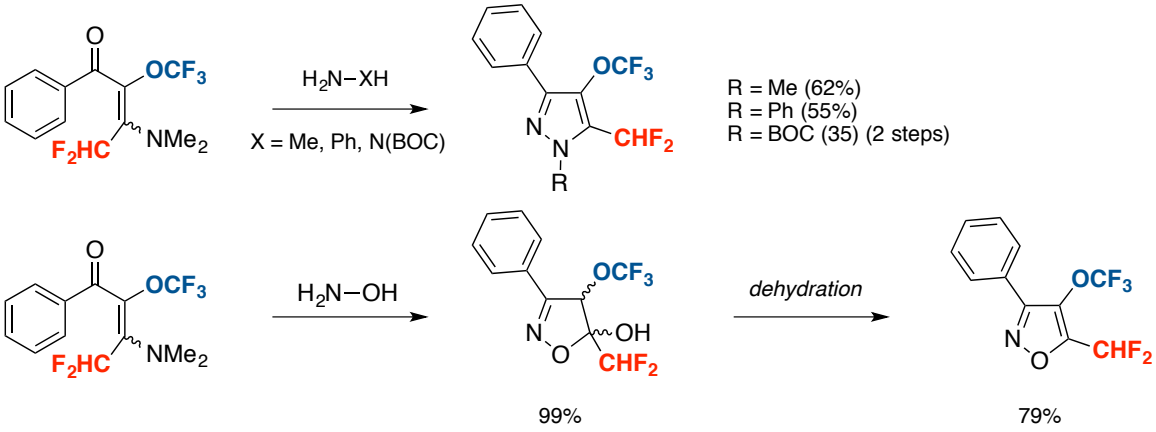


Figure C.13: Preparation of novel pyrazole and isoxazole building blocks bearing OCF_3 and CHF_2 groups

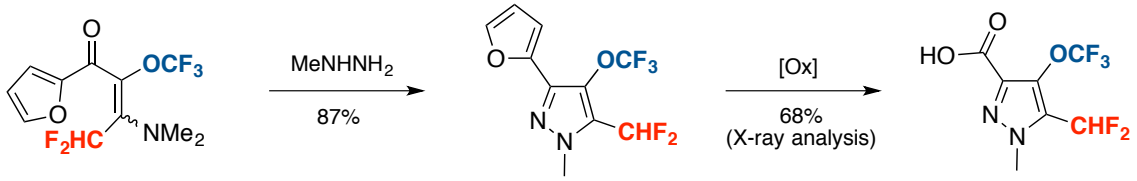


Figure C.14: First access to a pyrazole-3-carboxylic acid bearing both OCF_3 and CHF_2 groups in adjacent positions

PERSPECTIVES

As demonstrated along this manuscript, the potential of FARs is large in the perspective of introducing emergent fluorinated substituents into various aromatic and heterocyclic compounds. The development of new FARs is certainly a promising research field, which could facilitate the discovery of active ingredients in pharmaceutical and agrochemical research.

The use of other (per)fluorinated alkenes could lead to the development of new FARs allowing the introduction of more fluorinated substituents. The procedure using liquefied gases could be useful in this topic (Figure C.15).

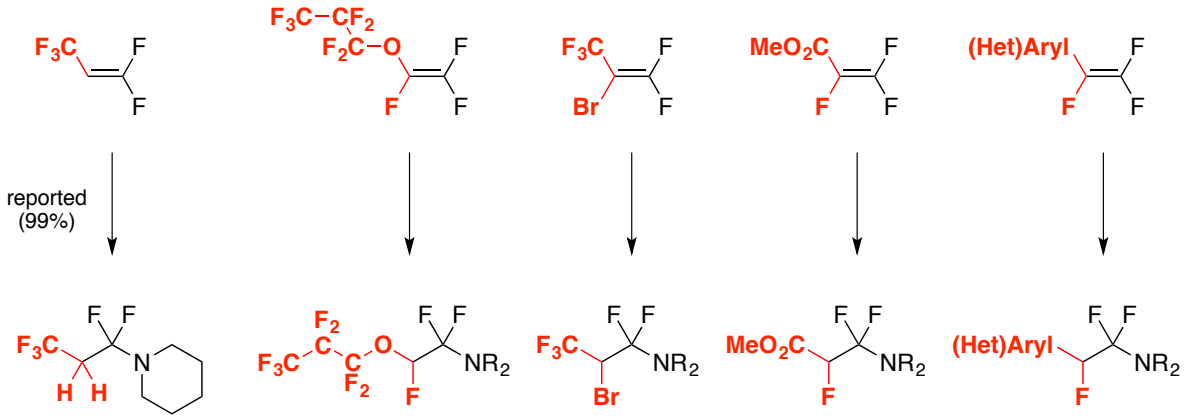


Figure C.15: Potential FARs prepared from commercial sources

Beside the development of new FARs, other perspectives can be developed. Vinamides intermediates presented in this manuscript could certainly be employed for the preparation of novel fluorinated heterocycles. Bis(fluoroalkyl)vinamides **II.60** and **II.61** could be used for the synthesis of simple bis(fluoroalkyl)pyrimidine building blocks after condensation with amidines. The 1,3-dielectrophile character of these vinamides can probably be further exploited (a, Figure C.16).

The side-products **II.100** and **II.102** resulting from the *N*-acylation of fluorinated ketimines **II.59** (c, Scheme II.29) could be employed as 1,5-dielectrophile if the reaction with activated FARs was efficient. The *in situ N*-debenzylation should be performed, perhaps by means of catalytic procedure involving palladium. This could lead to novel bis(fluoroalkyl)pyridine building blocks (b, Figure C.16).

The use of ethyl 2-(dimethylamino)acrylate in combination with activated FARs could provide a new approach in the preparation of 3-(fluoroalkyl)-pyrazole-5-carboxylate. These building blocks are very important in agrochemistry, as demonstrated by the preparation of a patent after the development of a new synthetic approach (see Scheme II.30-31) (c, Figure C.16).

These hypothesis are only a selection of the possibilities offered by the use of FARs in the preparation of valuable heterocycles bearing emergent fluorinated substituents.

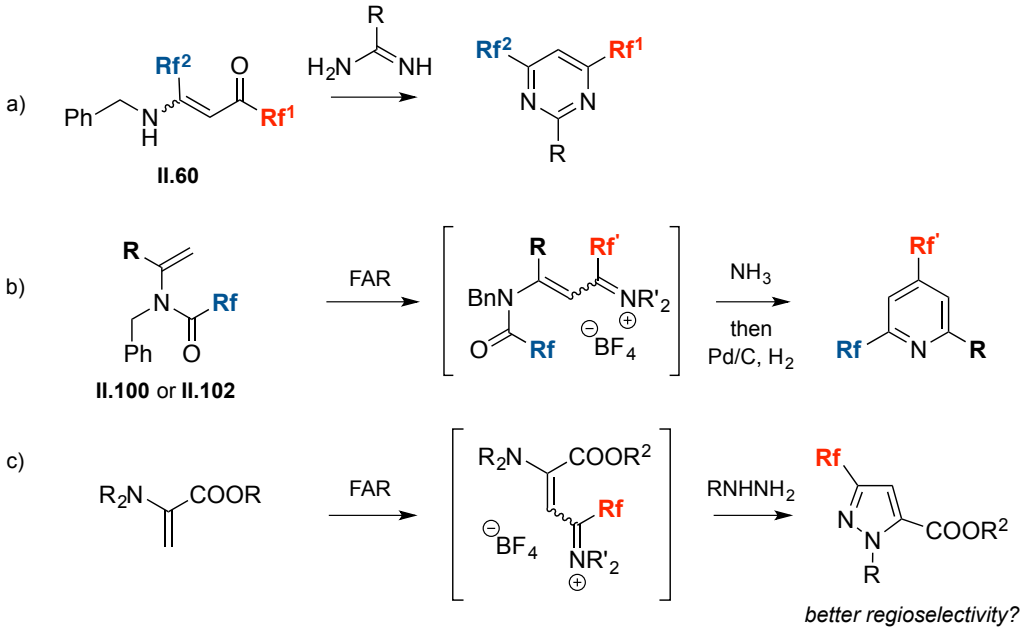


Figure C.16: Alternative approaches in the preparation of novel fluorinated heterocycles

The preparation of mono(fluoroalkyl)pyrimidine using FARs was initiated (see Scheme III.7), and the extension of the scope of this method is currently under investigation in our group. The condensation of the key adducts **II.48** and **II.49** could allow the preparation of a large variety of mono(fluoroalkyl)pyrimidines (a, Figure C.17). After a short retrosynthetic pathway (possibly involving protecting groups), these compounds could lead to unprecedented fluoroalkyl purine derivatives of high interest in life science oriented research (b, Figure C.17).

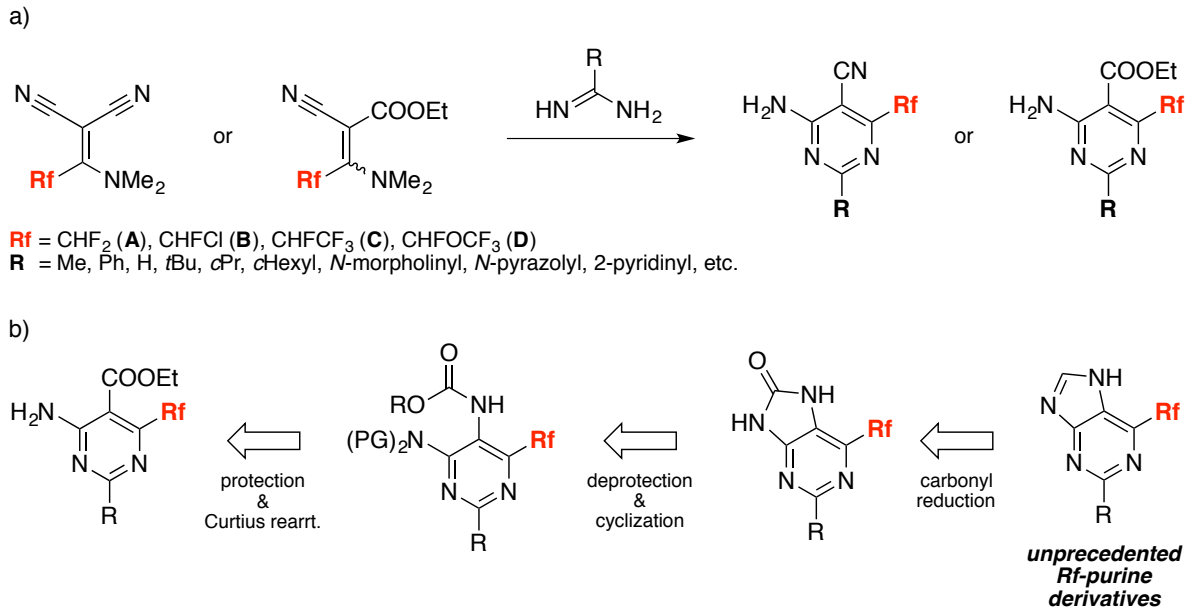


Figure C.17: Preparation of mono(fluoroalkyl)pyrimidine derivatives and possible access to fluoroalkyl purine derivatives after suitable transformations

The preparation of the side-product **III.34c** isolated during the pyrimidine route is very scarcely described in the literature. Its efficient but undesired synthesis was described in this manuscript, and it could possibly be employed in the preparation of CHF_2-pyrimidine diones. Analogues of this side-product bearing other fluoroalkyl groups were observed, and could lead to the corresponding pyrimidine diones (Figure C.18).

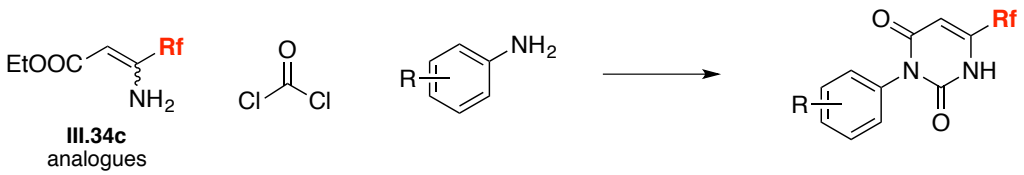


Figure C.18: Possible application of the side-product III.34c and its potential analogues

Further investigations could be achieved concerning the scope of this reaction, the determination of the mechanism of formation and the possible transformations of the novel cyclobutenes described in the Chapter III. These products could be used in [2+2] cyclizations (involving homolytic fragmentations), Diels-Alder reactions (with a suitable diene), or in Michael-type additions of nucleophiles. Recently, another example was prepared using different reaction conditions, which opens new interrogations concerning the mechanistic pathway of this reaction. This topic is highly valuable for fundamental research in the context of organofluorine chemistry (Figure C.19).

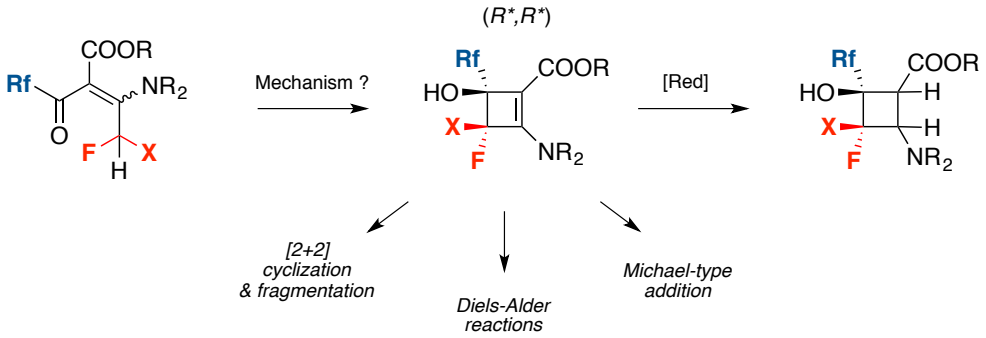


Figure C.19: Further possible studies concerning the cyclobutene route

The concept of vinylogous FAR could be further investigated as it showed great potential in the introduction of perfluoroalkyl chains into organic compounds. After the optimization of the preparation of the vinylogous FAR **5B** and its characterization, the development of other vinylogous FARs could be achieved due to the commercial availability of many perfluoroalkyl iodides.

In addition, the one-pot sequence described in Scheme III.9 could be applied using fluorinated acetoacetates **III.1**. The preparation of novel 2,4-bis[(per)fluoroalkyl]-pyridine-3-carboxylates could be achieved. The subsequent saponification could provide the corresponding 2,4-bis[(per)fluoroalkyl]-nicotinic acid analogues (a, Figure C.20).

A recent report described the efficient preparation of a perfluoroalkenyl pyrrolidin-2-one using Heck-type coupling with 81% yield. The reduction of the carbonyl group could allow the efficient preparation of a new vinylogous FAR for the introduction of the perfluoropentyl chain into various compounds. The preparation of the corresponding perfluoroalkyl vinylogous amide by hydrolysis could lead to valuable perfluoroalkyl enaminoketones, useful in the synthesis of pyrazoles and pyrimidines (b, Figure C.20).

Finally, the initial report of the preparation of perfluoroalkyl enamines from perfluoroalkyl iodides also reported on the hydrolysis of these compounds, providing the corresponding enaminoketones bearing various perfluoroalkyl chains. These enaminoketones could be used similarly in the synthesis of the corresponding pyrazoles and pyrimidines (c, Figure C.20).

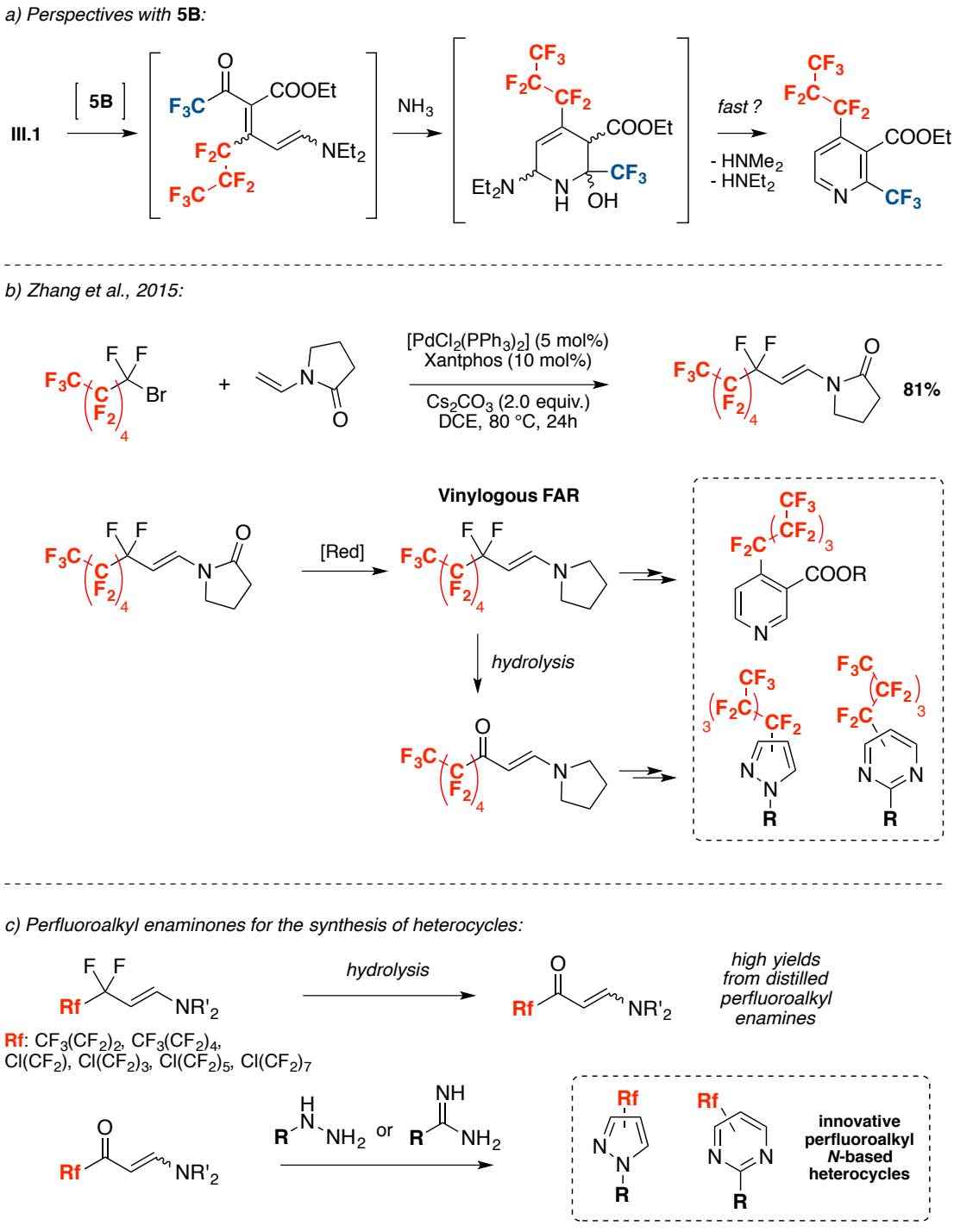


Figure C.20: Possible developments of the use of perfluoroalkyl halide chains

List of Scientific Contributions

Publications:

Valorisation of TFEDMA:
« *In situ* generated fluorinated iminium salts for difluoromethylation and difluoroacetylation », E. Schmitt, B. Rugeri, A. Panossian, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Lett.* **2015**, *17*, 4510-4513.

Azine route:
« A general approach towards *N*H-pyrazoles that bear diverse fluoroalkyl groups by means of fluorinated iminium salts », E. Schmitt, G. Landelle, J.-P. Vors, N. Lui, S. Pazenok, F. R. Leroux, *Eur. J. Org. Chem.* **2015**, 6052-6060.

Ketimine route (inside back cover):
« A Major Advance in the Synthesis of Fluoroalkyl Pyrazoles: Tuneable Regioselectivity and Broad Substitution Patterns », E. Schmitt, A. Panossian, J.-P. Vors, C. Funke, N. Lui, S. Pazenok, F. R. Leroux, *Chem. Eur. J.* **2016**, *22*, 11239-11244.

Quinoline route (second author):
« A new approach toward the synthesis of 2,4-bis(fluoroalkyl)-substituted quinoline derivatives using fluoroalkyl amino reagent chemistry », Aribi, F.; Schmitt, E.; Panossian, A.; Vors, J.-P.; Pazenok, S.; Leroux, F. R. *Org. Chem. Front.* **2016,** *3*, 1392-1415.

Patents:

Preparation of Bixafen analogues using the new FAR:
F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing substituted pyrazoles containing haloalkoxy-haloalkyl- and haloalkylthio-haloalkyl groups from α,α-dihaloalkylamines and ketimines, *BCS153048* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 24/06/2015).

Preparation of 3-Rf-pyrazole-5-carboxylates from Rf-vinamides without using FARs:
F. Leroux, E. Schmitt, S. Pazenok, J.-P. Vors, Process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates and 3- fluoroalkyl-5-pyrazolecarboxylic acids, *BCS163094* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 13/09/2016).

Preparation of bis(fluoroalkyl)-quinoline derivatives using FARs:
F. Leroux, F. Aribi, E. Schmitt, A. Pazenok, S. Pazenok, J.-P. Vors, Process for the preparation of polyfluoroalkylated quinolines, *BCS153082* (Bayer CropScience AG / CNRS / University of Strasbourg; filed 21/01/2016).

Experimental Part

General considerations

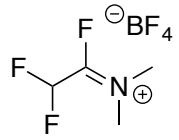
All reactions were performed in flame-dried glassware using sealed tube or Schlenk tube. Liquids and solutions were transferred with syringes. Air- and moisture- sensitive materials were stored protected and handled under an atmosphere of argon, with appropriate glassware. Solvents were purified and dried following standard procedures: tetrahydrofuran (THF) was distilled from sodium or sodium + benzophenone prior to use. Anhydrous MeCN was used from commercial source and was stored under Argon. Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, ether, toluene, and ethyl acetate) were used without purification. All reagents were purchased from standard supplier (Sigma Aldrich, ABCR, Alfa Aesar and Apollo scientific). FARs were purchased from ABCR or Aldrich and depicted purities were checked by NMR before use. Yarovenko and Ishikawa reagents were degrading upon storage and purity had to be checked frequently. Starting materials, if commercial, were purchased and used as such, provided that adequate checks (NMR) had confirmed the claimed purity. Analytical thin-layer chromatography (TLC) was performed on silica gel. Flash column chromatography was performed on silica gel 60 (40– 63 μm, 230–400 mesh, ASTM) by *Merck* using the indicated solvents. ^{1}H, ^{13}C, ^{11}B and ^{19}F-NMR spectra were recorded in $CDCl_3$ on *Bruker* AV 400 instruments (^{1}H: 400MHz, ^{19}F: 376MHz, ^{13}C: 100MHz, ^{11}B: 128MHz). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard ($CDCl_3$ (δ [^{1}H] = 7.26 and accordingly δ [^{13}C] = 77.16 ppm), CD_3CN (δ [^{1}H] = 1.94 and accordingly δ [^{13}C] = 1.32 ppm, MeOD-d_4 (δ [^{1}H] = 3.31 and accordingly δ [^{13}C] = 49.00 ppm), DMSO-d_6 (δ [^{1}H] = 2.50 and accordingly δ [^{13}C] = 39.52 ppm) or Acetone-d_6 (δ [^{1}H] = 2.05 and accordingly δ [^{13}C] = 29.84 ppm). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br d = broad doublet), coupling constant (Hz) and integration. Internal standard was used to measure yields *in-situ* (fluorobenzene: δ [^{19}F] = -113.15 ppm). The spectra were processed with the program NMR Notebook (Version 2.70, NMRtec). *Microwave* experiments were carried out in an *InitiatorTM* from Biotage, exact parameters are given with the procedures. Melting points (M.p.) were determined for crystalline or solid compounds with a Melting Point Apparatus M-560 and are not corrected. High resolution mass spectrometry (HRMS) analysis and elemental analysis (Anal.) were performed by the analytical facility at the University of Strasbourg (measurement accuracy ≤ 15 ppm). Spectral data's was recorded from samples purified by Hickmann distillation when necessary.

Chapter II

Fluoroalkyl Amino Reagents

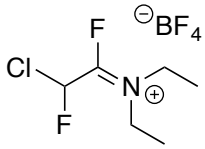
General procedure for the activation of commercially available FARs **1A-C**:
(Example of TFEDMA) BF_3•Et_2O (0.18 mL, 1.42 mmol) was added *via* syringe to a vigorously stirred solution of TFEDMA (0.17 mL, 1.38 mmol) in dry CH_2Cl_2 (2 mL) in Schlenk vessel at room temperature under argon. After 15 min, the solvent was evaporated *in vacuo* to yield quantitatively a white solid. FARs **1B** and **1C** are activated similarly over 45min, and provide brown solids.
FARs **1A-C** were previously reported in the literature, respectively in:
1A: Petrov, V. A.; Swearingen, S.; Hong, W.; Chris Petersen, W. *J. Fluorine Chem.* 2001, *109*, 25-31.
1B: Schaumburg, K. *J. Magn. Res. (1969)* **1972,** *7*, 177-183.
1C: Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 3377-3380.
FARs **1B-C** were available in mixtures with their corresponding enamine analogue resulting from HF elimination. The activated fluoro iminiums **2A-B** were characterized by NMR analysis.

_N_-methyl-_N_-(1,2,2-trifluoroethylidene)methanaminium tetrafluoroborate (2A)



^{1}H-NMR (400 MHz, CD_3CN): δ = 7.04 (td, C*H*F_2, $^2J_{H-F}$ = 50 Hz, $^3J_{H-F}$ = 8 Hz), 3.70 and 3.63 (2 x s, 6H, N(CH_3)$_2$) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -36.9 to -37.0 (m, C*F*N(CH_3)$_2$+), -128.8 (dd, CH*F*$_2$, $^2J_{H-F}$ = 50 Hz, $^3J_{H-F}$ = 12 Hz), -152.4 (br s, B*F*$_4^-$) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 164.0 (dt, *C*FN(CH_3)$_2$, $^1J_{C-F}$ = 332 Hz, $^2J_{C-F}$ = 29 Hz), 106.3 (td, *C*HF_2, $^1J_{C-F}$ = 250 Hz, $^2J_{C-F}$ = 27 Hz), 43.5 (2 x s, N(*C*H_3)$_2^+$) ppm.

_N_-(2-chloro-1,2-difluoroethylidene)-_N_-ethylethanaminium tetrafluoroborate (2B)

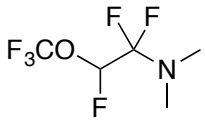


^{1}H-NMR (400 MHz, CD_3CN): δ = 7.52 (dd, C*H*FCl, J = 45 Hz, J = 11 Hz), 4.15 to 3.93 (m, 4H, N(CH_2CH$_3$)$_2$), 1.43 (td, 6H, N(CH$_2$CH_3)$_2$) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -39.0 (t, C*F*N(CH_2CH$_3$)$_2^+$, J = 12 Hz), -151.5 (s br, 4F, B*F*$_4^-$), -151.9 (dd, CH*F*Cl, J = 45.2 Hz, J = 13.6 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 165.7 (dt, *C*FN(CH_3)$_2^+$, $^1J_{C-F}$ = 326 Hz, $^2J_{C-F}$ = 28 Hz), 90.2 (dd, *C*HFCl, $^1J_{C-F}$ = 254 Hz, $^2J_{C-F}$ = 27 Hz), 51.0 and 50.7 (2 x d, N(*C*H$_2$CH$_3$)$_2$, $^3J_{C-F}$ = 5 Hz), 12.2 ((N(CH$_2$*C*H$_3$)$_2^+$) ppm
Full characterization also reported in:
Wakselman, C.; Tordeux, M. *J. Chem. Soc.-Chem. Commun.* **1975**, 956-956.

General procedure for the preparation and activation of FAR **1D:**

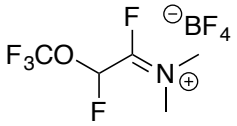
The required amount of 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (659 mg, 0.44 mL, 4.0 mmol) was liquefied at -78 °C into a Schlenk vessel under inert atmosphere by means of a double-layer balloon. Dimethylamine 2M in THF (2 mL, 4 mmol) was slowly added *via* syringe at -78 °C under vigorous stirring. The cold bath was removed and the mixture was raised to *ca*. 5-15 °C over 10min. A water-bath was placed before BF_3•Et_2O (559 mg, 0.50 mL, 3.95 mmol) was added slowly *via* syringe. The bis-layered mixture was vigorously stirred for 15min. This activated FAR **2D** can be used directly after addition of MeCN or precipitated to access the accurate mass isolated (by addition of an excess of dry DCM and decantation).

1,1,2-trifluoro-N,N-dimethyl-2-(trifluoromethoxy)ethan-1-amine (1D)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.85 (dt, C*H*FOCF_3, $^2J_{H-F}$ = 54.7 Hz, $^4J_{H-F}$ = 3.4 Hz), 2.49 (s, 6H, N(CH_3)$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.2 (m, OCF_3), -100.4 (m, CF_2), -142.1 (d, CH*F*OCF_3, $^2J_{F-H}$ = 54.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 121.0 (q, O*C*F_3, $^1J_{C-F}$ = 262 Hz), 118.9 (td, *C*F_2, $^1J_{C-F}$ = 250 Hz, $^2J_{C-F}$ = 26 Hz), 100.0 (ddq *C*H$FOCF_3$, $^1J_{C-F}$ = 241 Hz, $^2J_{C-F}$ = 45 Hz, $^3J_{C-F}$ = 3 Hz), 35.9 (N(*C*H_3)$_2$) ppm.

***N*-(1,2-difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate (2D)**



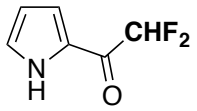
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.93 (dd, C*H*FOCF_3, $^2J_{H-F}$ = 54.6 Hz, $^3J_{H-F}$ = 6.5 Hz), 3.01 and 2.89 (2 x s, 6H, N(CH_3)$_2^+$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -57.9 (m, CHFOCF_3), -134.7 (d, CH*F*OCF_3, $^2J_{H-F}$ = 55.5 Hz), -148.2 (s, BF_4^-), -168.6 (s br, C*F*N$(CH_3)_2^+$) ppm.

It has to be noted that all FARs can be activated in distilled DCM and dried *in vacuo* in order to verify the clean activation illustrated by a white solid for TFEDMA **2A** and the new FAR **2D**, and brown solids for Yarovenko and Ishikawa reagents **2B-C**. It is actually possible to activate directly the FAR's in dry MeCN to perform the reaction more rapidly, without confirmation of the quality of the activated iminium salt.

Difluoroacylation

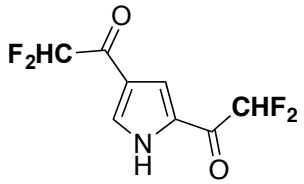
Difluoroacylation of electron-rich heterocycles

2,2-Difluoro-1-(1*H*-pyrrol-2-yl)ethan-1-one (II.21).



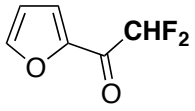
A solution of pyrrole (0.22 mL, 3.1 mmol) in dry MeCN (4 mL) was treated with a solution of **2A** (activated with $AlCl_3$) (3.42 mmol, 1.1 equiv.) in dry MeCN (4 mL) *via* syringe at 0 °C under inert atmosphere. The mixture was stirred for 24h at room temperature. The crude was purified by flash chromatography (Et_2O in cyclohexane: 0 to 10%), to yield a brown solid (451 mg, 100%). M.p.: 42.5 – 43.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.62 (br s, N*H*), 7.21 (s, 3',5'-CH_{arom}), 6.40 (q, 4'-CH_{arom}), 6.17 (t, C*H*F_2, $^2J_{H-F}$ = 54 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -122.9 (d, CH*F*$_2$, $^2J_{H-F}$ = 53.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.6 (*C*O), 127.7 (5'-*C*$_{arom}$), 127.4 (2'-*C*$_{arom}$), 120.4 (3'-*C*$_{arom}$), 112.3 (4'-*C*$_{arom}$), 110.6 (t, *C*HF_2, $^1J_{C-F}$ = 251 Hz) ppm.
Anal. calcd for $C_6H_5F_2NO$: C, 49.66; H, 3.47; F, 26.19; N, 9.65; O, 11.03. Found: C, 49.85; H, 3.55; N, 9.58.

1,1'-(1*H*-Pyrrole-2,4-diyl)bis(2,2-difluoroethan-1-one) (II.22).



A solution of 2,2-difluoro-1-(1*H*-pyrrol-2-yl)ethan-1-one **II.21** (210 mg, 1.45 mmol) in dry MeCN (2 mL) was treated with a solution of **2A** (1.54 mmol, 1.07 equiv.) in dry MeCN (2 mL) *via* syringe. The mixture was stirred for 36h at 80 °C. The mixture was partitioned between water and Et_2O. The aqueous was basified with saturated bicarbonate solution and reextracted. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 20%), to yield a colourless solid (270 mg, 84 %). M.p.: 78.4-78.6 °C.
^{1}H-NMR (400 MHz, CD_3CN): δ = 10.95 (br s, N*H*), 7.96 (5'-CH_{arom}), 7.62 (3'-CH_{arom}), 6.48 and 6.38 (2 x t, 2 x COC*H*F_2, $^2J_{H-F}$ = 53.2 and 53.4 Hz) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -126.7 and -126.6 (2 x d, CH*F*$_2$, $^2J_{H-F}$ = 53.4 and 53 2 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 183.8 and 179.0 (2 x t, 2 x *C*OCHF$_2$, $^2J_{C-F}$ = 25.0 and 25.6 Hz), 133.4 (5'-*C*$_{arom}$), 129.7 (2'-*C*$_{quat}$), 122.5 (4'-*C*$_{quat}$), 120.0 (3'-*C*$_{arom}$), 111.3 and 110.5 (2 x t, *C*HF_2, $^1J_{C-F}$ = 248.3 Hz) ppm.
Anal. calcd for $C_8H_5F_4NO_2$: C, 43.06; H, 2.26; F, 34.06; N, 6.28; O, 14.34. Found: C, 43.29; H, 2.30; N, 6.29.

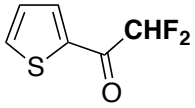
2,2-Difluoro-1-(furan-2-yl)ethan-1-one (II.23).



A solution of furan (0.20 mL, 2.75 mmol) in dry MeCN (4 mL) was treated with a solution of **2A** (3.3 mmol, 1.2 equiv.) in dry MeCN (4 mL) *via* syringe at 0 °C under inert atmosphere. The mixture was stirred for 72 h at room temperature. The solvent was removed under reduced pressure. The crude was distilled using Hickmann apparatus, to yield a colourless oil (237 mg, 59%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, 5'-C*H*), 7.48 (d, 4'-C*H*), 6.63 (dd, 3'-C*H*), 6.19 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.5 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -124.5 (d, CH*F*$_2$, $^{2}J_{H-F}$ = 53.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.0 (t, *C*OCHF$_2$, $^{2}J_{C-F}$ = 26.4 Hz), 149.3 (5'-*C*$_{arom}$), 148.2 (2'-*C*$_{arom}$), 122.8 (t, 3'-*C*$_{arom}$, $^{4}J_{C-F}$ = 3 Hz), 113.0 (4'-*C*$_{arom}$), 109.9 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 252.6 Hz) ppm.
HRMS (ESI) calcd for $C_6H_5F_2O_2$ [M+H]: 147.0252. Found: 147.0709.

Ref: S. R. Piettre, C. Girol, C. G. Schelcher, *Tetrahedron Lett.* **1996**, *37*, 4711-4712.

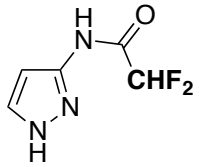
2,2-Difluoro-1-(thiophen-2-yl)ethan-1-one (II.24).



A solution of thiophene (0.50 mL, 3.74 mmol) in dry MeCN (5 mL) was treated with a solution of **2A** (5.0 mmol, 1.4 equiv.,) in dry MeCN (5 mL) *via* syringe at 0 °C under inert atmosphere. The mixture was stirred for 18 h at 50 °C. The solvent was removed under reduced pressure. The crude was distilled using Hickmann apparatus, to yield a colourless oil (148 mg, 30%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 5'-C*H*$_{arom}$), 7.84 (dd, 3'-C*H*$_{arom}$), 7.23 (t, 4'-C*H*$_{arom}$), 6.18 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.5 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -121.7 (d, CH*F*$_2$, $^{2}J_{H-F}$ = 53.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 181.2 (*C*O), 136.9 (2'-*C*$_{arom}$), 135.7 (3'-*C*$_{arom}$), 129.0 (4'-*C*$_{arom}$), 111.0 (t, CH*F*$_2$, $^{1}J_{C-F}$ = 254 Hz) ppm.
HRMS (ESI) calcd for $C_6H_5F_2OS$ [M+H]: 163.0024. Found: 163.0016.

Ref: G. K. Surya Prakash, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2001**, *112*, 355-360.

2,2-Difluoro-*N*-(1*H*-pyrazol-3-yl)acetamide (II.25).



A solution of 3-aminopyrazole (300 mg, 3.61 mmol) in dry MeCN (7 mL) was added to a solution of **2A** (4.0 mmol, 1.1 equiv.,) in dry MeCN (4 mL) at 0 °C. The mixture was stirred 30min at 0 °C and 15min at room temperature, and was treated with HCl 2M aq. (8mL) and stirred 30min. The solution was extracted with Et_2O (15 mL) and the layers were separated. The aqueous basified with saturated bicarbonate solution and reextracted with Et_2O (15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (MeOH in CH_2Cl_2: 0 to 5%), to yield a colourless solid (319 mg, 55%). M.p.: 194.0 – 194.4 °C.

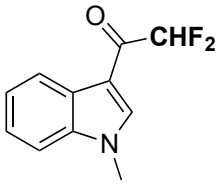
^{1}H-NMR (400 MHz, Acetone-d^6): δ = 11.80 (br s, N*H*), 10.33 (br s, CON*H*), 7.68 (dd, 4'-CH_{arom}), 6.70 (dd, 5'-CH_{arom}), 6.33 (t, C*H*F$_2$, $^2J_{H-F}$ = 53.7 Hz) ppm.

^{19}F-NMR (376 MHz, Acetone-d^6): δ = -126.9 (d, CH*F*$_2$, $^2J_{H-F}$ = 53.7 Hz) ppm.

^{13}C-NMR (100 MHz, Acetone-d^6): δ = 160.9 (t, *C*O, $^3J_{C-F}$ = 26.3 Hz), 146.8 (3'-C_{arom}), 130.2 (5'-C_{arom}), 109.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 248 Hz), 97.7 (4'-C_{arom}) ppm.

Anal calcd for $C_5H_5F_2N_3O$: C, 37.27; H, 3.13; F, 23.58; N, 26.08; O, 9.93. Found: C, 37.22; H, 3.25; N, 25.64.

2,2-Difluoro-1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (II.26).



A solution of **2A** (2.35 mmol, 1 equiv.) in dry MeCN (3 mL) was treated with 1-methylindole (0.30 mL, 2.33 mmol) *via* syringe. The mixture was stirred at room temperature for 1 h. The mixture was partitioned between water (15 mL) and Et_2O (10 mL). The aqueous layer was basified (bicarbonate solution) and reextracted with Et_2O (2 x 10 mL). The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was recrystallized in abs. EtOH to yield the pure product as colourless crystals (373 mg, 76%). M.p.: 113.5 - 113.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.38 (m, 1H, CH_{arom}), 7.93 (s, C*H*NMe), 7.34 (m, 3H, CH_{arom}), 6.11 (t, C*H*F$_2$, $^2J_{H-F}$ = 54.3 Hz), 3.81 (s, NCH_3) ppm.

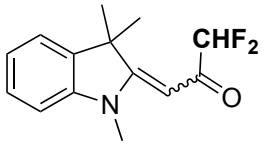
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.5 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.3 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 182.7 (t, *C*OCHF$_2$, $^2J_{C-F}$ = 25 Hz), 138.0 (t, 2'-*C*H, $^4J_{C-F}$ = 7 Hz), 137.2 (C_{quat}NMe), 126.9 (C_{quat}CO), 124.3, 123.6, 122.5 (4',5',6'-C_{arom}), 112.0 (t, *C*HF$_2$, $^1J_{C-F}$ = 253 Hz), 110.4 (3'-C_{arom}), 110.0 (7'-C_{arom}), 33.8 (N*C*H$_3$) ppm.

Anal calcd for $C_{11}H_9F_2NO$: C, 63.16; H, 4.34; F, 18.16; N, 6.70; O, 7.65. Found: C, 63.17; H, 4.30; N, 6.80.

Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in AcOEt.

1,1-Difluoro-3-(1,3,3-trimethylindolin-2-ylidene)propan-2-one (II.27).



Into a solution of **2A** (1.78 mmol, 1.05 equiv.) in dry MeCN (2 mL) was added 1,3,3-trimethyl-2-methyleneindoline (0.30 mL, 1.71 mmol) *via* syringe. The mixture was stirred for 30 min and was partitioned between water (10 mL) and Et_2O (10 mL), the layers separated. The aqueous layer was basified with 2M NaOH until pH 13-14 (the aqueous layer turned pink) and reextracted with Et_2O (2 x 10 mL). The aqueous layer was brought to pH 7 with diluted HCl and reextracted with Et_2O (10 mL). The organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a pale solid (425mg, 99%). M.p.: 128.8 - 129.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 to 7.22 (m, 2H, CH_{arom}), 7.10 (t, 1H, CH_{arom}), 6.88 (d, 1H, 7'-CH_{arom}), 5.78 (t, CHF$_2$, $^2J_{H-F}$ = 55.4 Hz), 5.50 (CHCO), 3.35 (NCH_3), 1.73 (s, C(CH_3)$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -123.1 (d, CHF_2, $^2J_{H-F}$ = 55.4 Hz) ppm.

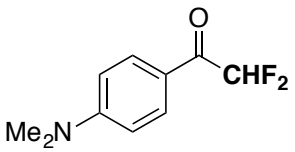
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 182.2 (t, COCHF$_2$, $^2J_{C-F}$ = 22 Hz), 176.3 (2'-C_{arom}), 143.2 (C_{quat}NMe), 140.2 (C_{quat}C(CH$_3$)$_2$), 127.9, 123.7, 122.1 (4',5',6'-C_{arom}), 112.0 (t, CHF$_2$, $^1J_{C-F}$ = 255 Hz), 108.8 (7'-C_{arom}), 85.5 (CHCO), 49.2 (C(CH$_3$)$_2$), 30.8 (NCH$_3$), 23.0 (C(CH$_3$)$_2$) ppm.

Anal calcd for $C_{14}H_{15}F_2NO$: C, 66.92; H, 6.02; F, 15.12; N, 5.57; O, 6.37. Found: C, 66.85; H, 6.08; N, 5.50.

Difluoroacylation of electron-rich arenes under microwave irradiation – General procedure

A solution of **2A** in dry MeCN (6 mL) was mixed with electron-rich arene and was irradiated with microwaves at 150 °C for 20 min (40 W, 9 bars). The reaction mixture was evaporated *in vacuo*, taken up in Et_2O, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel with Pentane/Et_2O mixtures (0 to 20% Et_2O gradient).

1-(4-(Dimethylamino)phenyl)-2,2-difluoroethanone (II.28)



The product was prepared from N,N-dimethylaniline (380 mg, 0.40 mL, 3.14 mmol) and **2A** (3.2 mmol), to yield an orange solid (500 mg, 80 %).

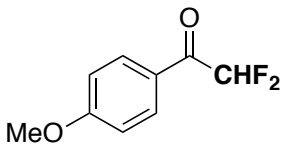
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 2',6'-CH_{arom}), 6.65 (d, 3',5'-CH_{arom}), 6.23 (t, CHF$_2$, $^2J_{H-F}$ = 54.2 Hz), 3.73 (s, N(CH_3)$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = −121.1 (d, CHF_2, $^2J_{H-F}$ = 54.2 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 185.2 (t, C=O, $^2J_{C-F}$ = 24.6 Hz), 154.56 (C-N(CH$_3$)$_2$), 133.2 (s, 3',5'-C_{arom}), 119.4 (CCO), 111.87 (t, CHF$_2$, $^1J_{C-F}$ = 253.1 Hz), 111.0 (2',6'-C_{arom}), 40.2 (CH$_3$) ppm.

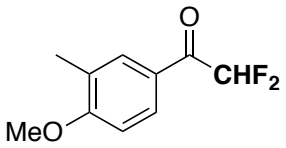
Anal. calcd for $C_{10}H_{11}F_2NO$: C, 60.30; H, 5.57; N, 7.03. Found: C, 60.22; H, 5.69; N, 6.97.

2,2-Difluoro-1-(4-methoxyphenyl)ethanone (II.22)



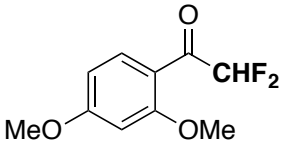
The product was prepared from anisole (0.49 mL, 4.5 mmol) and **2A** (4.5 mmol), to yield a colourless solid (460 mg, 55 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, 2',6'-CH_{arom}), 6.97 (d, 3',5'-CH_{arom}), 6.23 (t, CHF$_2$, $^{2}J_{H-F}$ = 53.9 Hz), 3.88 (s, OCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −121.4 (d, CHF_2, $^{2}J_{H-F}$ = 54.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.3 (t, COCHF$_2$, $^{2}J_{C-F}$ = 25.3 Hz), 165.1 (CCH$_3$), 132.4 (s, 2',6'-C_{arom}), 124.7 (s, 1'-C_{arom}), 114.5 (s, 3',5'-C_{arom}), 111.7 (t, CHF$_2$, $^{1}J_{C-F}$ = 255.0 Hz), 55.9 (CH$_3$) ppm.
Anal. calcd for $C_9H_8F_2O_2$: C, 58.07; H, 4.33; N, 0.00; Found: C, 58.48; H, 4.57; N, 0.00.
Ref: K. Boonkitpattarakul, D. Soorukram, P. Tuchinda, V. Reutrakul, M. Pohmakotr, *J. Fluorine Chem.* **2011**, *132*, 987-990.

2,2-Difluoro-1-(4-methoxy-3-methylphenyl)ethanone (II.30)



The product was prepared from 2-methylanisole (0.43 mL, 3.5 mmol) and **2A** (3.5 mmol, 1 equiv.), to yield a colourless solid (378 mg, 52 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 6'-CH_{arom}), 7.84 (s, 2'-CH_{arom}), 6.87 (d, 5'-CH_{arom}), 6.24 (t, CHF$_2$, $^{2}J_{H-F}$ = 53.7 Hz), 3.90 (OCH_3), 2.23 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −121.5 (d, CHF_2, $^{2}J_{H-F}$ = 53.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.4 (t, COCHF$_2$, $^{2}J_{C-F}$ = 24.8 Hz), 163.5 (COCH$_3$), 132.2 (6'-C_{arom}), 130.5 (2'-C_{arom}), 127.8 (3'-C_{arom}), 124.2 (1'-C_{arom}), 111.6 (t, CHF$_2$, $^{1}J_{C-F}$ = 253.7 Hz), 109.8 (5'-C_{arom}), 55.9 (OCH$_3$), 16.4 (CH$_3$) ppm.

2,2-Difluoro-1-(2,4-dimethoxyphenyl)ethanone (II.31)

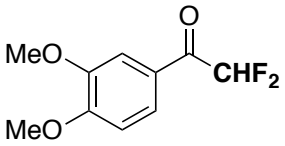


The product was prepared from 1,3-dimethoxybenzene (0.20 mL, 1.5 mmol) and **2A** (1.5 mmol, 1 equiv.) at 160 °C, to yield a colourless solid (306 mg, 92 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, 6'-CH_{arom}), 6.57 (d, 5'-CH_{arom}), 6.55 (t, CHF$_2$, $^{2}J_{H-F}$ = 53.9 Hz), 6.44 (s, 3'-CH_{arom}), 3.90 (s, OCH_3), 3.86 (s, OCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −128.12 (d, CHF_2, $^{2}J_{H-F}$ = 53.9 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.8 (t, *C*OCHF$_2$, $^2J_{C\text{-}F}$ = 23.9 Hz), 166.6 (2'-*C*OCH$_3$), 161.9 (4'-*C*OCH$_3$), 134.1 (6'-*C*$_{arom}$), 116.6 (*C*CO), 109.9 (t, *C*HF$_2$, $^1J_{C\text{-}F}$ = 244.9 Hz), 106.7 (5'-*C*$_{arom}$), 98.5 (3'-*C*$_{arom}$), 56.1 (*C*H$_3$), 55.9 (*C*H$_3$) ppm.
Anal. calcd for $C_{10}H_{10}F_2O_3$: C, 55.56; H, 4.66; N, 0.00; Found: C, 55.72; H, 4.67; N, 0.00.

Ref: K. Boonkitpattarakul, D. Soorukram, P. Tuchinda, V. Reutrakul, M. Pohmakotr, *J. Fluorine Chem.* **2011**, *132*, 987-990.

1-(3,4-Dimethoxyphenyl)-2,2-difluoroethanone (II.32)



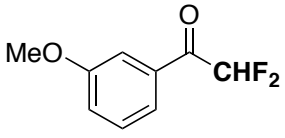
The product was prepared from 1,2-dimethoxybenzene (0.38 mL, 3 mmol) and **2A** (3 mmol, 1 equiv.), to yield a colourless solid (335 mg, 52 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 6'-C*H*$_{arom}$), 7.53 (s, 2'-C*H*$_{arom}$), 6.91 (d, 5'-C*H*$_{arom}$), 6.25 (t, C*H*F$_2$, $^2J_{H\text{-}F}$ = 53.2 Hz), 3.94 (s, 4'-OC*H*$_3$), 3.90 (s, 3'-OC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −121.02 (dd, CH*F*$_2$, $^2J_{H\text{-}F}$ = 53.2 Hz, $^3J_{H\text{-}F}$ = 26 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.2 (t, *C*O, $^2J_{C\text{-}F}$ = 26.3 Hz), 155.1 (4'-*C*OCH$_3$), 149.6 (s, 3'-*C*OCH$_3$), 125.2 (5'-*C*$_{arom}$), 124.8 (*C*CO), 111.5 (t, *C*HF$_2$, $^1J_{C\text{-}F}$ = 253 Hz), 111.3 and 110.5 (2',6'-*C*$_{arom}$), 56.4 and 56.2 (3',4'-OCH$_3$) ppm.
Anal. calcd for $C_{10}H_{10}F_2O_3$: C, 55.56; H, 4.66; N, 0.00. Found: C, 55.89; H, 4.72; N, 0.00.

Ref: K. Boonkitpattarakul, D. Soorukram, P. Tuchinda, V. Reutrakul, M. Pohmakotr, *J. Fluorine Chem.* **2011**, *132*, 987-990.

Difluoroacylation of electron-rich arenes *via* organolithium reagents – General procedure

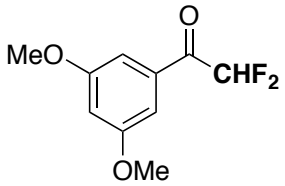
A solution of freshly titrated *t*BuLi 1.7M in pentane (9.2 mmol, 2 equiv.) was added dropwise at 0 °C to a solution of bromoarene (4.6 mmol) in dry toluene (20 mL) cooled to 0 °C into a Schlenk vessel under inert atmosphere. After 5-10min, The mixture was canulated dropwise onto an solution of 2,2-difluoro-*N,N*-dimethylacetamide **1d** (0.4 mL, 4.6 mmol, 1 equiv.) in dry toluene (5 mL) into a second Schlenk vessel at 0 °C. The mixture was slowly raised to room temperature and stirred for 6h. The mixture was quenched with a saturated NH_4Cl aqueous solution (30 mL) and extracted with DCM (3 x 15 mL), washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel with Pentane/Et_2O mixtures (0 to 20% gradient).

2,2-Difluoro-1-(3-methoxyphenyl)ethan-1-one (II.33)



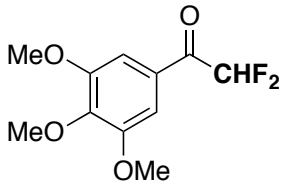
The product was prepared from 3-bromoanisole (2.21 g, 1.5 mL, 11.8 mmol) and **3A** (17.7 mmol, 1.5 equiv.), to yield a colourless oil (840 mg, 38 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 6'-CH_{arom}), 7.49 (s, 2'-CH_{arom}), 7.36 (t, 5'-CH_{arom}), 7.14 (dd, 4'-CH_{arom}), 6.22 (t, CHF$_2$, $^{2}J_{H-F}$ = 53.6 Hz), 3.80 (s, OCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -121.9 (d, CHF_2, $^{2}J_{H-F}$ = 53.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.5 (t, COCHF$_2$, $^{2}J_{C-F}$ = 25.2 Hz), 160.1 (COCH$_3$), 132.9 (CCOCHF$_2$), 130.1 (5'-C_{arom}), 122.4 (6'-C_{arom}), 121.8 (4'-C_{arom}), 113.6 (2'-C_{arom}), 111.1 (t, CHF$_2$, $^{1}J_{C-F}$ = 253.6 Hz), 55.6 (OCH$_3$) ppm.
HRMS (ESI) calcd for $C_9H_9F_2O_2$ [M+H]: 187.0565. Found: 187.0601.

2,2-Difluoro-1-(3,5-diimethoxyphenyl)ethanone (II.34).



The product was prepared from 1-bromo-3,5-dimethoxybenzene (1.0 g, 4.6 mmol) and **3A** (0.4 mL, 4.6 mmol, 1 equiv.), to yield a colourless solid (627 mg, 63 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 2',6'-CH_{arom}), 6.72 (s, 4'-CH_{arom}), 6.28 (t, CHF$_2$ $^{2}J_{H-F}$ = 53.4 Hz), 3.83 (s, 3',5'-OCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −122.0 (d, CHF_2, $^{2}J_{H-F}$ = 53.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.2 (t, COCHF$_2$, $^{2}J_{C-F}$ = 25.1 Hz), 161.1 (3',5'-COCH$_3$), 133.2 (CCO), 110.9 (t, CHF$_2$, $^{1}J_{C-F}$ = 253 Hz), 107.5 (4'-C_{arom}), 107.3 (3',5'-COCH$_3$), 56.1 (3',5'-OCH$_3$) ppm.
HRMS (ESI) calcd for $C_{10}H_{10}F_2O_3$ [M+H]: 217.0671. Found: 217.0695.

2,2-Difluoro-1-(3,4,5-trimethoxyphenyl)ethanone (II.35).

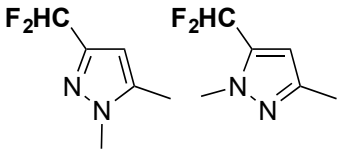


The product was prepared from 5-bromo-1,2,3-trimethoxybenzene (618 mg, 2.5 mmol) and ethyl difluoroacetate (1.33 equiv., 0.33 mL, 3.33 mmol), to yield a colourless solid (431 mg, 70 %). M.p.: 65.5 – 67.4 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 2',6'-CH_{arom}), 6.26 (t, CHF$_2$, $^{2}J_{H-F}$ = 54.2 Hz), 3.94 (s, 4'-OCH_3), 3.91 (s, 3',5'-OCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = −120.6 (d, CHF_2, $^{2}J_{H-F}$ = 54.2 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.5 (t, COCHF$_2$, $^{2}J_{C-F}$ = 25.2 Hz), 153.3 (3',5'-COCH$_3$), 144.4 (4'-COCH$_3$), 126.5 (CCO), 111.6 (t, CHF$_2$ $^{1}J_{C-F}$ = 252.2 Hz), 107.3 (2',6'-C_{arom}), 61.2 (4'-OCH$_3$), 56.5 (3',5'-OCH$_3$) ppm.
HRMS (ESI) calcd for $C_{11}H_{12}F_2NaO_4$ [M+Na]: 269.0596. Found: 269.0594.

TFEDMA as CHF_2-transfer reagent

Vinyl ethers and analogues

3-(Difluoromethyl)-1-methyl-5-phenyl-1*H*-pyrazole and 5-(difluoromethyl)-1-methyl-3-phenyl-1*H*-pyrazole, 1:1 mixture (II.36a/II.36b)

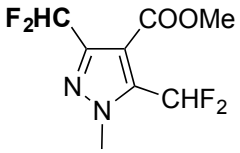


A solution of 2-methoxypropene (0.2 mL, 2.16 mmol) in dry MeCN (2 mL) was added to a solution of **2A** (1.05 equiv.) in dry MeCN (4 mL) at 0 °C, the mixture stirred from 0 °C to room temperature over 1 h. Methyl hydrazine (0.18 mL, 3.36 mmol) was added *via* syringe, the mixture stirred 1 h at room temperature. Internal standard: fluorobenzene (0.2 mL, 2.12 mmol), ^{19}F-NMR showed quantitative conversion to 1/1 mixture of **II.36a/II.36b**. The mixture was left to evaporate overnight. The crude was purified by flash chromatography on neutral alumina (Et_2O in pentane: 0 to 20%), to yield **II.36a/II.36b** as colourless oil (70:30 mixture, 254 mg, 89wt.%, 71%). NMR spectrum for **II.36b** was obtained after purification by silica gel chromatography (Et_2O in pentane: 0 to 20%).

5-(Difluoromethyl)-1,3-dimethyl-1*H*-pyrazole (II.36a)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.65 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 53.9 Hz), 6.21 (s, C*H*$_{arom}$), 3.88 (s, NC*H*$_3$), 2.24 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.5 (d, CH*F*$_2$, $^2J_{H\text{-}F}$ = 55 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.6 (*C*CH_3), 135.7 (t, *C*CHF_2, $^2J_{C\text{-}F}$ = 25.7 Hz), 108.9 (t, *C*HF_2, $^1J_{C\text{-}F}$ = 236 Hz), 106.6 (t, *C*H$_{arom}$, $^4J_{H\text{-}F}$ = 4.4 Hz), 37.5 (N*C*H_3), 13.3 (*C*H_3) ppm.

3-(Difluoromethyl)-1,5-dimethyl-1*H*-pyrazole (2b).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.60 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 55.4 Hz), 6.22 (s, 1H, C*H*$_{arom}$), 3.77 (s, NC*H*$_3$), 2.28 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.2 (d, CH*F*$_2$, $^2J_{H\text{-}F}$ = 55.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.4 (t, N*C*$_{quat}$, $^2J_{C\text{-}F}$ = 29 Hz), 140.0 (*C*$_{quat}CH_3$), 111.5 (t, *C*HF_2, $^1J_{C\text{-}F}$ = 233 Hz), 102.7 (*C*H$_{arom}$), 36.4 (N*C*H_3), 11.3 (*C*H_3), ppm.
Anal. calcd for $C_6H_8F_2N_2$: C, 49.31; H, 5.52; F, 26.00; N, 19.17. Found: C, 49.40; H, 5.52; N, 18.82.

Methyl 3,5-bis(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate (II.37)



A solution of 1,1-difluoro-4,4-dimethoxybut-3-en-2-one (506 mg, 3.0 mmol, 1.5 equiv.) in dry MeCN (2 mL) was added to a solution of **2A** (2.0 mmol) in dry MeCN (2 mL) *via* syringe. The mixture was stirred for 18 h. Methyl hydrazine (0.17 mL, 3.17 mmol) was added *via* syringe. The mixture was stirred 24 h more, then was evaporated *in vacuo*. The resulting orange oil was purified by flash chromatography (Et_2O in pentane: 0 to 20%), to yield a colourless solid (340 mg, 70 %). M.p.: 65.0 - 65.3 °C.

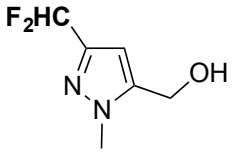
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (t, 5-CC*H*F_2, $^2J_{H-F}$ = 52.4 Hz), 6.98 (t, 3-CC*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 4.06 (s, OC*H*$_3$), 3.86 (s, NC*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -116.7 (2 x d, 3- and 5-CH*F*$_2$, $^2J_{H-F}$ = 52.4 Hz, $^2J_{H-F}$ = 53.9 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.6 (*C*O), 145.4 (t, 3-*C*CHF$_2$, $^2J_{C-F}$ = 24.8 Hz), 138.3 (t, 5-*C*CHF$_2$, $^2J_{C-F}$ = 24.3 Hz), 112.6 (*C*CO$_2$Me), 109.1 (t, 3-*C*HF$_2$, $^1J_{C-F}$ = 238 Hz), 107.3 (t, 5-*C*HF$_2$, $^1J_{C-F}$ = 236 Hz), 52.3 (O*C*H$_3$), 39.7 (N*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{10}H_{12}F_4N_3O2$ [M + MeCN + H]+: 282.0860. Found: 282.0859.

[3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl]methanol (II.38)



A solution of 2,2-dimethyl-4-methylidene-1,3-dioxolane (400 mg, 3.5 mmol) in dry MeCN (4 mL) was added to a solution of **2A** (1.09 equiv.) in dry MeCN (2 mL), the mixture stirred 18 h at room temperature, then methyl hydrazine (0.28 mL, 5.23 mmol) was added *via* syringe. The mixture was stirred 24h at room temperature. Internal standard: fluorobenzene (0.2 mL, 2.12 mmol), ^{19}F-NMR showed 42% of **4**. The mixture was treated with water (15 mL) and extracted with Et_2O (2 x 15mL). The organic layer was washed (brine), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 100%), to yield a brown oil (125 mg, 22 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.59 (t, C*H*F_2, $^2J_{H-F}$ = 55.2 Hz), 6.36 (s, C*H*$_{arom}$), 4.62 (s, C*H*$_2$), 3.84 (s, NC*H*$_3$), 2.84, (br s, O*H*) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.4 (d, CH*F*$_2$, $^2J_{H-F}$ = 55,2 Hz) ppm.

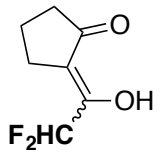
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 29.3 Hz), 143.0 (*C*NMe), 111.2 (t, *C*HF$_2$, $^1J_{C-F}$ = 233.5 Hz), 103.3 (4-*C*$_{arom}$), 55.3 (*C*H$_2$), 36.9 (N*C*H$_3$) ppm.

Anal. calcd for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; F, 23.43; N, 17.28; O, 9.87. Found: C, 44.95; H, 5.19; N, 16.91.

Silyl enol ethers – General procedure

A solution of **2A** (1.87 mmol) in dry MeCN (4mL) was cooled to 0 °C under inert atmosphere and a solution of silyl enol ether (1.70 mmol, 1 equiv.) in dry MeCN (2 mL) was added at 0 °C *via* syringe. The mixture was raised from 0 °C to room temperature over 30min. The corresponding cyclization reagent was added *via* syringe, the mixture stirred as specified for each case.

2-(2,2-Difluoro-1-hydroxyethylidene)cyclopentan-1-one (II.39)



Same procedure with (cyclopent-1-en-1-yloxy)trimethylsilane (440 mg, 0.5 mL, 2.8 mmol). The mixture was carefully concentrated *in vacuo*. The crude was distilled using Hickmann apparatus (55 °C / 3 mbar), to yield colourless oil (350mg, 77%, 90wt.% purity).

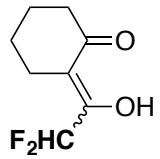
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.98 (br s, O*H*), 6.05 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.5 Hz), 2.74 (m, $C_{quat}CH_2$), 2.46 (t, 4H, C(O)C*H*$_2$), 1.99 (q, $CH_2CH_2CH_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -124.8 (dt, CH*F*$_2$, $^{2}J_{H-F}$ = 53.7 Hz, $^{4}J_{H-F}$ = 3.4Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 210.9 (*C*=O), 161.7 (t, *C*CHF_2, $^{2}J_{C-F}$ = 25.7 Hz), 110.7 (C_{quat}CO), 110.7 (t, *C*HF_2, $^{1}J_{C-F}$ = 243.4 Hz), 37.3 (*C*H_2CO), 24.6 and 20.9 (CH_2CH_2) ppm.

HRMS (ESI) calcd for $C_7H_9F_2O_2$ [M + H]: 163.0565. Found: 163.0580.

2-(2,2-Difluoro-1-hydroxyethylidene)cyclohexan-1-one (II.40)



Same procedure with 1-cyclohexenyloxytrimethylsilane (437 mg, 0.5 mL, 2.57 mmol). The mixture was carefully concentrated *in vacuo*. The crude was distilled using Hickmann apparatus (60 °C / 3 mbar), to yield colourless oil (333 mg, 74%, 90wt.% purity).

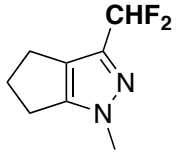
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.06 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.7 Hz), 2.46 (m, COC*H*$_2$ and C=CC*H*$_2$), 1.72 (m, 4H, C*H*$_2$C*H*$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -126.0 (d, CH*F*$_2$, $^{2}J_{H-F}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.0 (*C*=O), 184.1 (t, *C*OH, $^{2}J_{C-F}$ = 23.8 Hz), 110.4 (t, *C*HF_2, $^{1}J_{C-F}$ = 249.4 Hz), 105.9 (C=*C*CO), 32.0, 22.4, 21.7, 21.1 (4 x *C*H_2 aliph) ppm.

HRMS (ESI) Calcd for $C_{10}H_9F_2O_2$ [M + H]: 199.0565. Found: 199.0558.

3-(Difluoromethyl)-1-methyl-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (II.41a)



Same procedure with (cyclopent-1-en-1-yloxy)trimethylsilane (264 mg, 0.3 mL, 1.69 mmol). After 30min at room temperature, methyl hydrazine (0.14 mL, 2.61 mmol) was added *via* syringe, rapidly followed by H_2SO_4 conc. (0.05 mL, 0.91 mmol). The mixture was stirred 15min at room temperature. The mixture was filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane: 0 to 10%), to yield a colourless solid (290 mg, 99%, 92/8 with **5d**). M.p.: 62.9 - 63.6 °C.

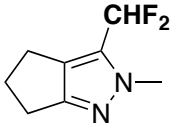
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.52 (t, C*H*F$_2$, $^2J_{H-F}$ = 55.4 Hz), 3.69 (NC*H*$_3$), 2.64 (m, 4H, 4,6-C*H*$_2$), 2.51 (m, 2H, 5-C*H*$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.2 (d, CH*F*$_2$, $^2J_{H-F}$ = 55.2 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.0 (*C*NCH$_3$), 139.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 30.0 Hz), 124.4 (*C*CCHF$_2$), 111.8 (t, *C*HF$_2$, $^1J_{C-F}$ = 232.3 Hz), 37.2 (N*C*H$_3$), 30.9 (5-*C*H$_2$), 23.3, 23.1 (4,6-*C*H$_2$) ppm.

HRMS (ESI) calcd for $C_8H_{11}F_2N_2$ [M+H]: 173.0885. Found: 173.0882.

3-(Difluoromethyl)-2-methyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (II.41b)

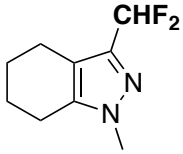


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.64 (t, C*H*F$_2$, $^2J_{H-F}$ = 54.4 Hz), 3.83 (NC*H*$_3$), 2.51 (m, 4H, 4,6-C*H*$_2$), 2.36 (m, 2H, 5-C*H*$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.7 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.1 (*C*NNCH$_3$), 128.6 (t, *C*CHF$_2$, $^2J_{C-F}$ = 27.6 Hz), 126.5 (t, *C*CCHF$_2$, $^3J_{C-F}$ = 3.8 Hz), 109.1 (t, *C*HF$_2$, $^1J_{C-F}$ = 235.2 Hz), 37.8 (N*C*H$_3$), 29.9 (5-*C*H$_2$), 24.4, 22.9 (4,6-*C*H$_2$) ppm.

3-(Difluoromethyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-indazole (II.42a)



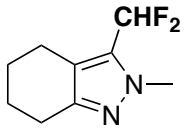
Same procedure with 1-cyclohexenyloxytrimethylsilane (289 mg, 0.33 mL, 1.69 mmol). After 30min at room temperature, methyl hydrazine (0.14 mL, 2.61 mmol) was added *via* syringe, rapidly followed by conc H_2SO_4. (0.05 mL, 0.91 mmol). The mixture was stirred 15min at room temperature. ^{19}F-NMR yield: 99%. The mixture was filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane: 0 to 10%). Yield: 228mg of colourless solid (72%). M.p.: 62.2 - 62.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.61 (t, C*H*F$_2$, $^2J_{H-F}$ = 54.8 Hz), 3.71 (s, NC*H*$_3$), 2.58 (td, 4H, 4,7-C*H*$_2$), 1.77 (m, 4H, 5,6-C*H*$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.8 (d, CH*F*$_2$, $^2J_{H-F}$ = 55.3 Hz) ppm.

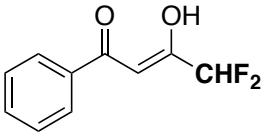
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.1 (t, *C*CHF_2, $^2J_{C-F}$ = 28.9 Hz), 140.2 (*C*NCH_3), 114.6 (*C*$CCHF_2$), 112.8 (t, *C*HF_2, $^1J_{C-F}$ = 232.5 Hz), 35.8 (N*C*H_3), 22.6, 22.5, 21.5, 20.2 (*C*H_2 aliph) ppm.
HRMS (ESI) calcd for $C_9H_{13}F_2N_2$ [M+H]: 187.1041. Found: 187.1039.

3-(Difluoromethyl)-2-methyl-4,5,6,7-tetrahydro-2*H*-indazole (II.42b)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.65 (t, C*H*F_2, $^2J_{H-F}$ = 53.7 Hz), 3.89 (s, NC*H*$_3$), 2.60 (td, 4H, 4,7-C*H*$_2$), 1.78 (m, 4H, 5,6-C*H*$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.1 (d, CH*F*$_2$, $^2J_{H-F}$ = 53.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.2 (*C*NCH_3), 130.4 (t, *C*CHF_2, $^2J_{C-F}$ = 24.9 Hz), 117.7 (t, *C*$CCHF_2$, $^3J_{C-F}$ = 4.2 Hz), 109.0 (t, *C*HF_2, $^1J_{C-F}$ = 234.3 Hz), 37.8 (N*C*H_3), 23.2, 23.1, 23.0, 20.0 (*C*H_2 aliph) ppm.

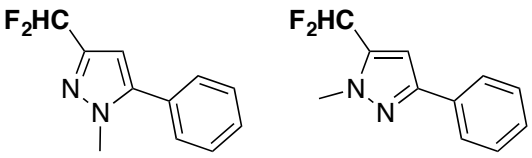
4,4-Difluoro-3-hydroxy-1-phenylbut-2-en-1-one (II.43)



Same procedure with trimethyl[(1-phenylethenyl)oxy]silane (612 mg, 3.18 mmol). After 45min, the mixture was treated with HCl 2M aq. (8mL) then was extracted with Et_2O. The aqueous was treated with sat. aq. bicarbonate solution until pH 8-9 and reextracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 20%), to yield colourless crystals (330 mg, 52%). M.p.: 45.2 - 45.9 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (m, 2'6'-C*H*$_{arom}$), 7.60 (m, 4'-C*H*$_{arom}$), 7.49 (m, 3',5'-C*H*$_{arom}$), 6.57 (s, 1H, C*H*CO), 6.01 (t, C*H*F_2, $^2J_{H-F}$ = 54.3 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -126.5 (d, CH*F*$_2$, $^2J_{H-F}$ = 53.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.8 (s, *C*O), 182.2 (t, *C*OH, $^2J_{C-F}$ = 25.2 Hz), 133.8, 133.7, 129.0, 127.6 (*C*$_{arom.}$), 109.8 (t, *C*HF_2, $^1J_{C-F}$ = 247 Hz), 92.7 (*C*HCO) ppm.
HRMS (ESI) calcd for $C_{10}H_8F_2NaO_2$ [M + Na]: 221.0385. Found: 221.0368. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in Et_2O. *Z*-configuration was observed.

Ref: K. I. Pashkevich, A. N. Fomin, V. I. Saloutin, D. V. Bazhenov, Y. K. Grishin, *Russ. Chem. Bull.* **1982**, *31*, 1210-1217.

3-(Difluoromethyl)-1-methyl-5-phenyl-1*H*-pyrazole and 5-(difluoromethyl)-1-methyl-3-phenyl-1*H*-pyrazole, 1:1 mixture (II.44a/II.44b)



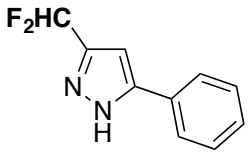
A solution of **II.45** (257 mg, 1.3 mmol) and pyridine (0.32 mL, 4.0 mmol, 3.1 equiv.) in dry MeCN (2 mL) was stirred at room temperature for 15 min. Methyl hydrazine (0.10 mL, 1.95 mmol, 1.5 equiv.) was added slowly, and the reaction mixture was stirred at room temperature for 24h. The solution was evaporated *in vacuo* and taken up in Et_2O (5 mL). The organic phase was washed with aq. HCl 1M solution (3 x 2 mL) and brine, then dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by silica gel chromatography (Et_2O in pentane: 10 to 30%) to yield a 1:1 mixture of regioisomers (220 mg, colourless oil, 82%).

For regioselective preparation:

3-(Difluoromethyl)-1-methyl-5-phenyl-1*H*-pyrazole (II.44a)
Same procedure with trimethyl[(1-phenylethenyl)oxy]silane (347 mg, 1.62 mmol). After 30min at room temperature, methyl hydrazine (0.12 mL, 2.24 mmol) was added *via* syringe, rapidly followed by H_2SO_4 conc. (0.04 mL, 0.75 mmol). After 45min, the mixture was filtered through a Na_2SO_4 layer and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%), to yield 360 mg of colourless oil (94/6 mixture with other regioisomer).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 5H, C$H_{arom.}$), 6.70 (t, CHF$_2$, $^2J_{H-F}$ = 55.3 Hz), 6.52 (s, 4-CH), 3.88 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.4 (d, CHF_2, $^2J_{H-F}$ = 55.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.8 (t, CCHF$_2$, $^2J_{C-F}$ = 29.1 Hz), 145.2 (5-C), 129.9, 129.1, 128.9, 128.8 (C_{arom}), 111.4 (t, CHF$_2$, $^1J_{C-F}$ = 234.0 Hz), 103.5 (4-CH), 37.8 (NCH$_3$) ppm.
HRMS (ESI) calcd for $C_{11}H_{10}F_2N_2Na$ [M + Na]: 231.0704. Found: 231.0690.
Ref: R. J. Linderman, K. S. Kirollos, *Tetrahedron Letters* **1989**, *30*, 2049-2052.

5-(Difluoromethyl)-1-methyl-3-phenyl-1*H*-pyrazole (II.44b)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, 2',6'-CH), 7.40 (m, 2H, 3',5'-CH), 7.32 (m, 1H, 4'-CH), 6.75 (t, CHF$_2$, $^2J_{H-F}$ = 53.9 Hz), 6.75 (s, 4-CH), 4.02 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.7 (d, CHF_2, $^2J_{H-F}$ = 53.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.6 (3-C), 136.5 (t, CCHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 132.6, 128.8, 128.1, 125.6 (C_{arom}), 108.8 (t, CHF$_2$, $^1J_{C-F}$ = 236.2 Hz), 104.3 (t, 4-CH, $^3J_{C-F}$ = 4.5 Hz), 38.1 (NCH$_3$) ppm.

3-(Difluoromethyl)-5-phenyl-1*H*-pyrazole (II.45)

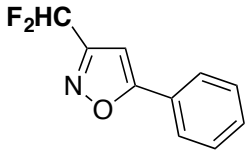


A solution of trimethyl[(1-phenylethenyl)oxy]silane (500 mg, 2.6 mmol) in dry MeCN (4 mL) was added to a solution of **2A** (2.65 mmol, 1.02 equiv.) in dry MeCN (3 mL) at 0 °C, and the reaction mixture was stirred from 0 °C to room temperature over 1 h. Hydrazine hydrate (0.19 mL, 3.87 mmol, 1.49 equiv.) was added

via syringe. The mixture was stirred 18 h at 50 °C. The mixture was evaporated *in vacuo*, and the crude was purified by flash chromatography (Et_2O in pentane: 0 to 10%), to yield a yellow solid (344 mg, 68 %). M.p.: 90.4 - 90.9 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.92 (s br., N*H*), 7.56 (m, 2H, 2',6'-C*H*), 7.39 (m, 3H, 3',4',5'-CH_{arom}), 6.66 (s, CH_{arom}), 6.54 (t, C*H*F_2, $^2J_{H-F}$ = 55.2 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.4 (d, CHF_2, $^2J_{H-F}$ = 55.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.3 (m, *C*CHF_2), 145.5 (m, *C*Ph), 129.2 (3',5'-C_{arom}), 129.3 (4'-C_{arom}), 128.8 (NHCC_{quat}), 125.8 (2',6'-C_{arom}), 110.8 (t, *C*HF_2, $^1J_{C-F}$ = 236.5 Hz), 100.6 (4-C_{arom}) ppm.
Anal. calcd for $C_{10}H_8F_2N_2$: C, 61.85; H, 4.15; F, 19.57; N, 14.43. Found: C, 61.75; H, 4.35; N, 14.45.

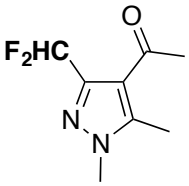
Ref: R. J. Linderman, K. S. Kirollos, *Tetrahedron Letters* **1989**, *30*, 2049-2052.

3-(Difluoromethyl)-5-phenyl-1,2-oxazole (II.46)



A solution of trimethyl[(1-phenylethenyl)oxy]silane (500 mg, 2.6 mmol) in dry MeCN (2 mL) was added to a solution of **2A** (2.6 mmol, 1 equiv.) in dry MeCN (4 mL) at 0 °C, and the reaction mixture was stirred from 0 °C to room temperature over 1 h . Hydroxylamine hydrochloride (270 mg, 3.88 mmol, 1.54 equiv.,) was added under argon flux, the mixture stirred 3 days at 50 °C. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 20%) to yield a colourless oil (347mg, 68%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 2H, 2',6'-CH_{arom}), 7.48 (m, 3H, 3',4',5'-CH_{arom}), 6.80 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 6.72 (s, 4-CH_{arom}) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.3 (d, CHF_2, $^2J_{H-F}$ = 53.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8 (OC_{quat}Ph), 159.5 (t, *C*CHF_2, $^2J_{C-F}$ = 30.2 Hz), 131.0 (4'-C_{arom}), 129.3 (3',5'-C_{arom}), 126.7 (1'-C_{arom}), 126.1 (2',6'-C_{arom}), 109.2 (t, *C*HF_2, $^1J_{C-F}$ = 237 Hz), 96.2 (4'-C_{arom}) ppm.
HRMS (ESI) calcd for $C_{10}H_8F_2NO$ [M + H]: 196.0568. Found: 196.0565.

1-[3-(Difluoromethyl)-1,5-dimethyl-1*H*-pyrazol-4-yl]ethan-1-one (II.47)

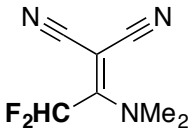


A solution of (3*Z*)-4-[(trimethylsilyl)oxy]pent-3-en-2-one (500 mg, 2.9 mmol) in dry MeCN (5 mL) was added to a solution of **2A** (2.9 mmol, 1 equiv.) in dry MeCN (5 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Methyl hydrazine (0.22 mL, 4.11 mmol, 1.49 equiv.) was finally added *via* syringe. The mixture was stirred 16h at 50 °C and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 10%), to yield a brown oil (169mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.83 (t, C*H*F_2, $^2J_{H-F}$ = 54.1 Hz), 3.80 (s, NCH_3), 2.52 (s, 6H, COCH_3 and 5-CH_3) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.9 (d, CHF_2, $^2J_{H-F}$ = 54.1 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 193.5 (*C*=O), 144.5

(*C*-5CH_3), 144.5 (t, *C*CHF_2, $^2J_{C\text{-}F}$ = 27.6 Hz), 118.3 (*C*CO), 111.5 (t, *C*HF_2, $^1J_{C\text{-}F}$ = 235 Hz), 36.6 (N*C*H_3), 30.7 (CO*C*H_3), 11.6 (5-*C*H_3) ppm. HRMS (ESI) calcd for $C_8H_{10}F_2N_2ONa$ [M + Na]: 211.0653. Found: 211.0555.

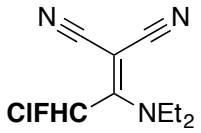
CH-acidic compounds – Preparation of key adducts **II.48A-C** and **II.49A**

2-[1-(Dimethylamino)-2,2-difluoroethylidene]propanedinitrile (II.48A)



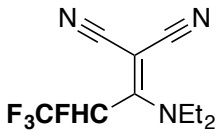
A solution of **2A** (3.33 mmol, 1.1 equiv.) in dry MeCN (4 mL) was prepared under inert atmosphere. A solution of malononitrile (200 mg, 3.03 mmol) in dry MeCN (4 mL) was added *via* syringe, rapidly followed by Hünig's base (0.75 mL, 4.54 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 1 h, and was diluted with Et_2O. An excess of neutral alumina was added, the suspension was evaporated *in vacuo* to give a solid deposit, which was taken up in cyclohexane. After filtration, the solid was rinsed several times with cyclohexane. The combined filtrate was evaporated *in vacuo*, to yield beige crystals (95wt.%, 480mg, 93%). M.p.: 67.6 - 68.6 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.70 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 51.4 Hz), 3.39 (s, 6H, N(C*H*$_3$)$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.4 (d, CH*F*$_2$, $^2J_{H\text{-}F}$ = 51.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.9 (t, *C*CHF_2, $^2J_{C\text{-}F}$ = 22 Hz), 114.5 and 114.3 (*C*N and *C*'N'), 110.6 (t, *C*HF_2, $^1J_{C\text{-}F}$ = 248 Hz), 55.9 (t, *C*(CN)$_2$, J = 7 Hz), 43.9 (N(*C*H_3)$_2$) ppm.
Anal. calcd for $C_7H_7F_2N_3$: C, 49.12; H, 4.12; F, 22.20; N, 24.55. Found: C, 49.32; H, 4.31; N, 24.34.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in Et_2O.

2-(2-chloro-1-(diethylamino)-2-fluoroethylidene)malononitrile (II.48B)



Same procedure with activated Yarovenko's reagent **2B** (1.06 equiv.). Characterization after purification by flash chromatography (AcOEt in cyclohexane 0 to 20%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, C*H*FCl, $^2J_{H\text{-}F}$ = 47.8 Hz), 3.89 to 3.60 (m, 4H, N(C*H*$_2$CH$_3$)$_2$), 1.32 (t, 6H, N(CH$_2$C*H*$_3$)$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -139.5 (d, CH*F*Cl, $^2J_{F\text{-}H}$ = 47.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.2 (d, *C*CHFCl, $^2J_{C\text{-}F}$ = 20.1 Hz), 114.9 (2 x s, *C*N(CH$_2$CH$_3$)$_2$, J = 5.6 Hz), 94.7 (d, *C*HFCl, J = 253 Hz), 47.5 (N(*C*H$_2$CH$_3$)$_2$), 13.2 (N(CH$_2$*C*H$_3$)$_2$) ppm.
HRMS (ESI) calcd for $C_9H_{11}ClFN_3Na$ [M+Na]: 238.0518 + 240.0490. Found: 238.0510 + 240.0485.

2-(1-(diethylamino)-2,3,3,3-tetrafluoropropylidene)malononitrile (II.48C)



Same procedure with activated Ishikawa's reagent **2C** (1.05 equiv.). Characterization after purification by flash chromatography (AcOEt in cyclohexane 0 to 20%).

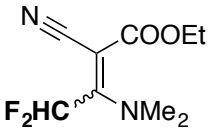
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.99 (dq, C*H*FCF_3, $^{2}J_{H-F}$ = 43.7 Hz, $^{3}J_{H-F}$ = 6.8 Hz), 3.78 to 3.57 (m, 4H, $N(CH_2CH_3)_2$), 1.31 (t, 6H, $N(CH_2CH_3)_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -72.9 (dd, CHFC*F*$_3$, $^{3}J_{F-F}$ = 12.3 Hz, $^{3}J_{F-H}$ = 6.8 Hz), -196.7 (dq, CH*F*CF_3, $^{2}J_{F-H}$ = 43.3 Hz, $^{3}J_{F-F}$ = 12.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.7 (d, *C*$N(CH_2CH_3)_2$, $^{2}J_{C-F}$ = 17.3 Hz), 120.9 (qd, CF3, $^{1}J_{C-F}$ = 285 Hz, $^{2}J_{C-F}$ = 26 Hz), 115.0 and 114.6 (2 x *C*N), 86.4 (qd, *C*$HFCF_3$, $^{1}J_{C-F}$ = 203 Hz, $^{2}J_{C-F}$ = 37 Hz), 48.3 (d, $N(CH_2CH_3)_2$), 13.4 ($N(CH_2CH_3)_2$) ppm.

HRMS (ESI) calcd for $C_{10}H_{11}F_4N_3Na$ [M+Na]: 272.0781. Found: 272.0759.

Ethyl 2-cyano-3-(dimethylamino)-4,4-difluorobut-2-enoate (II.49)



A solution of **2A** (1.95 mmol, 1.04 equiv.) in dry MeCN (3 mL) was prepared under inert atmosphere. A solution of ethyl cyanoacetate (212 mg, 0.2 mL, 1.87 mmol) in dry MeCN (3 mL) was added *via* syringe, rapidly followed by Hünig's base (0.47 mL, 2.84 mmol, 1.52 equiv.). The mixture was stirred at room temperature for 1 h, and was diluted with Et_2O. An excess of neutral alumina was added, the suspension was evaporated *in vacuo* to give a solid deposit, which was taken up in cyclohexane. After filtration, the solid was rinsed several times with cyclohexane. The combined filtrate was evaporated *in vacuo*, to yield an orange oil (95wt.%, 285mg, 70%, 8:2 mixture of *E*/*Z* isomers).

Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (t, C*H*F_2, $^{2}J_{H-F}$ = 52.4 Hz), 4.20 (q, O*C*H_2), 3.34 (s, $N(CH_3)_2$), 1.30 (t, CH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.4 (d, CH*F*$_2$, $^{2}J_{H-F}$ = 52.3 Hz) ppm.

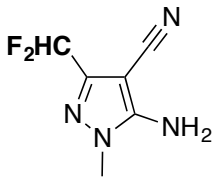
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.3 (*C*O), 162.1 (t, *C*CHF_2, $^{2}J_{C-F}$ = 21 Hz), 117.5 (*C*N), 108.6 (t, *C*HF_2, $^{1}J_{C-F}$ = 245 Hz), 76.2 (t, *C*CN, $^{3}J_{C-F}$ = 6 Hz), 61.5 (O*C*H_2), 44.6 ($N(CH_3)_2$), 14.3 (*C*H_3) ppm.

HRMS (ESI) calcd for $C_9H_{12}F_2N_2NaO_2$ [M + Na]: 241.0759. Found: 241.0765.

CH-acidic compounds - 3-CHF_2-5-amino-4-pyrazole or isoxazole carbonitriles or carboxylates **II.50-55**

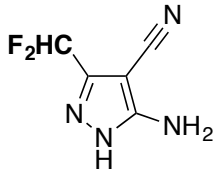
The corresponding heterocycles were prepared using malononitrile or ethyl cyanoacetate in dry MeCN (1 mol/L) and adding the corresponding cyclization reagent (except **II.54**). The mixture was stirred 1 h and was evaporated *in vacuo*. ^{19}F-NMR yields were measured using fluorobenzene as internal standard.

5-Amino-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonitrile (II.50)



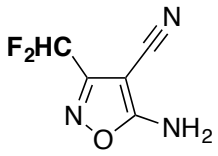
Prepared from **II.48A** (80 mg, 0.47 mmol) and *N*-methylhydrazine (0.04 mL, 0.75 mmol, 1.6 equiv.). Internal standard: fluorobenzene (0.68 equiv., 0.03 mL, 0.32 mmol). ^{19}F-NMR yield: 99%. The corresponding crude was evaporated *in vacuo* and purified by flash chromatography (MeOH in CH_2Cl_2: 0 to 2.5%) to yield a beige solid. M.p.: 96 - 99 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.52 (t, C*H*F_2, $^2J_{H-F}$ = 54.1 Hz), 4.54 (br s, NH_2), 3.66 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -114.0 (d, CHF_2, $^2J_{H-F}$ = 53.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.4 (*C*NH_2), 145.7 (t, *C*CHF_2, $^2J_{H-F}$ = 29.2 Hz), 112.6 (*C*N), 110.2 (t, *C*HF_2, $^1J_{C-F}$ = 236.5 Hz), 73.5 (*C*-CN), 35.2 (N*C*H_3) ppm.
HRMS calcd for $C_6H_6F_2N_4Na$ [M + Na]: 195.0453 + 196.0485. Found: 195.0434 + 196.0467.

5-Amino-3-(difluoromethyl)-1*H*-pyrazole-4-carbonitrile (II.51)



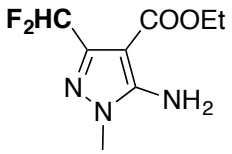
Prepared from **II.48A** (102 mg, 0.60 mmol) and hydrazine hydrate (0.05 mL, 1.02 mmol, 1.71 equiv.). Internal standard: fluorobenzene (0.71 equiv., 0.04 mL, 0.42 mmol). ^{19}F-NMR yield: 99%. The crude was purified by flash chromatography (MeOH in CH_2Cl_2: 0 to 2%), to yield an orange solid. M.p.: 163.7 - 164.3 °C.
^{1}H-NMR (400 MHz, Acetone-d^6): δ = 11.70 (br s, N*H*), 6.70 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 6.23 (br s, NH_2) ppm.
^{19}F-NMR (376 MHz, Acetone-d^6): δ = -114.5 (d, CHF_2, $^2J_{H-F}$ = 53.5 Hz) ppm.
^{13}C-NMR (100 MHz, Acetone-d^6): δ = 155.3 (*C*NO), 147.9 (t, *C*CHF_2, $^2J_{C-F}$ = 30 Hz), 113.3 (*C*N), 112.3 (t, *C*HF_2, $^1J_{C-F}$ = 232.3 Hz), 71.3 (*C*CN) ppm.
Anal. calcd for $C_5H_4F_2N_4$: C, 37.98; H, 2.55; F, 24.03; N, 35.44. Found: C, 38.23; H, 2.83; N, 34.80.

5-Amino-3-(difluoromethyl)-1,2-oxazole-4-carbonitrile (II.52)



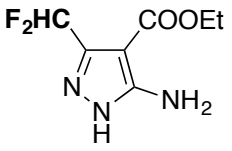
Prepared from **II.48A** (500 mg, 2.92 mmol) and hydroxylamine (50% aq. solution; 0.2 mL, 3.2 mmol, 1.1 equiv.). The crude was purified by flash chromatography (Et_2O in pentane: 0 to 80%), to yield a colourless solid (500 mg, >99%). M.p.: 135.3 - 135.9 °C.
^{1}H-NMR (400 MHz, CD_3CN): δ = 7.00 (br s, NH_2), 6.77 (t, CHF$_2$, $^2J_{H-F}$ = 52.6 Hz) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -119.6 (d, CHF_2, $^2J_{H-F}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 174.7 (CNH$_2$), 159.2 (t, CCHF$_2$, $^2J_{C-F}$ = 28.6 Hz), 111.5 (CN), 110.1 (t, CHF$_2$, $^1J_{C-F}$ = 237 Hz), 64.6 (CCN) ppm.
HRMS (ESI) calcd for $CH_2F_2N_3O$ [M - H]: 158.0160. Found: 158.0159.

Ethyl 5-amino-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate (II.53)



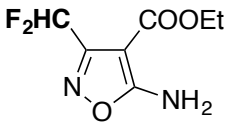
Prepared from **II.49** (100 mg, 0.46 mmol) and *N*-methylhydrazine (0.04 mL, 0.75 mmol, 1.6 equiv.). Internal standard: fluorobenzene (0.70 equiv., 0.03 mL, 0.32 mmol). ^{19}F-NMR yield: 99%. The crude was purified by flash chromatography (MeOH in CH_2Cl_2: 0 to 2.5%), to yield a yellow solid. M.p.: 73.4 - 74.2 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.88 (t, CHF$_2$, $^2J_{H-F}$ = 53.4 Hz), 5.12 (br s, NH_2), 4.29 (q, OCH_2), 3.64 (s, NCH_3), 1.34 (t, CH$_2$CH_3) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -116.9 (d, CHF_2, $^2J_{H-F}$ = 53.7 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.7 (CO), 150.5 (CNH$_2$), 143.9 (t, CCHF$_2$, $^2J_{C-F}$ = 24.4 Hz), 110.0 (t, CHF$_2$, $^1J_{C-F}$ = 235.8 Hz), 94.0 (CCO$_2$Et), 60.3 (NCH$_3$), 34.4 (OCH$_2$), 14.4 (CH$_2$CH$_3$) ppm. Anal. calcd for $C_8H_{11}F_2N_3O_2$: C, 43.84; H, 5.06; F, 17.34; N, 19.17; O, 14.60. Found: C, 44,10; H, 5.22; N, 18,98.

Ethyl 5-amino-3-(difluoromethyl)-1*H*-pyrazole-4-carboxylate (II.54)



Prepared from **II.49** (250 mg, 1.15 mmol) and *N*-BOC-hydrazine (230 mg, 1.74 mmol, 1.52 equiv.). The mixture was stirred 18 h at 50 °C and was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane: 0 to 80%), to yield the NH-pyrazole as colourless solid (204mg, 87%). M.p.: 151.5 - 151.9 °C. The BOC-pyrazole was isolated as colourless oil (15mg, 4%) and characterized. ^{1}H-NMR (400 MHz, CD_3CN): δ = 10.39 (br s, NH), 6.94 (t, CHF$_2$, $^2J_{H-F}$ = 54 Hz), 5.52 (br s, NH_2), 4.23 (q, OCH_2CH$_3$), 1.29 (t, CH$_2$CH_3) ppm. ^{19}F-NMR (376 MHz, CD_3CN): δ = -117.8 (d, CHF_2, $^2J_{H-F}$ = 54.3 Hz) ppm. ^{13}C-NMR (100 MHz, CD_3CN): δ = 164.4 (C=O), 153.6 (CNH$_2$), 145.9 (t, CCHF$_2$, $^2J_{C-F}$ = 24 Hz), 111.6 (t, CHF$_2$, $^1J_{C-F}$ = 235 Hz), 93.2 (CCOOEt), 60.8 (OCH$_2$), 14.7 (CH$_2$CH$_3$) ppm. HRMS (ESI) calcd for $C_7H_{10}F_2N_3O_2$ [M+H]: 206.0736. Found: 206.0745.

Ethyl 5-amino-3-(difluoromethyl)isoxazole-4-carboxylate (II.55)



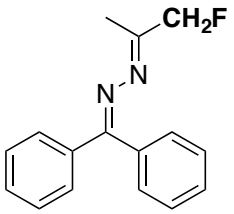
Prepared from **II.49** (100 mg, 0.46 mmol) and hydroxylamine (50% aq. solution; 0.05 mL, 0.82 mmol, 1.7 equiv.). Internal standard: fluorobenzene (0.70 equiv., 0.03 mL, 0.32 mmol). ^{19}F-NMR yield: 99%. The crude was purified by flash chromatography (MeOH in CH_2Cl_2: 0 to 2.5%), to yield a brown solid. M.p.: 124.6 - 125.4 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (t, C*H*F$_2$, $^{2}J_{H\text{-}F}$ = 52.6 Hz), 6.17 (br s, N*H*$_2$), 4.31 (q, C*H*$_2$), 1.35 (t, C*H*$_3$) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.4 (d, CH*F*$_2$, $^{2}J_{H\text{-}F}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.24 (*C*O), 162.4 (*C*NH$_2$), 156.5 (t, *C*CHF$_2$, $^{2}J_{C\text{-}F}$ = 26 Hz), 108.7 (t, *C*HF$_2$, $^{1}J_{C\text{-}F}$ = 240.2 Hz), 85.5 (*C*COOEt), 60.9 (O*C*H$_2$), 14.3 (CH$_2$*C*H$_3$) ppm.
Anal. calcd for $C_7H_8F_2N_2O_3$: C, 40.78; H, 3.91; F, 18.43; N, 13.59; O, 23.28. Found: C, 41,05; H, 4.00; N, 13,44. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in Et_2O.

Azine route

Preparation of fluorinated azines **II.56**

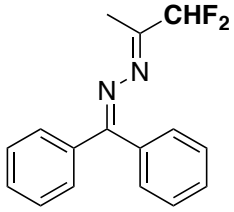
Fluoroalkyl azines. Cold fluorinated propan/butan-2-one (102 mmol) was introduced *via* a precooled syringe to recrystallized benzophenone hydrazone (10 g, 51 mmol) at room temperature in a sealed vial under argon. The mixture was stirred at 50 °C over 18 h and then diluted with Et_2O, dried ($MgSO_4$), filtered and evaporated *in vacuo*.
Fluoroaryl azines. Cold fluorinated acetophenone (11.2 mmol) was introduced *via* a precooled syringe to recrystallized benzophenone hydrazone (2 g, 10.2 mmol) in chloroform (3.2 mL) into a sealed vial under argon. The mixture was stirred at room temperature for 48h, then diluted with CH_2Cl_2, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude mixture was crystallized from pentane and dried *in vacuo*.

1-(Diphenylmethylene)-2-(1-fluoropropan-2-ylidene)hydrazine (II.56a)



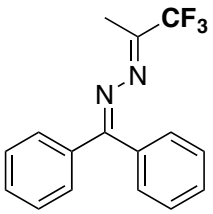
Prepared from benzophenone and fluoroacetone. Yield: 2.17 g (81%); yellow oil (purity 75%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73-7.23 (m, 10H, arom), 4.87 (d, C*H*$_2$F, $^2J_{H-F}$ = 47 Hz), 2.13 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -224.2 (t, CH_2*F*, $^2J_{H-F}$ = 47.2 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.9 (*C*N), 158.0 (d, *C*CH$_2$F), 128.0-130.1 (arom), 85.1 (d, *C*H$_2$F, $^1J_{C-F}$ = 167 Hz), 14.8 (*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{16}H_{16}FN_2$ [M+H]$^+$: 255.1292 + 256.1325. Found: 255.1282 + 256.1300.

1-(1,1-Difluoropropan-2-ylidene)-2-(diphenylmethylene)hydrazine (II.56b)



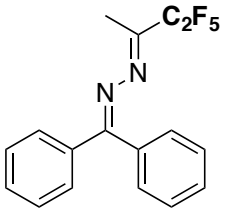
Prepared from benzophenone and 1,1-difluoroacetone. Yield: 14.0 g (>99%); yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.62 (m, 2H), 7.46-7.30 (m, 6H), 7.20-7.10 (m, 2H), 5.92 (d, C*H*$_2$F, $^2J_{H-F}$ = 56 Hz), 2.04 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.1 (d, CH*F*$_2$, $^2J_{H-F}$ = 55 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.1 (*C*N), 154.5 (t, *C*CHF$_2$, $^2J_{C-F}$ = 32 Hz), 137.4 and 134.4 (*CC*'C=N), 132.4-128.1 (arom), 114.4 (t, *C*HF$_2$, $^1J_{C-F}$ = 239 Hz), 11.0 (*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{16}H_{14}F_2N_2Na$ [M+Na]$^+$: 295.102. Found: 295.102.

1-(Diphenylmethylene)-2-(1,1,1-trifluoropropan-2-ylidene)hydrazine (II.56c)



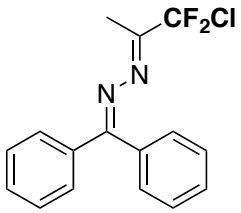
Prepared from benzophenone and 1,1,1-trifluoroacetone. Yield: 15 g (>99%); yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.63 (m, 2H), 7.47-7.33 (m, 6H), 7.21-7.13 (m, 2H), 2.08 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.4 (s, CF_3) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.8 (*C*N), 148.2 (q, *C*CF_3, $^{2}J_{C-F}$ = 34 Hz), 137.2 and 134.0 (*CC'*C=N), 132.4-128.1 (arom), 120.4 (q, *C*F_3, $^{1}J_{C-F}$ = 276 Hz), 12.8 (*C*H_3) ppm. HRMS (ESI) calcd for $C_{16}H_{14}F_3N_2$ $[M+H]^+$: 291.111. Found: 291.110.

1-(Diphenylmethylene)-2-(3,3,4,4,4-pentafluorobutan-2-ylidene)hydrazine (II.56d)



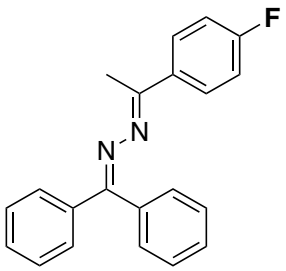
Prepared from benzophenone and 3,3,4,4,4-pentafluorobutan-2-one. Yield: 4.42 g (91%); yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70-7.64 (m, 2H), 7.45-7.33 (m, 6H), 7.20-7.12 (m, 2H), 2.09 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.9 (CF_3), -117.5 (CF_2) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.7 (*C*C_2F_5), 159.8 (*C*N), 148.6 (t, *C*CF_2, $^{2}J_{C-F}$ = 27 Hz), 137.7-128.0 (arom), 118.7 (qt, *C*F_2, $^{1}J_{C-F}$ = 286 Hz, $^{2}J_{C-F}$ = 35 Hz), 110.6 (qt, *C*F_3, $^{1}J_{C-F}$ = 254 Hz, $^{2}J_{C-F}$ = 38 Hz), 12.9 (*C*H_3) ppm.
HRMS (ESI) calcd for $C_{17}H_{13}F_5N_2Na$ $[M+Na]^+$: 363.089. Found: 363.089.

1-(1-Chloro-1,1-difluoropropan-2-ylidene)-2-(diphenylmethylene)hydrazine (II.56e)



Prepared from benzophenone and 1-chloro-1,1-difluoroacetone. Yield: 1.52 g (91%); yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83-7.76 (m, 4H), 7.62-7.54 (m, 2H), 7.51-7.44 (m, 4H), 2.03 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.1 (s, CF_2Cl) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.7 (*C*CF_2Cl), 159.8 (*C*N), 152.5 (t, *C*CF_2Cl, $^{2}J_{C-F}$ = 28 Hz), 137.6-128.3 (arom), 123.0 (t, *C*F_2Cl, $^{1}J_{C-F}$ = 289 Hz), 12.5 (*C*H_3) ppm.
HRMS (ESI) calcd for $C_{16}H_{13}ClF_2N_2Na$ $[M+Na]^+$: 329.063. Found: 329.063.

1-(Diphenylmethylene)-2-(1-(4-fluorophenyl)ethylidene)hydrazine (II.56f)



Prepared from benzophenone and 4-fluoroacetophenone. Yield: 1.14 g (70%); yellow needles. M.p.: 81.4 - 81.7 °C).

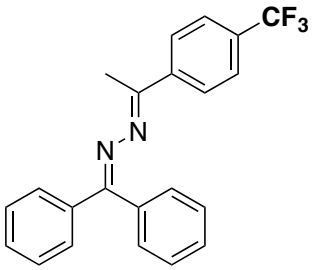
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91-7.62 (6H, p-Harom and 2',6'-Harom), 7.50-7.22 (8H, arom), 6.98 (t, 2H, 3',5'-Harom), 2.40 (s, CH_3), ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.6 (m, 4'-*F*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.9 and 162.5 (*C*N and *C'*N), 159.1 and 158.2 (d, 4'-Carom, $^{1}J_{C\text{-}F}$ = 219 Hz), 138.3 and 135.6 (d, *CC'*C=N), 134.5 (dd, CH_3*C*N), 129.9-127.8 (*o*,*m*-*C*arom), 115.3 (d, 3',5'-*C*arom), 15.5 (*C*H_3) ppm.

HRMS (ESI) calcd for $C_{21}H_{17}F_1N_2Na$ $[M+Na]^+$: 339.127. Found: 339.127.

1-(Diphenylmethylene)-2-(1-(4-(trifluoromethyl)phenyl)ethylidene)hydrazine (II.56g)



Same procedure with 4-(trifluoromethyl)acetophenone. Yield: 3.1 g (81%); yellow needles (m.p.: 93.6 - 93.8 °C).

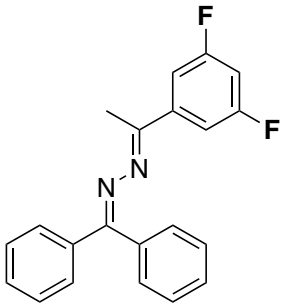
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.25 (14H, arom), 2.42 and 2.33 (s, CH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -62.6 (s, CF_3) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.9 and 157.3 (*C*N and *C'*N), 141.5-135.7 (arom), 131.1 (q, *C*CF_3, $^{2}J_{C\text{-}F}$ = 33 Hz), 130.0-126.9 (arom), 121.4 (q, *C*F_3, $^{1}J_{C\text{-}F}$ = 272 Hz), 15.5 (*C*H_3) ppm.

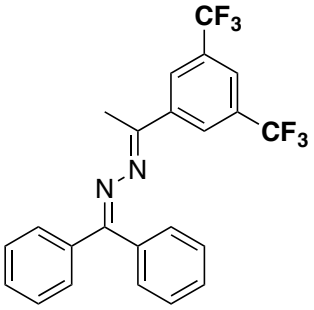
HRMS (ESI) calcd for $C_{22}H_{17}ClF_3N_2Na$ $[M+Na]^+$: 389.124. Found: 389.124.

1-(1-(3,5-Difluorophenyl)ethylidene)-2-(diphenylmethylene)hydrazine (II.56h)



Prepared from benzophenone and 3',5'-difluoroacetophenone. Yield: 2.72 g (80%); pale yellow solid (m.p.: 98.6 - 98.8 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75-7.68 (m, 2H), 7.46-7.34 (m, 6H), 7.25 (m, 2H), 7.18 (m, 2H), 6.78 (m, 1H), 2.37 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -109.8 (m, 2*F*) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.3 and 156.5 (*C*N and *C'*N), 141.6 (t, *C*C(CH_3)N, $^{3}J_{C-F}$ = 7 Hz), 137.9 and 135.2 (*CC'*C=N), 130.1-127.9 (arom), 109.5 (m), 104.7 (t, $^{2}J_{C-F}$ = 25 Hz), 15.4 (*C*H_3) ppm.
HRMS (ESI) calcd for $C_{21}H_{16}F_2N_2Na$ [M+Na]$^+$: 357.118. Found: 357.117.

1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethylidene)-2-(diphenylmethylene)hydrazine (II.56i)

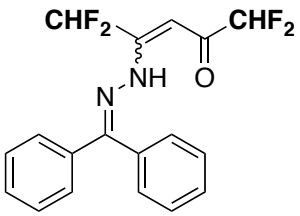


Same procedure with 3',5'-bis(trifluoromethyl)acetophenone. Yield: 2.7 g (61%); pale yellow solid. (m.p.: 97.5 - 98.0 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 2H), 7.83 (m, 1H), 7.78-7.72 (m, 2H), 7.45-7.37 (m, 6H), 7.29-7.23 (m, 2H), 2.46 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -62.9 (s, 6*F*) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.1 and 155.9 (*C*N and *C'*N), 140.2-135.2 (arom), 131.7 (q, *C*CF_3, $^{2}J_{C-F}$ = 32 Hz), 130.3-126.6 (arom), 123.3 (q, *C*F_3 $^{1}J_{C-F}$ = 275 Hz), 122.9 (m, 4'C, J = 3.5 Hz), 15.3 (*C*H_3) ppm.
HRMS (ESI) calcd for $C_{23}H_{16}F_6N_2Na$ [M+Na]$^+$: 457.111. Found: 457.111.

Preparation of β-(diphenylmethylidene)-bis(fluoroalkyl)-enones **II.57**

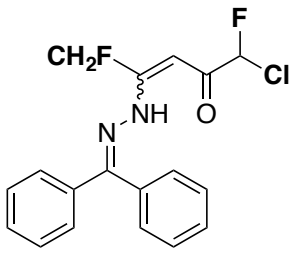
From TFEDMA: $BF_3{\cdot}Et_2O$ (0.16 mL, 1.26 mmol) was added *via* syringe to a vigorously stirred solution of TFEDMA (0.15 mL, 1.22 mmol) in distilled CH_2Cl_2 (2 mL) in a Schlenk vessel under inert atmosphere. After 15min, the solvent was removed *in vacuo*. The residual white solid was taken up in dry MeCN (2 mL). A solution of fluorinated azine **3** (1.83 mmol, 1.5 equiv.) in dry MeCN (2 mL) was added to the FAR solution *via* syringe, the mixture was heated at 50 °C over 18 h. The reaction mixture was treated with 1N aq. HCl solution (5 mL), and extracted with Et_2O (2 x 15 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude mixture was purified by flash chromatography (Et_2O in pentane: see examples).
From Yarovenko and Ishikawa reagents: Same conditions but all steps performed in distilled CH_2Cl_2. The mixture is finally treated with conc. HCl (3 equiv.) before work up. For electron-deficient azines (*e.g.* **II.56d**), the stoichiometry was modified (*ca.* 2.5 equiv.) to increase the conversion, despite the difficulties to separate the residual benzophenone afterwards.

4-(2-(Diphenylmethylene)hydrazinyl)-1,1,5,5-tetrafluoropent-3-en-2-one (II.57A.b)



The crude mixture was purified by flash chromatography (Et_2O in pentane 2% to 10%). Yield: 345 mg (81%); yellow solid (m.p.: 97.7 - 98.4 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.48 (s, N*H*), 7.66-7.20 (arom), 7.15 (t, C*H*F$_2$, $^2J_{H\text{-}F}$ = 53.8 Hz), 5.89 (s, C*H*), 5.65 (t, C*H*F$_2$, $^2J_{H\text{-}F}$ = 54.5 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -123.9 (dd, CH*F*$_2$, $^2J_{H\text{-}F}$ = 53.4 Hz, $^3J_{C\text{-}F}$ = 2.0 Hz), -125.2 (d, CH*F*$_2$, $^2J_{H\text{-}F}$ = 54.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.5 (t, *C*O, $^3J_{C\text{-}F}$ = 24.8 Hz), 156.2 (*C*N), 154.1 (t, NH*C*, $^3J_{C\text{-}F}$ = 24.9 Hz), 136.3 and 131.4 (*CC*'C=N), 130.7-128.1 (arom.), 110.1 (t, *C*O, $^1J_{C\text{-}F}$ = 251.7 Hz), 108.3 (t, *C*NH, $^1J_{C\text{-}F}$ = 241.9 Hz), 86.1 (t, *C*H, $^3J_{C\text{-}F}$ = 6 Hz) ppm.
HRMS (ESI) calcd for $C_{18}H_{14}F_4N_2NaO$ $[M+Na]^+$: 373.0934. Found: 373.0917.

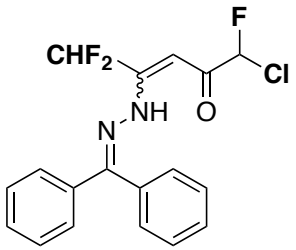
1-Chloro-4-(2-(diphenylmethylene)hydrazinyl)-1,5-difluoropent-3-en-2-one (II.57B.a)



The crude mixture was purified by flash chromatography (Et_2O in pentane: 0 to 10%). Yield: 139 mg (39%); brown residue, 90% purity.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.45 (s, N*H*), 7.68-7.28 (arom.), 6.10 (d, C*H*FCl, $^2J_{H\text{-}F}$ = 51.2 Hz), 5.78 (t, C*H*CO), 5.65 (d, C*H*$_2$F, $^2J_{H\text{-}F}$ = 47.4 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -143.3 (dt, CH*F*Cl, $^2J_{H\text{-}F}$ = 51 Hz, $^4J_{H\text{-}F}$ = 2.7 Hz), <210 (CH$_2$*F*) ppm.

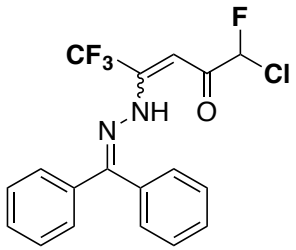
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.0 (d, *C*O), 160.6 (d, *C*NH), 155.0 (s, *C*NNH), 136.6-127.9 (arom.), 96.6 (d, *C*HFCl, $^{1}J_{C-F}$ = 257 Hz), 85.0 (d, *C*HCO), 78.6 (d, *C*H_2F, $^{2}J_{H-F}$ = 176 Hz) ppm.
HRMS (ESI) calcd for $C_{18}H_{15}ClF_2N_2NaO$ [M+Na]$^+$: 371.0733. Found: 371.0744.

1-Chloro-4-(2-(diphenylmethylene)hydrazinyl)-1,5,5-trifluoropent-3-en-2-one (II.57B.b)



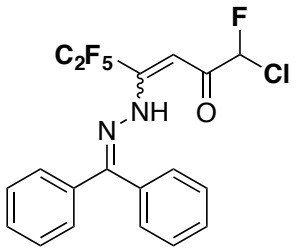
The crude mixture was purified by flash chromatography (Et_2O in pentane: 0 to 10%). Yield: 294 mg (91%); yellow solid (m.p.: 107.5 - 109.1 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.41 (s, N*H*), 7.68-7.56 and 7.44-7.30 (10H, arom.), 7.17 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.5 Hz), 6.10 (d, C*H*FCl, $^{2}J_{H-F}$ = 51 Hz), 5.90 (d, C*H*CO, $^{4}J_{H-F}$ = 2.7 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -123.9 (ddd + sat., CH*F*$_2$, $^{2}J_{H-F}$ = 53.5 Hz, $^{3}J_{C-F}$ = 27.5 Hz, $^{4}J_{H-F}$ = 2.2 Hz), -144.1 (dt, CH*F*Cl, $^{2}J_{H-F}$ = 51.2 Hz, $^{4}J_{H-F}$ = 2.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 188.3 (d, CO, $^{2}J_{C-F}$ = 24 Hz), 155.8 (*C*NNH), 154.0 (t, *C*CHF_2, $^{2}J_{C-F}$ = 24.8 Hz), 136.4-128.2 (arom), 108.4 (t, *C*HF_2, $^{1}J_{C-F}$ = 241.5 Hz), 96.4 (d, *C*HFCl, $^{1}J_{C-F}$ = 257 Hz), 85.9 (t, *C*HCO, $^{4}J_{H-F}$ = 6.5 Hz) ppm.
Anal. calcd for $C_{18}H_{14}ClF_3N_2O$: C, 58.95; H, 3.85; N, 7.64. Found: C, 58.77; H, 3.91; N, 7.81.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in Et_2O.

1-Chloro-4-(2-(diphenylmethylene)hydrazinyl)-1,5,5,5-tetrafluoropent-3-en-2-one (II.57B.c)



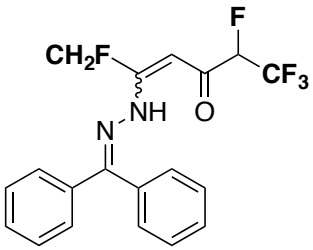
The crude mixture was purified by silica gel chromatography (Et_2O in pentane 0 to 5%). Yield: 400 mg (85%); yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.44 (s, N*H*), 7.66-7.60 and 7.42-7.32 (10H, arom.), 6.09 (d, C*H*FCl, $^{2}J_{H-F}$ = 51 Hz), 5.93 (d, C*H*CO) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -65.0 (d, C*F*$_3$, $^{4}J_{H-F}$ = 2 Hz), -144.5 (d, CH*F*Cl, $^{2}J_{H-F}$ = 51 Hz, $^{4}J_{H-F}$ = 2.7 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 188.2 (d, *C*O, $^{2}J_{C-F}$ = 24.3 Hz), 156.2 (*C*N), 148.7 (q, *C*CF_3, $^{2}J_{C-F}$ = 32 Hz), 136.3 and 131.3 (*CC'*C=N), 130.6-128.2 (arom.), 119.5 (q, *C*F_3, $^{1}J_{C-F}$ = 278 Hz), 96.2 (d, *C*HFCl, $^{1}J_{C-F}$ = 257 Hz), 87.5 (d, *C*HCO) ppm. HRMS (ESI) Calcd for $C_{18}H_{13}ClF_4N_2NaO$ [M+Na]$^+$: 407.0545 + 409.0516. Found: 407.0544 + 409.0514.

1-Chloro-4-(2-(diphenylmethylene)hydrazinyl)-1,5,5,6,6,6-hexafluorohex-3-en-2-one (II.57B.d)



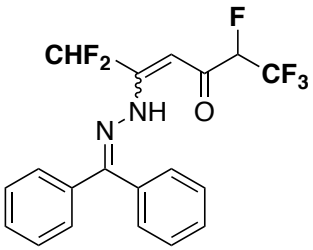
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 28 mg (12%).
^{1}H-NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 12.42 (s, N*H*), 7.68-7.60 and 7.42-7.32 (arom.), 6.09 (d, C*H*FCl, $^2J_{H-F}$ = 51 Hz), 5.93 (d, C*H*CO) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -65 (C*F*$_3$), -111.9 (C*F*$_2$) -144.5 (d, CH*F*Cl, $^2J_{H-F}$ = 51 Hz, $^4J_{H-F}$ = 2.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.5 (t, *C*O, $^2J_{C-F}$ = 25 Hz), 156.2 (*C*N), 154.1 (t, NH*C*, $^2J_{C-F}$ = 25 Hz), 136.3 and 131.4 (*CC*'C=N), 130.7-128.1 (arom), 110.1 (t, CO*C*HF$_2$, $^1J_{C-F}$ = 252 Hz), 108.3 (t, *C*CHF$_2$, $^1J_{C-F}$ = 242 Hz), 86.1 (t, CH, J = 6Hz) ppm.
HRMS (ESI) calcd for $C_{19}H_{13}ClF_6N_2NaO$ [M+Na]$^+$: 457.0513. Found: 457.0507.

5-(2-(Diphenylmethylene)hydrazinyl)-1,1,1,2,6-pentafluorohex-4-en-3-one (II.57C.a)



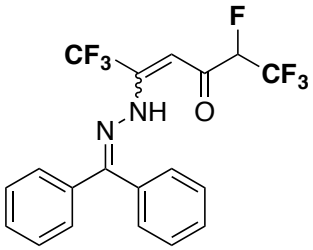
The crude mixture was purified by silica gel chromatography (Et_2O in pentane 0 to 5%). Yield: 305 mg (58%); yellow solid (m.p.: 139.8 - 140.2 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.60 (s, N*H*), 7.65 (m, 3H), 7.55 (d, 2H, arom.), 7.45-7.31 (5H, arom), 5.80 (s, C*H*CO), 5.65 (d, C*H*$_2$F, $^2J_{H-F}$ = 47.3 Hz), 4.86 (qd, C*H*FCF$_3$, $^2J_{H-F}$ = 46.6, $^3J_{H-F}$ = 6.5 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -75.8 (dd, CHFC*F*$_3$, $^3J_{H-F}$ = 12.1 Hz, $^3J_{H-F}$ = 6.9 Hz), -201.6 (dqd, CH*F*CF$_3$, $^2J_{H-F}$ = 47.4 Hz, $^4J_{H-F}$ = 4.0 Hz), -230.5 (td, CH$_2$*F*, $^2J_{H-F}$ = 46.6 Hz, $^4J_{H-F}$ = 1.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 185.1 (d, *C*O, $^2J_{C-F}$ = 20 Hz), 160.0 (d, *C*NH, $^2J_{C-F}$ = 22 Hz), 155.3 (*C*N), 136.6 and 131.5 (*CC*'C=N), 130.6-128.0 (arom.), 121.1 (dd, *C*F$_3$, $^1J_{C-F}$ = 282 Hz, $^2J_{C-F}$ = 26 Hz), 88.1 (dq, *C*HFCF$_3$, $^1J_{C-F}$ = 200 Hz, $^2J_{C-F}$ = 33 Hz), 86.8 (d, *C*H, $^3J_{C-F}$ = 11.8 Hz), 78.4 (d, CH$_2$F, $^1J_{C-F}$ = 176 Hz) ppm.
HRMS (ESI) calcd for $C_{19}H_{15}F_5N_2NaO$ [M+Na]$^+$: 405.0997. Found: 405.1005.

5-(2-(Diphenylmethylene)hydrazinyl)-1,1,1,2,6,6-hexafluorohex-4-en-3-one (II.57C.b)



The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 286 mg (52%); orange solid (m.p.: 127.0 - 127.6 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.57 (s, N*H*), 7.65-7.32 (10H, arom), 7.17 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 5.90 (s, C*H*CO), 4.86 (qd, C*H*FCF_3, $^2J_{H-F}$ = 46.6 Hz, $^3J_{H-F}$ = 6.7 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -75.7 (dd, CHFC*F*$_3$, $^3J_{H-F}$ = 11.9 Hz, $^3J_{H-F}$ = 6.5 Hz), -123.9 (dd + sat., CH*F*$_2$, $^2J_{H-F}$ = 84 Hz, $^2J_{H-F}$ = 53.4 Hz), -202.1 (dqd, CH*F*CF_3, $^2J_{H-F}$ = 46.5 Hz, $^3J_{H-F}$ = 11.7 Hz, $^4J_{H-F}$ = 4.2 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.8 (d, *C*O, $^2J_{C-F}$ = 20.7 Hz), 156.2 (*C*N), 153.5 (t, *C*CHF2, $^2J_{H-F}$ = 25.8 Hz), 136.4 and 131.3 (*CC*'C=N), 130.7-128.1 (arom), 121.1 (dd, *C*F_3, $^1J_{C-F}$ = 281.9, $^2J_{H-F}$ = 25.9 Hz), 108.4 (t, *C*HF_2, $^1J_{C-F}$ = 241 Hz), 88.2 (qd, *C*HFCF_3, $^1J_{C-F}$ = 202 Hz, $^3J_{H-F}$ = 33.2 Hz), 87.5 (d, *C*HCO) ppm.
HRMS (ESI) calcd for $C_{19}H_{14}F_6N_2NaO$ $[M+Na]^+$: 423.0903. Found: 423.0872.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in Et_2O.

5-(2-(diphenylmethylene)hydrazinyl)-1,1,1,2,6,6,6-heptafluorohex-4-en-3-one (II.57C.c)



The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 535 mg (37%); yellow solid (m.p.: 125.7 - 126.4 °C).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.62 (s, N*H*), 7.69-7.33 (m, 10H, arom), 5.96 (d, C*H*CO, $^3J_{H-F}$ = 4 Hz), 4.86 (qd, C*H*FCF3, $^2J_{H-F}$ = 46.5 Hz, $^3J_{H-F}$ = 6.7 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -65.7 (d, C*F*$_3$, $^4J_{H-F}$ = 2.0 Hz), -75.7 (dd, CHFC*F*$_3$, $^3J_{H-F}$ = 11.9 Hz, $^3J_{H-F}$ = 6.6 Hz), -202.3 (dqd, CH*F*CF_3, $^2J_{H-F}$ = 46.4 Hz, $^3J_{H-F}$ = 12.0 Hz, $^4J_{H-F}$ = 3.9 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.8 (d, *C*O, $^2J_{C-F}$ = 21.5 Hz), 156.6 (*C*=N), 148.3 (q, NH*C*CF3, $^2J_{C-F}$ = 32.6 Hz), 136.3 and 131.3 (*CC*'C=N), 130.7-128.1 (arom.), 120.9 (qd, CHF*C*F_3, J = 283 Hz, J = 26 Hz), 119.5 (q, NHC*C*F_3, $^1J_{C-F}$ = 278 Hz), 89.0 (s, *C*HCO), 88.2 (qd, *C*HFCF_3, $^1J_{C-F}$ = 201 Hz, $^2J_{C-F}$ = 32 Hz) ppm.
HRMS (ESI) calcd for $C_{19}H_{13}F_7N_2NaO$ $[M+Na]^+$: 441.0808. Found: 441.0770.

Preparation of 3,5-bis(fluoroalkyl)-1*H*-pyrazoles **II.58** – General procedures

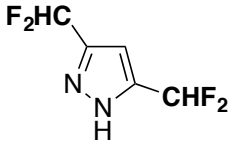
One-pot – TFEDMA: $BF_3{\cdot}Et_2O$ (0.18 mL, 1.42 mmol) was added *via* syringe to a vigorously stirred solution of TFEDMA (0.17 mL, 1.38 mmol) in dry CH_2Cl_2 (2 mL) in a Schlenk vessel at room temperature under argon. After 15 min, the solvent was evaporated *in vacuo*. The residual white solid was taken up in dry

MeCN (2 mL). A solution of fluorinated azine **II.56** (2.12 mmol, 1.5 equiv.) in dry MeCN (2 mL) was added to the FAR solution *via* syringe, the mixture stirred over 18 h at 50 °C under inert gas atmosphere. The reaction mixture was treated with conc. HCl (3.5 equiv.) and stirred 1 h at room temperature. The mixture was treated with NaOH 2N (2 equiv.), diluted with water (15 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under mild vacuum. The crude mixture was purified by silica gel flash chromatography (Et_2O in pentane: see examples).

One-pot – Yarovenko / Ishikawa: Same conditions with condensation step occurring in distilled DCM (followed by solvent evaporation) and cyclization step in dry MeCN after addition of 3-5 equiv. of conc. HCl until complete cyclization.

From β-(diphenylmethylidene)-bis(fluoroalkyl)-enones II.57B-C: The corresponding precursor in MeCN (1 mol/L) was cyclized in presence of conc. HCl (3-5 equiv.), the mixture stirred at 50 °C for 1-2 h. Similar work-up was achieved to access the desired pyrazoles.

3,5-Bis(difluoromethyl)-1*H*-pyrazole (II.58A.b)



The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 40%). Yield: 4.0 g (74%); yellow solid (m.p.: 69.2 - 69.7 °C).

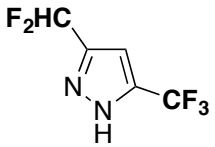
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.5 (br s, N*H*), 6.77 (t, C*H*F_2, $^2J_{H-F}$ = 54.8 Hz), 6.74 (s, C*H*) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.2 (d, 4F, $^2J_{H-F}$ = 54.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 142.9 (*C*CHF_2), 109.3 (t, *C*HF_2, $^1J_{C-F}$ = 236 Hz), 103.3 (*C*H) ppm.

HRMS (ESI) calcd for $C_5H_5F_4N_2$ $[M+H]^+$: 169.039. Found: 169.038.

3-(Difluoromethyl)-5-(trifluoromethyl)-1*H*-pyrazole (II.58A.c)



The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 40%). Yield: 220 mg (83%); yellow solid (m.p.: 72-73 °C).

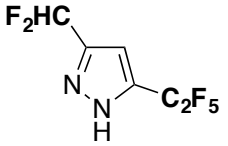
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.6 (br s, N*H*), 6.81 (s, C*H*), 6.76 (t, C*H*F_2, $^2J_{H-F}$ = 54.5 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -61.7 (s, C*F*$_3$), -112.9 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.7 (*C*CHF_2), 128.8 (*C*CF_3), 120.3 (q, $^1J_{C-F}$ = 266 Hz), 108.5 (t, *C*HF_2, $^1J_{C-F}$ = 237 Hz), 103.8 (*C*H) ppm.

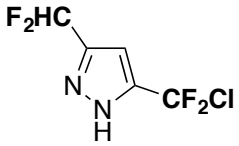
HRMS (ESI) calcd for $C_5H_4F_5N_2$ $[M+H]^+$: 187.029. Found: 187.029.

3-(Difluoromethyl)-5-(perfluoroethyl)-1*H*-pyrazole (II.58A.d)



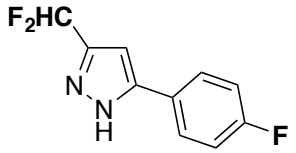
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 40%). Yield: 310 mg (51%); pale yellow solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.3 (br s, N*H*), 6.83 (s, C*H*), 6.77 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -85.0 (s, C*F*$_3$), -113.4 (s, C*F*$_2$), -113.8 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.7 and 128.3 (*C*CHF_2 and *C*C_2F_5), 118.6 (qt, $^1J_{C-F}$ = 285 Hz, $^2J_{C-F}$ = 37 Hz), 109.9 (qt, C*F*$_3$, $^1J_{C-F}$ = 251 Hz, $^2J_{C-F}$ = 40 Hz), 108.4 (t, *C*HF_2, $^1J_{C-F}$ = 239 Hz), 105.1 (*C*H) ppm.
HRMS (ESI) calcd for $C_6H_4F_7N_2$ [M+H]$^+$: 237.100. Found: 237.100.

5-(Chlorodifluoromethyl)-3-(difluoromethyl)-1*H*-pyrazole (II.58A.e)



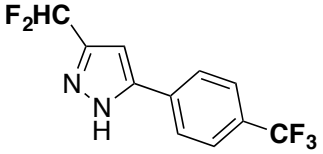
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 40%). Yield: 160 mg (31%); pale yellow solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.7 (br s, N*H*), 6.78 (s, C*H*), 6.74 (t, C*H*F_2, $^2J_{H-F}$ = 54.7 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -47.6 (s, C*F*$_2$Cl), -113.7 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.0 Hz) ppm.
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 145.5 and 141.1 (*C*CF_3 and *C*CHF_2), 121.3 (t, $^1J_{C-F}$ = 284 Hz), 108.5 (t, *C*HF_2, $^1J_{C-F}$ = 239 Hz), 103.2 (*C*H) ppm.
HRMS (ESI) calcd for $C_5H_4ClF_4N_2$ [M+H]$^+$: 202.999. Found: 202.998.

3-(Difluoromethyl)-5-(4-fluorophenyl)-1*H*-pyrazole (II.58A.f)



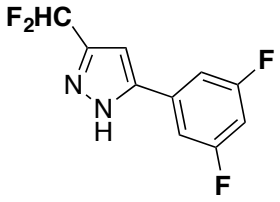
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 50%). Yield: 285 mg (53%); off-white solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.7 (br s, N*H*), 7.55-7.45 (2H, arom), 7.12-7.01 (2H, arom), 6.59 (s, C*H*), 6.56 (t, C*H*F_2, $^2J_{H-F}$ = 54.2 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.7 (m, *F*), -112.5 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.2 (d, *C*F, $^1J_{C-F}$ = 253 Hz), 147.0 and 144.9 (*C*CHF_2 and *C*Ph), 127.6 (d, 2',6'-*C*H, $^3J_{C-F}$ = 8 Hz), 125.0 (NHC*C*), 116.2 and 116.1 (3',5'-*C*H), 110.5 (t, *C*HF_2, $^1J_{C-F}$ = 236 Hz), 100.5 (*C*H) ppm. HRMS (ESI) calcd for $C_{10}H_8F_3N_2$ [M+H]$^+$: 213.064. Found: 213.063.

3-(Difluoromethyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (II.58A.g)



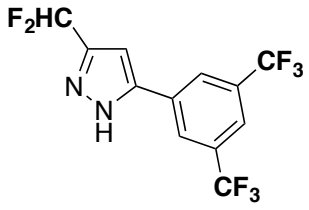
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 50%). Yield: 280 mg (42%); pale yellow solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.4 (br s, N*H*), 7.75-7.55 (4H, arom), 6.76 (s, C*H*), 6.66 (t, C*H*F_2, $^2J_{H-F}$ = 55.2 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -62.9 (s, C*F*$_3$), -112.6 (d, CH*F*$_2$, $^2J_{H-F}$ = 55 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.2 and 144.9 (*C*Ar and *C*CHF$_2$), 132.2-125.8 (arom), 123.9 (q, *C*F$_3$, $^1J_{C-F}$ = 272 Hz), 110.2 (t, *C*HF$_2$, $^1J_{C-F}$ = 235 Hz), 101.7 (*C*H) ppm.
HRMS (ESI) calcd for $C_{11}H_8F_5N_2$ [M+H]$^+$: 263.060. Found: 263.060.

3-(Difluoromethyl)-5-(3,5-difluorophenyl)-1*H*-pyrazole (II.58A.h)



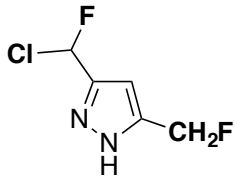
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 50%). Yield: 180 mg (31%); off-white solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.1 (br s, N*H*), 7.12-6.93 (2H, arom), 6.82-6.72 (m, 1H), 6.66 (s, C*H*), 6.63 (t, C*H*F_2, $^2J_{H-F}$ = 54.9 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -108.1 (s, 2*F*), -113.1 (d, CH*F*$_2$, $^2J_{H-F}$ = 53.5 Hz) ppm.
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.6 (dd, bis C*F*, $^1J_{C-F}$ = 249 Hz, $^3J_{C-F}$ = 13 Hz), 145.8 and 144.6 (*C*ar and *C*CHF$_2$), 128.7 (d, *C*(CH)$_2$, $^3J_{C-F}$ = 28 Hz), 109.9 (t, *C*HF$_2$, $^1J_{C-F}$ = 236 Hz), 108.8 and 108.5 (2',6'-C*H*), 104.3 (t, 4'-C*H*, $^2J_{C-F}$ = 26 Hz), 101.7 (*C*H) ppm.
HRMS (ESI) calcd for $C_{10}H_7F_4N_2$ [M+H]$^+$: 231.054. Found: 231.055.

5-(3,5-Bis(trifluoromethyl)phenyl)-3-(difluoromethyl)-1*H*-pyrazole (II.58A.i)



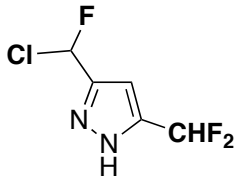
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 50%). Yield: 350 mg (42%); off-white solid.
^{1}H-NMR (400 MHz, CD_3CN): δ = 12.1 (br s, N*H*), 8.28 (m, 2H), 7.34-7.17 (m, 1H), 7.07 (s, 1H), 6.89 (t, C*H*F_2, $^2J_{H-F}$ = 54.6 Hz) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -63.6 (s, bis C*F*$_3$), -113.1 (d, CH*F*$_2$, $^2J_{H-F}$ = 55 Hz) ppm.
^{13}C-NMR (75 MHz, CD_3CN): δ = 143.2 (*C*$_{Ar}$), 132.9 (q, bis*C*CF$_3$, $^2J_{C-F}$ = 39 Hz), 122.8-130.1 (arom), 124.6 (q, *C*F$_3$, $^1J_{C-F}$ = 272 Hz), 111.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 233 Hz), 103.0 (*C*H) ppm.
HRMS (ESI) calcd for $C_{12}H_7F_8N_2$ [M+H]$^+$: 331.048. Found: 331.048.

3-(Chlorofluoromethyl)-5-(fluoromethyl)-1*H*-pyrazole (II.58B.a)



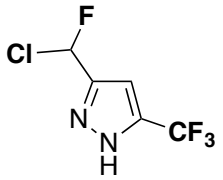
The crude mixture was purified by flash chromatography (Et_2O in pentane: 0 to 20%). Yield: 18.3 mg (64%); colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ =10.45 (br s, N*H*), 7.13 (d, C*H*FCl, $^2J_{H-F}$ = 50 Hz), 5.45 (d, CH_2F, $^2J_{H-F}$ = 47.7 Hz), 6.61 (s, C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -126.0 (d, CH*F*Cl, $^2J_{H-F}$ = 50 Hz), -211.3 (td, CH_2*F*, $^2J_{H-F}$ = 47.6, $^4J_{H-F}$ = 2.7 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.6 (d, *C*CHFCl, $^2J_{C-F}$ = 26.4 Hz), 140.8 (d, NH*C*, $^2J_{C-F}$ = 20.5 Hz), 103.7 (*C*H), 94.8 (d, *C*HFCl, $^1J_{C-F}$ = 237 Hz), 75.0 (d, *C*H_2F, $^1J_{C-F}$ = 166 Hz) ppm.
HRMS (ESI) calcd for $C_5H_6ClF_2N_2$ [M+H]$^+$: 167.0182 + 169.0153. Found: 167.0165 + 169.0134.

3-(Chlorofluoromethyl)-5-(difluoromethyl)-1*H*-pyrazole (II.58B.b)



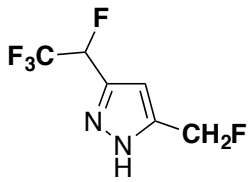
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 214 mg (69%); colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.6 (br s, N*H*), 7.15 (d, C*H*FCl, $^2J_{H-F}$ = 50 Hz), 6.76 (t, C*H*F_2, $^2J_{H-F}$ = 54.7 Hz), 6.74 (s, C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.9 (d, CH*F*$_2$, $^2J_{H-F}$ = 55.2 Hz), -127.8 (d, CH*F*Cl, $^2J_{H-F}$ = 49.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.4 (m, *C*CHFCl), 143.1 (m, *C*CHF$_2$), 109.5 (t, *C*HF$_2$, $^1J_{C-F}$ = 238 Hz), 103.3 (d, *C*H, J = 2.4 Hz), 93.3 (d, *C*HFCl, $^1J_{C-F}$ = 238 Hz) ppm.
HRMS (ESI) calcd for ($C_5H_4ClF_3N_2H$) [M+H]$^+$: 185.0088. Found: 185.0078.

3-(Chlorofluoromethyl)-5-(trifluoromethyl)-1*H*-pyrazole (II.58B.c)



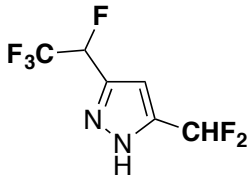
The crude mixture was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 76 mg (47%) (85% pure); colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.18 (br s, N*H*), 7.17 (d, C*H*FCl, $^2J_{H-F}$ = 50 Hz), 6.80 (s, C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -61.9 (s, C*F*$_3$), -128.8 (d, CH*F*Cl, $^2J_{H-F}$ = 49.6 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.5 (d, *C*CHFCl, $^2J_{C-F}$ = 30.5, $^4J_{C-F}$ = 5 Hz), 141.4 (q, *C*CF$_3$, $^2J_{C-F}$ = 40.7, $^4J_{C-F}$ = 5 Hz), 120.3 (q, *C*F$_3$, $^1J_{C-F}$ = 269 Hz), 103.8 (*C*H), 92.4 (d, *C*HFCl, $^1J_{C-F}$ = 239 Hz) ppm.
HRMS (ESI) calcd for $C_5H_4ClF_4N_2$ [M+H]$^+$: 202.999. Found: 202.999.

5-(Fluoromethyl)-3-(1,2,2,2-tetrafluoroethyl)-1*H*-pyrazole (II.58C.a)



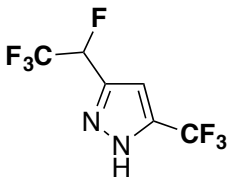
The residue was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 40% (0.45 equiv. of fluorobenzene as internal standard); brown oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (N*H*), 6.54 (C*H*), 5.70 (qd, C*H*FCF_3, $^2J_{H-F}$ = 44.8 Hz, $^3J_{H-F}$ = 6.3 Hz), 5.36 (d, C*H*F_2, $^2J_{H-F}$ = 48.1 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -78.5 (dd, CHFC*F*$_3$, $^3J_{H-F}$ = 13.7 Hz, $^4J_{H-F}$ = 6.2 Hz), -191.2 (dq, CH*F*CF_3, $^2J_{H-F}$ = 44.4 Hz, $^3J_{H-F}$ = 14.1 Hz), -210.8 (td, CH_2*F*, $^2J_{H-F}$ = 47.8 Hz, $^4J_{H-F}$ = 2.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.1 (d, *C*CHFCF_3, $^2J_{C-F}$ = 24.5 Hz), 141.5 (d, *C*CH_2F, $^2J_{C-F}$ = 20 Hz), 121.8 (qd, *C*F_3, $^1J_{C-F}$ = 280 Hz, $^2J_{C-F}$ = 29 Hz), 105.4 (*C*H), 83.9 (qd, *C*HFCF_3, $^1J_{C-F}$ = 184 Hz, $^2J_{C-F}$ = 36 Hz), 75.1 (d, *C*H_2F, $^1J_{C-F}$ = 166 Hz) ppm.
HRMS (ESI) calcd for $C_6H_6F_5N_2$ $[M+H]^+$: 201.0446. Found: 201.0461.

5-(Difluoromethyl)-3-(1,2,2,2-tetrafluoroethyl)-1*H*-pyrazole (II.58C.b)



The residue was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 93% (0.59 equiv. of fluorobenzene as internal standard); colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.8 (br s, N*H*), 6.78 (t, C*H*F_2, $^2J_{H-F}$ = 54.9 Hz), 6.76 (s, C*H*), 5.79 (dq, C*H*FCF_3, $^2J_{H-F}$ = 44.6 Hz, $^3J_{H-F}$ = 6.1 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -78.6 (dd, CHFC*F*$_3$, $^3J_{H-F}$ = 14.0 Hz, $^4J_{H-F}$ = 6.0 Hz), -112.6 (d, CH*F*$_2$, $^2J_{H-F}$ = 54.8 Hz), -192.7 (dq, CH*F*CF_3, $^2J_{H-F}$ = 44.3 Hz, $^3J_{H-F}$ = 14.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.6 (*C*CHF_2), 139.6 (N*C*CHFCF_3), 121.6 (dq, C*F*$_3$, $^1J_{C-F}$ = 281 Hz, $^2J_{C-F}$ = 28.6 Hz), 109.3 (t, CHF_2, $^1J_{C-F}$ = 237.4 Hz), 105.0 (*C*H), 83.2 (qd, CHFCF_3, $^1J_{C-F}$ = 185 Hz, $^2J_{C-F}$ = 38 Hz) ppm.
HRMS (ESI) calcd for $C_6H_5F_6N_2$ $[M+H]^+$: 219.0351. Found: 219.0341.

3-(1,2,2,2-Tetrafluoroethyl)-5-(trifluoromethyl)-1*H*-pyrazole (II.58C.c)

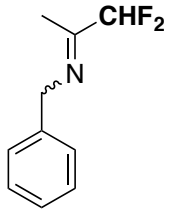


The residue was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 94% (0.59 equiv. of fluorobenzene as internal standard); colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.66 (br s, N*H*), 6.83 (s, C*H*), 5.81 (dq, C*H*FCF_3, $^{2}J_{H-F}$ = 44.4 Hz, $^{3}J_{H-F}$ = 5.9 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -61.8 (s, C*F*$_3$), -78.6 (dd, CHFC*F*$_3$, $^{3}J_{H-F}$ = 14.2 Hz, $^{4}J_{H-F}$ = 6.1 Hz), -193.6 (m, CH*F*CF_3) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.0 (*C*CF_3), 137.7 (*C*CHFCF_3), 121.4 (dq, CHF*C*F$_3$, $^{1}J_{C-F}$ = 281 Hz, $^{2}J_{C-F}$ = 27.2 Hz), 120.2 (q, C*F*$_3$, $^{1}J_{C-F}$ = 269.5 Hz), 105.5 (*C*H), 82.5 (dq, *C*HFCF_3, $^{1}J_{C-F}$ = 186.8 Hz, $^{2}J_{C-F}$ = 37.2 Hz) ppm.
HRMS (ESI) calcd for $C_6H_4F_7N_2$ $[M+H]^+$: 237.0257. Found: 237.0270.

Ketimine route

Preparation of fluorinated ketimines **II.59**

N-benzyl-1,1-difluoropropan-2-imine (II.59b)



1,1-difluoroacetone (2 equiv., 1.74 g, 1.50 mL, 18.5 mmol) (previously cooled in dry-ice container) was added to distilled benzylamine (1 equiv., 0.98 g, 1.00 mL, 9.15 mmol) *via* syringe (previously placed into dry-ice container) at room temperature into a Schlenk vessel in presence of MS 4Å (excess) under Argon. The solution was stirred for 2 h at room temperature. The mixture was filtered through Celite (rinsing with DCM), the filtrate was evaporated *in vacuo*. Yield: 1.64 g, pale oil (98 %).

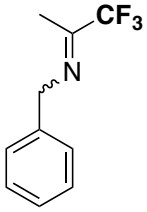
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 to 7.29 (m, 5H, C_6H_5), 5.99 (t, CHF_2, $^{2}J_{H-F}$ = 55.6 Hz), 4.60 (s, NCH_2), 2.07 (s, CH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -120.6 (tt, CHF_2, $^{2}J_{F-H}$ = 56 Hz, $^{4}J_{F-H}$ = 3 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.1 (t, $CCHF_2$, $^{2}J_{C-F}$ = 28.5 Hz), 138.7 (CCH_2), 128.7 (*m*-CH), 127.8 (*o*-CH), 127.2 (*p*-CH), 115.7 (t, CHF_2, $^{1}J_{C-F}$ = 243 Hz), 55.2 (CH_2), 11.3 (CH_3) ppm.

HRMS (ESI) calcd for $C_{10}H_{12}F_2N$ [M+H]: 184.0932. Found: 184.0943.

N-benzyl-1,1,1-trifluoropropan-2-imine (II.59c)



Trifluoroacetone (1.1 equiv., 2250 mg, 1.8 mL, 20.1 mmol) (previously cooled in dry-ice container) was added to a solution of distilled benzylamine (1 equiv., 0.98 g, 1 mL, 9.15 mmol) in dry Toluene (20 mL) *via* syringe (previously placed into dry-ice container) into a Schlenk vessel in presence of 4Å MS under Argon. The solution was stirred for 2 h at room temperature. Additional trifluoroacetone (1.83 equiv., 3750 mg, 3 mL, 33.5 mmol) and MS 4Å were added at room temperature. After 18 h more, the mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. Yield: 3.91 g, colourless oil, (quant., 95wt.%).

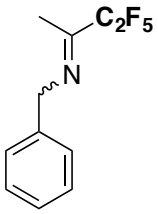
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 to 7.30 (m, 5H, C_6H_5), 4.67 (s, NCH_2), 2.12 (s, CH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -74.6 (t, CF_3, $^{4}J_{F-H}$ = 1.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 157.1 (q, CCF_3, $^{2}J_{C-F}$ = 33.5 Hz), 138.0, 128.7, 127.7, 127.3 (C_6H_5), 119.9 (q, CF_3, $^{1}J_{C-F}$ = 278 Hz), 55.2 (NCH_2), 13.0 (CH_3) ppm.

HRMS (ESI) calcd for $C_{10}H_{11}F_3N$ [M+H]: 202.0838. Found: 202.0866.

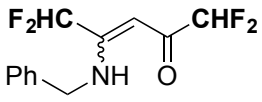
_N_-benzyl-3,3,4,4,4-pentafluorobutan-2-imine (II.59d)



3,3,4,4,4-pentafluorobutan-2-one (1.1 equiv., 2.57 g, 2 mL, 15.1 mmol) was added to a solution of distilled benzylamine (1 equiv., 1.47 g, 1.5 mL, 13.7 mmol) in dry toluene (30 mL). The mixture was stirred at room temperature into a sealed vial in presence of excess MS 4A for 3 days. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. Yield: 3.5 g, colourless oil (>99%, 85 wt.%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 to 7.13 (m, 5H, C_6H_5), 4.58 (s, NCH_2), 1.99 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.3 (s, CF_3), -118.2 (s, CF_2) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.3 (t, CC_2F_5, $^{2}J_{C-F}$ = 27 Hz), 138.2, 128.7, 127.4, 127.2 (C_6H_5), 118.8 (qt, CF_3, $^{1}J_{C-F}$ = 286.6 Hz, $^{2}J_{C-F}$ = 36 Hz), 110.4 (tq, CF_2, $^{1}J_{C-F}$ = 255.7 Hz, $^{2}J_{C-F}$ = 36.5 Hz), 55.4 (CH_2N), 13.2 (CH_3) ppm. HRMS (ESI) calcd for $C_{11}H_{11}F_5N$ [M+H]: 252.0806. Found: 252.0808.

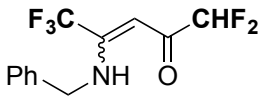
Preparation of vinamides **II.60** and **II.61**

4-(benzylamino)-1,1,5,5-tetrafluoropent-3-en-2-one (II.60A.b)



The corresponding vinamidinium specie was prepared according to general procedure from **II.59b** (1 equiv., 2.00 g, 10.92 mmol) and **2A** (1.05 equiv.). After 15min at room temperature (step 1), the mixture was diluted with DCM (25 mL) and treated with HCl 1N aq. (20 mL). Layers were separated, and the organic layer was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Yield: 2.26 g, pale solid (79%) (>95wt.% purity). M.p.: 71.5 - 73.8 °C.
Major isomer:
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.56 (br s, N*H*), 7.30 to 7.18 (C_6H_5), 6.08 (t, NHCC*H*F_2, $^{2}J_{H-F}$ = 53 Hz), 5.67 (t, COC*H*F_2, $^{2}J_{H-F}$ = 54.8 Hz), 5.60 (s, C*H*CO), 4.53 (d, CH_2N, $^{3}J_{H-H}$ = 6.4 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -119.4 (d, NHCCHF_2, $^{2}J_{F-H}$ = 53 Hz), -125.7 (d, COCHF_2, $^{2}J_{F-H}$ = 54.6 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.3 (t, *C*=O, $^{2}J_{C-H}$ = 24.3 Hz), 157.0 (t, NH*C*, $^{2}J_{C-H}$ = 22 Hz), 136.2 (CCH_2NH), 129.1 (*m*-*C*H), 128.3 (*p*-*C*H), 127.2 (*o*-*C*H), 111.0 (t, NHC*C*HF_2, $^{1}J_{C-H}$ = 244 Hz), 110.3 (t, CO*C*HF_2, $^{1}J_{C-H}$ = 251 Hz), 87.7 (t, *C*HCO, $^{3}J_{C-H}$ = 7 Hz), 48.0 (CH_2N) ppm.
Anal. calcd for $C_{12}H_{11}F_4NO$: C, 55.18; H, 4.24; F, 29.09; N, 5.36; O, 6.12. Found: C, 55.21; H, 4.47; N, 5.40. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in DCM/Et_2O.

4-(benzylamino)-1,1,5,5,5-pentafluoropent-3-en-2-one (II.60A.c)



The corresponding vinamidinium specie was prepared similarly from **II.59c** (1 equiv., 770 mg, 3.63 mmol) and **2A** (1.09 equiv.), and after 15min at room temperature, the mixture was diluted with DCM (15 mL) and Water (0.5 mL) was added. The mixture was vigorously stirred 1 h at room temperature (open flask), then was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 750 mg, colourless oil (74%).

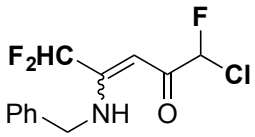
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.74 (br s, N*H*), 7.35 (m, C_6H_5), 5.92 (s, C*H*CO), 5.79 (t, C*H*F_2, $^2J_{H-F}$ = 54.6 Hz), 4.63 (d, NHC*H*$_2$, $^3J_{H-H}$ = 6.3 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.7 (s, C*F*$_3$), -125.9 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.8 (t, *C*=O, $^2J_{C-F}$ = 24.6 Hz), 152.6 (q, *C*CF_3, $^2J_{C-F}$ = 32.4 Hz), 135.8, 129.3, 128.5, 127.5 (*C*$_6$H$_5$), 119.5 (q, *C*F_3, $^1J_{C-F}$ = 278.5 Hz), 110.1 (t, *C*HF_2, $^1J_{C-F}$ = 251.8 Hz), 87.0 (q, *C*HCO, $^3J_{C-F}$ = 4.8 Hz), 48.9 (q, *C*H_2NH, $^4J_{C-F}$ = 2.5 Hz) ppm.

HRMS (ESI) calcd for $C_{12}H_{11}F_5NO$ [M+H]: 280.0755. Found: 280.0775.

4-(benzylamino)-1-chloro-1,5,5-trifluoropent-3-en-2-one (II.60B.b)



The corresponding vinamidinium specie was prepared according to the general procedure from **II.59b** (1 equiv., 500 mg, 2.46 mmol) and **2B** (1.2 equiv.), and after 1 h at 50-60 °C, the mixture was treated with HCl 1N aq. (15 mL). After 1 h of stirring at room temperature (open flask), layers were separated. The organic layer was washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (DCM in cyclohexane 0 to 50). **II.61B.b** was isolated mixed with **II.60B.b**.

II.60B.b (92/8 mixture of isomers): Yield: 233mg, yellow oil (31%).

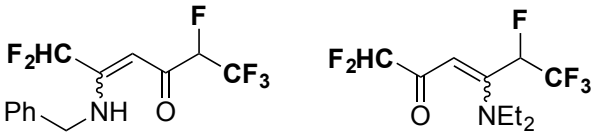
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.5 (br s, N*H*), 7.41 to 7.29 (m, C_6H_5), 6.21 (d, C*H*FCl, $^2J_{H-F}$ = 51.1 Hz), 6.18 (t, C*H*F_2, $^2J_{H-F}$ = 53.1 Hz), 5.70 (d, C*H*CO, $^4J_{H-F}$ = 2.6 Hz), 4.64 (d, C*H*$_2$NH, $^3J_{H-H}$ = 6.4 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -119.2 (d, CHF_2, $^2J_{F-H}$ = 53.1 Hz), -144.4 (dt, CH*F*Cl, $^2J_{F-H}$ = 51.0 Hz, $^4J_{F-H}$ = 2.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 188.2 (d, *C*CHFCl, $^2J_{C-F}$ = 23.6 Hz), 156.9 (t, *C*CHF_2, $^2J_{C-F}$ = 22.0 Hz), 136.3, 129.2, 128.4, 127.4 (*C*$_6$H$_5$), 111.3 (t, *C*HF_2, $^1J_{C-F}$ = 245 Hz), 96.6 (d, *C*HFCl, $^1J_{C-F}$ = 256 Hz), 87.3 (td, *C*HCO, $^3J_{C-F}$ = 7.2 Hz, $^3J_{C-H}$ = 1.7 Hz), 48.1 (t, *C*H_2NH, $^4J_{C-F}$ = 2.5 Hz) ppm.

HRMS (ESI) calcd for $C_{12}H_{12}ClF_3NO$ [M+H]: 278.0554 (+ 280.0527). Found: 278.0522 (+ 280.0485).

4-(diethylamino)-1,1,5,6,6,6-hexafluorohex-3-en-2-one compound with 5-(benzylamino)-1,1,1,2,6,6-hexafluorohex-4-en-3-one (55:45) (II.60C.b/II.61C.b)



The corresponding vinamidinium specie was prepared according to the general procedure from **II.59b** (1 equiv., 1.0 g, 5.46 mmol) and **2C** (1.05 equiv.), and after 1 h at room temperature, the mixture was diluted with MeOH (10 mL) and treated with HCl 1N aq. solution (10 mL). The mixture was vigorously stirred for 30 min, and then extracted with DCM (2 x 25 mL). The layers were separated. The organic layer was washed (brine 15 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%), to yield *ca.* 60/40 mixture [**II.60C.b**: 420mg, brown oil (25%), **II.61C.b**: 266mg, pure colourless oil (18%]. **II.61C.b** could be separated from **II.60C.b** by distillation but **II.60C.b** could not be isolated pure.

II.60C.b (major isomer):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.65 (br s, N*H*), 7.40 to 7.28 (m, C_6H_5), 6.18 (t, C*H*F_2, $^2J_{H-F}$ = 53 Hz), 5.71 (d, C*H*CO, $^4J_{H-F}$ = 4 Hz), 4.93 (dq, C*H*FCF_3, $^2J_{H-F}$ = 46.6 Hz, $^3J_{H-F}$ = 6.7 Hz), 4.62 (d, CH_2NH, $^3J_{H-H}$ = 6.4 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -75.9 (dd, CHFC*F*$_3$, $^3J_{F-F}$ = 11.6 Hz, $^3J_{F-H}$ = 6.9 Hz), -119.4 (dd, CH*F*$_2$, $^2J_{F-H}$ = 53.4 Hz, $^4J_{F-H}$ = 2.7 Hz), -203.0 (dqd, CH*F*CF_3, $^2J_{F-H}$ = 46.6 Hz, $^3J_{F-F}$ = 11.4 Hz, $^4J_{F-H}$ = 4.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.5 (d, *C*=O, $^2J_{C-F}$ = 20.5 Hz), 156.5 (t, *C*CHF_2, $^2J_{C-F}$ = 22 Hz), 136.1, 129.2, 128.4, 127.4 (C_6H_5), 121.2 (dq, CHF*C*F_3, $^1J_{C-F}$ = 283 Hz, $^2J_{C-F}$ = 24 Hz), 111.2 (t, *C*HF_2, $^1J_{C-F}$ = 244 Hz), 89.0 (m, *C*HCO), 88.0 (dq, *C*HFCF_3, $^1J_{C-F}$ = 201 Hz, $^2J_{C-F}$ = 32 Hz), 48.1 (NH*C*H_2Ph) ppm.

HRMS (ESI) calcd for $C_{13}H_{12}F_6NO$ [M+H]: 312.0818. Found: 3120846.

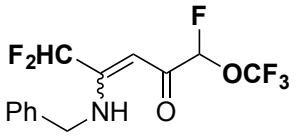
II.61C.b:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (dq, C*H*FCF_3, $^2J_{H-F}$ = 44.5 Hz, $^3J_{H-F}$ = 7.3 Hz), 5.70 (t, C*H*F_2, $^2J_{H-F}$ = 55.4 Hz), 5.43 (d, C*H*CO, $^4J_{H-F}$ = 4.7 Hz), 3.65 and 3.34 (br s and m, 2H + 2H, N($CH_2$$CH_3$)$_2$), 1.26 (t, 6H, N($CH_2$$CH_3$)$_2$) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -73.8 (dd, C*F*$_3$, $^3J_{F-F}$ = 12.2 Hz, J_{F-H} = 7.5 Hz), -123.7 (dd, 1F, $^2J_{F-F}$ = 307 Hz, $^2J_{F-H}$ = 56 Hz), -124.2 (dd, 1F, $^2J_{F-F}$ = 307 Hz, $^2J_{F-H}$ = 56 Hz), -203.1 (dqd, CH*F*CF_3, $^2J_{F-H}$ = 43.2 Hz, $^3J_{F-F}$ = 12.7 Hz, $^3J_{F-H}$ = 4.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 183.6 (t, *C*OCHF_2, $^2J_{C-F}$ = 22.7 Hz), 153.9 (d, *C*N$(Et)_2$, $^2J_{C-F}$ = 14.9 Hz), 121.8 (qd, *C*F_3, $^1J_{C-F}$ = 283.7 Hz, $^2J_{C-F}$ = 26 Hz), 111.6 (t, *C*HF_2, $^1J_{C-F}$ = 255 Hz), 90.0 (*C*HCO), 84.7 (dq, *C*HFCF_3, $^1J_{C-F}$ = 195 Hz, $^2J_{C-F}$ = 35 Hz), 46.9 (br s, N($CH_2$$CH_3$)$_2$), 12.5 (br s, N($CH_2$*C*$H_3$)$_2$) ppm.

HRMS (ESI) calcd for $C_{10}H_{14}F_6NO$ [M+H]: 278.0974. Found: 278.0994.

4-(benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (II.60D.b)



The corresponding vinamidinium specie was prepared according to the general procedure from **II.59b** (1 equiv., 728 mg, 3.63 mmol) and **2D** (1 equiv.), and after 15min at room temperature, the mixture was diluted with Et_2O (20 mL) and treated with HCl 1N aq. solution (10 mL). The mixture was vigorously stirred 15min at room temperature (open flask), then was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield 1.08 g, brown oil (83%, 95wt.%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.64 (br s, N*H*), 7.40 to 7.28 (m, C_6H_5), 6.18 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.2 Hz), 5.81 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 56.9 Hz), 5.70 (d, C*H*CO, $^{4}J_{H-F}$ = 1.6 Hz), 4.65 (d, NHCH_2, $^{3}J_{H-H}$ = 6.4 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.4 (d, CHFOCF_3, $^{4}J_{F-F}$ = 4.7 Hz), -119.3 (d, CHF_2, $^{2}J_{F-H}$ = 53.1 Hz), -135.5 (dqd, CH*F*OCF_3, $^{2}J_{F-H}$ = 56.9 Hz, $^{4}J_{F-F}$ = 4.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 185.5 (d, *C*=O, $^{2}J_{C-F}$ = 25.3 Hz), 157.3 (t, *C*CHF_2, $^{2}J_{C-F}$ = 22.0 Hz), 136.1, 129.2, 128.4, 127.3 (C_6H_5), 121.2 (q, *C*F_3, $^{1}J_{C-F}$ = 261 Hz), 111.0 (t, *C*HF_2, $^{1}J_{C-F}$ = 245 Hz), 101.3 (dq, *C*H$FOCF_3$, $^{1}J_{C-F}$ = 243 Hz, $^{3}J_{C-F}$ = 3 Hz), 87.8 (t, *C*HCO, $^{3}J_{C-F}$ = 77.2 Hz), 48.1 (*C*H_2NH) ppm.
HRMS (ESI) calcd for $C_{13}H_{12}F_6NO_2$ [M+H]: 328.0767. Found: 328.0728.

Preparation of 3,5-bis(fluoroalkyl)-1*H*-pyrazoles **II.58** – General procedure

A solution of FAR **2A-D** (1.2 equiv., 297 mg, 0.24 mL, 1.95 mmol) in dry MeCN (2 mL) was activated by addition of BF_3•Et_2O (1.2 equiv., 291 mg, 0.26 mL, 1.95 mmol) and further stirring at room temperature, under argon atmosphere into a Schlenk vessel. TFEDMA and our FAR required both 10-15 min of activation, while Ishikawa and Yarovenko reagents required 60 min. A solution of fluorinated ketimine (1 equiv., 300 mg, 1.64 mmol) in dry MeCN (2 mL) was canulated onto the FAR solution at room temperature. The mixture was stirred for 1 h at described temperature (20-50 °C). Hydrazine hydrate (1.51 equiv., 123 mg, 0.12 mL, 2.47 mmol) was added *via* syringe at the described temperature (20-50 °C), rapidly followed by conc. H_2SO_4 (0.56 equiv., 92 mg, 0.05 mL, 0.91 mmol). The mixture was stirred at described temperature for 1-18 h. (For TFEDMA, only 1.05 equiv. were required, our FAR was similarly reactive but its preparation was less accurate and so 1.2-1.4 equiv. were used).

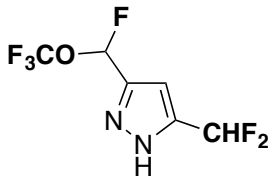
Preparation of 3,5-bis(fluoroalkyl)-*N*-methyl pyrazoles **II.62** and **II.63** – General procedure

Same procedure for the preparation of vinamidinium intermediates. Methyl hydrazine (1.51 equiv., 123 mg, 0.12 mL, 2.47 mmol) was added *via* syringe at the described temperature (20-50 °C), followed by cc H_2SO_4 (0.56 equiv., 92 mg, 0.05 mL, 0.91 mmol). The mixture stirred at described temperature for 1-18 h.

Several examples of NH- and NMe-pyrazoles were reported in F. Giornal's PhD project or in the azine route project:

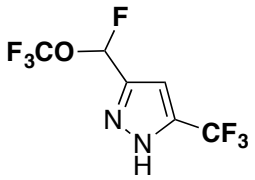
Pyrazoles **II.58A-C** were described previously, and yields were measured by using fluorobenzene as internal standard. Spectral data's were in accordance with the previous results:
F. Giornal, G. Landelle, N. Lui, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Proc. Res. Dev.* **2014**, *18*, 1002-1009.
E. Schmitt, G. Landelle, J.-P. Vors, N. Lui, S. Pazenok, F. R. Leroux, *Eur. J. Org. Chem.* **2015**, *2015*, 6052-6060.

5-(difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1*H*-pyrazole (II.58D.b)



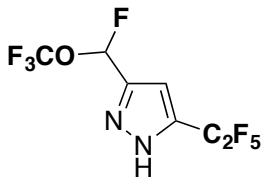
Prepared according to general procedure from **II.59b** (1 equiv., 600 mg, 3.27 mmol) and **2D** (*ca.* 1.2 equiv.). After 1 h at room temperature (step 2), further addition of cc H_2SO_4 (1 equiv.) and further 2 h stirring at 50 °C were performed. The mixture was evaporated *in vacuo* (>200mbar, 40 °C max.). The crude was purified by flash chromatography (Et_2O in pentane 0 to 30%). Yield: 650mg, brown oil (85%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.3 (br s, N*H*), 6.80 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57 Hz), 6.74 (t, C*H*F_2, $^2J_{H-F}$ = 55 Hz), 6.72 (s, 4-C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (d, OC*F*$_3$, $^4J_{F-H}$ = 5.3 Hz), -113.0 (d, CH*F*$_2$, $^2J_{F-H}$ = 55 Hz), -120.6 (d, CH*F*OCF_3, $^2J_{F-H}$ = 57.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.6 (m, *C*CHF_2 and *C*CHFOCF_3), 121.0 (q, OC*F*$_3$, $^1J_{C-F}$ = 262 Hz), 109.1 (t, *C*HF_2, $^1J_{C-F}$ = 237 Hz), 103.3 (4-*C*H), 100.0 (d, *C*HFOCF_3, $^1J_{C-F}$ = 228 Hz) ppm.
HRMS (ESI) calcd for $C_6H_5F_6N_2O$ [M+H]: 235.0301. Found: 235.0317.

3-(fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1*H*-pyrazole (II.58D.c)



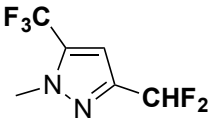
Prepared according to general procedure from **2b** (1 equiv., 660 mg, 3.28 mmol) and **1d** (*ca*. 1.2 equiv.). The mixture was evaporated *in vacuo* (>200mbar, 40°C max.). The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 500mg, brown oil (60%). ^{19}F NMR yield: 81%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.2 (br s, N*H*), 6.78 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57.5 Hz), 6.77 (s, 4-C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.0 (d, OC*F*$_3$, $^4J_{F-H}$ = 5.5 Hz), -62.3 (s, C*F*$_3$), -121.7 (qd, CH*F*OCF_3, $^2J_{F-H}$ = 57 Hz, $^4J_{F-H}$ = 5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.8 (m, *C*CF_3 and *C*CHFOCF_3), 120.3 and 121.0 (2 x q, CF_3 and OCF_3, $^1J_{C-F}$ = 269 and 262 Hz), 104.0 (4-*C*H), 99.1 (d, *C*HFOCF_3, $^1J_{C-F}$ = 230 Hz) ppm.
HRMS (ESI) calcd for $C_6H_4F_7N_2O$ [M+H]: 253.0206. Found: 253.0213.

3-(fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1*H*-pyrazole (II.58D.d)



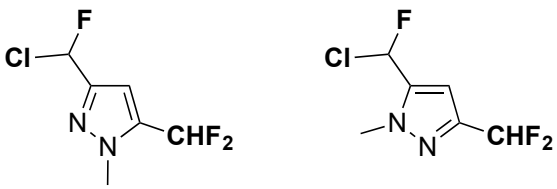
Prepared according to general procedure from **2c** (1 equiv., 500 mg, 1.69 mmol, 85wt.%) and **1d** (*ca*. 1.2 equiv.), with further 18 h stirring at 50 °C. The mixture was evaporated *in vacuo* (>200mbar, 40°C max.). The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 211mg, brown oil (40%). ^{19}F NMR yield: 99%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.59 (br s, N*H*), 6.82 (s, 4-C*H*), 6.79 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 57.5 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.9 (d, OC*F*$_3$, $^{4}J_{F-H}$ = 5 Hz), -85.1 (s, C*F*$_3$), -113.6 (s, C*F*$_2$), -121.8 (dq, CH*F*OCF_3, $^{2}J_{F-H}$ = 57.4 Hz, $^{4}J_{F-H}$ = 4.9 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.1 and 139.4 (m, *C*CHFOCF_3 and *C*C$_2$F$_5$), 120.7 (q, O*C*F$_3$, $^{1}J_{C-F}$ = 263 Hz), 118.4 (qt, *C*F$_3$, $^{1}J_{C-F}$ = 286 Hz, $^{2}J_{C-F}$ = 40 Hz), 109.8 (tq, *C*F$_2$, $^{1}J_{C-F}$ = 252 Hz, $^{2}J_{C-F}$ = 40 Hz), 105.4 (4-*C*H), 99.0 (d, *C*HFOCF_3, $^{1}J_{C-F}$ = 230 Hz) ppm. HRMS (ESI) calcd for $C_7H_4F_9N_2O$ [M+H]: 303.0174. Found: 303.0168.

5-(difluoromethyl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole (II.63A.c)



Prepared from **II.60A.c** (1 equiv., 300 mg, 1.07 mmol), methyl hydrazine (1.5 equiv.) and conc. H_2SO_4 (0.5 equiv.) after 1h at room temperature. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 50%), to give 5-(difluoromethyl)-1-methyl-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol (224 mg, 1.03 mmol, 96 %) as a yellow oil. Distillation using Hickmann apparatus (<10mbar, 80 °C) provided pure 5-(difluoromethyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole **II.63A.c** (206 mg, 1.03 mmol, 96 %) as colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.73 (t, 5-C*H*F$_2$, $^{2}J_{H-F}$ = 53.4 Hz), 6.72 (s, 4-C*H*), 4.03 (s, NC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -62.3 (s, C*F*$_3$), -113.7 (d, 5-CH*F*$_2$, $^{2}J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.6 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 39.1 Hz), 136.7 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 27 Hz), 120.8 (q, *C*F$_3$, $^{1}J_{C-F}$ = 268 Hz), 108.1 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 237 Hz), 105.8 (m, 4-*C*H), 38.8 (N*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_6H_6F_5N_2$ [M+H]: 201.0446. Found: 201.0453.

3-(chlorofluoromethyl)-5-(difluoromethyl)-1-methyl-1*H*-pyrazole compound with 5-(chlorofluoromethyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole (II.62B.b/II.63B.b)



Prepared according to the general procedure from **II.59b** (1 equiv., 200 mg, 1.09 mmol) and **2B** (*ca*. 1.2 equiv.), with 18 h at 50 °C (step 2). The mixture was evaporated *in vacuo* (>200 mbar, 40°C max). The

crude was purified by flash chromatography (Et_2O in pentane 0 to 3%). Brown oil. ^{19}F NMR yield: 33%/12% (45%). The regioisomeric ratio was not reproducible.

II.62B.b:

^1H-NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, C*H*FCl, $^2J_{H-F}$ = 50 Hz), 6.73 (s, 4-C*H*), 6.72 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 3.99 (s, NC*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.3 (d, CH*F*$_2$, $^2J_{F-H}$ = 54 Hz), -125.5 (d, CH*F*Cl, $^2J_{F-H}$ = 50 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.5 (d, *C*CHFCl, $^2J_{C-F}$ = 27 Hz), 136.7 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26 Hz), 108.4 (t, *C*HF$_2$, $^1J_{C-F}$ = 237 Hz), 105.4 (t, 4-*C*H, $^3J_{C-F}$ = 4 Hz), 94.9 (d, *C*HFCl, $^1J_{C-F}$ = 237 Hz), 38.4 (N*C*H$_3$) ppm.

II.63B.b:

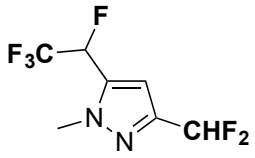
^1H-NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, C*H*FCl, $^2J_{H-F}$ = 48.6 Hz), 6.64 (t + s, C*H*F$_2$ + 4-C*H*, $^2J_{H-F}$ = 55 Hz), 4.03 (s, NC*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.0 (d, CH*F*$_2$, $^2J_{H-F}$ = 55 Hz), -129.3 (d, CH*F*Cl, $^2J_{H-F}$ = 48.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.5 (t, *C*CHF$_2$, $^2J_{C-F}$ = 30 Hz), 138.8 (d, *C*CHFCl, $^2J_{C-F}$ = 24 Hz), 110.8 (t, *C*HF$_2$, $^1J_{C-F}$ = 234 Hz), 104.2 (4-*C*H), 91.7 (d, *C*HFCl, $^2J_{C-F}$ = 239 Hz), 38.3 (N*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_6H_7ClF_3N_2$ [M+H]: 199.0244. Found: 199.0253.

3-(difluoromethyl)-1-methyl-5-(1,2,2,2-tetrafluoroethyl)-1*H*-pyrazole (II.63C.b)



Prepared according to the general procedure from **II.59b** (1 equiv., 200 mg, 1.09 mmol) and **2C** (*ca*. 1.2 equiv.). The mixture was evaporated *in vacuo* (>200 mbar, 40°C max). The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%). Brown oil. ^{19}F NMR yield: 84% (31/69 **II.62C.b** / **II.63C.b**). (**II.63C.a** not isolated pure).

II.63C.b:

^1H-NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 4-C*H*), 6.66 (t, C*H*F_2, $^2J_{H-F}$ = 54.8 Hz), 5.75 (dq, C*H*FCF_3, $^2J_{H-F}$ = 45.3 Hz, $^4J_{H-F}$ = 5.9 Hz), 3.98 (s, NC*H*$_3$) ppm.

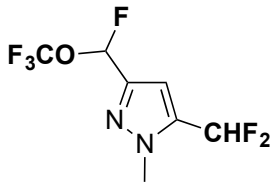
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -77.3 (dd, C*F*$_3$, $^3J_{F-F}$ = 14.9 Hz, $^3J_{H-F}$ = 5.6 Hz), -111.3 (dd, CH*F*$_2$, $^2J_{F-H}$ = 55 Hz, $^4J_{F-H}$ = 6.9 Hz), -190.7 (dq, CH*F*CF$_3$, $^2J_{F-H}$ = 45 Hz, $^3J_{F-F}$ = 15 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 30 Hz), 132.8 (d, *C*CHFCF$_3$, $^2J_{C-F}$ = 23 Hz), 121.6 (dq, *C*F$_3$, $^1J_{C-F}$ = 280 Hz, $^2J_{C-F}$ = 28.5 Hz), 110.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 234 Hz), 105.9 (4-*C*H), 81.5 (dq, *C*HFCF$_3$, $^1J_{C-F}$ = 188 Hz, $^2J_{C-F}$ = 37 Hz), 38.2 (N*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_7H_7F_6N_2$ [M+H]: 233.0508. Found: 233.0516.

Preparation of 3,5-bis(fluoroalkyl)-1*H*-pyrazoles **II.58D** with the new FAR **2D**

5-(difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole (II.62D.d)



Prepared according to general procedure from **2a** (1 equiv., 610 mg, 3.33 mmol) and **1d** (*ca*. 1.2 equiv.). The mixture was evaporated *in vacuo* (>200mbar, 40°C max). The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: **10a**, 320mg, brown oil (39%); **10b**, 135mg, brown oil (16%). ^{19}F NMR yield (**10a**/**10b**): >99% (71/29).

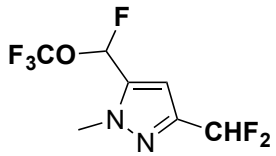
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.71 (t, C*H*F_2, $^2J_{H-F}$ = 53.5 Hz), 6.70 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57 Hz), 6.68 (s, 4-C*H*), 4.00 (s, NCH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.4 (d, OCF_3, $^4J_{F-H}$ = 5.5 Hz), -113.4 (d, CHF_2, $^2J_{F-H}$ = 53.5 Hz), -119.8 (dq, CH*F*OCF_3, $^2J_{F-H}$ = 57 Hz, $^4J_{F-H}$ = 5.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.8 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 29 Hz), 136.9 (t, *C*CHF_2, $^2J_{C-F}$ = 26 Hz), 121.1 (q, O*C*F_3, $^1J_{C-F}$ = 261 Hz), 108.3 (t, *C*HF_2, $^2J_{C-F}$ = 237 Hz), 105.3 (t, 4-*C*H, $^3J_{C-F}$ = 4 Hz), 101.0 (qd, *C*HFOCF_3, $^1J_{C-F}$ = 227 Hz, $^3J_{C-F}$ = 4 Hz), 38.5 (N*C*H_3) ppm.

HRMS (ESI) calcd for $C_7H_7F_6N_2O$ [M+H]: 249.0457. Found: 249.0460.

3-(difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole (II.63D.b)



Separated from **10a** by flash chromatography (Et_2O in pentane 0 to 5%).

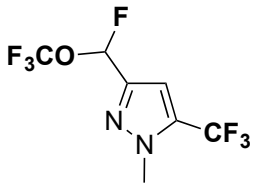
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, C*H*FOCF_3, $^2J_{H-F}$ = 56 Hz), 6.68 (s, 4-C*H*), 6.64 (t, C*H*F_2, $^2J_{H-F}$ = 55 Hz), 3.98 (m, NCH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (d, OCF_3, $^4J_{F-H}$ = 5.5 Hz), -112.2 (d, CHF_2, $^2J_{F-H}$ = 55 Hz), -121.6 (qd, CH*F*OCF_3, $^2J_{F-H}$ = 56 Hz, $^4J_{F-H}$ = 5.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.7 (t, *C*CHF_2, $^2J_{C-F}$ = 30 Hz), 135.5 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 26 Hz), 120.8 (q, O*C*F_3, $^1J_{C-F}$ = 263 Hz), 110.5 (t, *C*HF_2, $^1J_{C-F}$ = 234 Hz), 104.8 (4-*C*H), 98.5 (dq, *C*HFOCF_3, $^1J_{C-F}$ = 228 Hz, $^3J_{C-F}$ = 4 Hz), 38.5 (N*C*H_3) ppm.

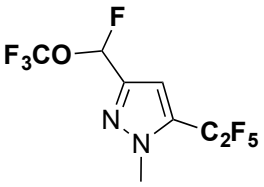
HRMS calcd for $C_7H_7F_6N_2O$ [M+H]: 249.0457. Found: 249.0458.

3-(fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (II.62D.c)



Prepared according to the general procedure from **2b** (1 equiv., 675 mg, 3.35 mmol) and **1d** (*ca*. 1.2 equiv.). The mixture was evaporated *in vacuo* (>200 mbar, 40 °C max). The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 187mg, brown oil (21%). ^{19}F NMR yield: 61%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 4-C*H*), 6.71 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 57 Hz), 4.02 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.3 (d, OCF_3, $^{4}J_{F-H}$ = 5 Hz), -60.9 (s, CF_3), -120.1 (qd, CH*F*OCF_3, $^{2}J_{F-H}$ = 57 Hz, $^{4}J_{F-H}$ = 5.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.8 (d, *C*CHFOCF_3, $^{2}J_{C-F}$ = 30 Hz), 133.6 (*C*CF_3, $^{2}J_{C-F}$ = 40 Hz), 121.0 and 119.6 (2 x q, O*C*F_3 and *C*F_3, $^{1}J_{C-F}$ = 261 Hz and $^{1}J_{C-F}$ = 269 Hz), 105.8 (4-*C*H), 100.8 (dq, *C*HFOCF_3, $^{1}J_{C-F}$ = 227 Hz, $^{3}J_{C-F}$ = 4 Hz), 38.6 (N*C*H_3) ppm.
HRMS (ESI) calcd for $C_7H_6F_7N_2O$ [M+H]: 267.0363. Found: 267.0347.

3-(fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1*H*-pyrazole (10d)

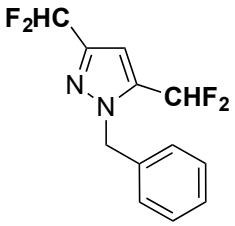


Prepared according to the general procedure with addition of fluorinated ketimine **2c** (1 equiv., 920 mg, 3.11 mmol) at 0 °C to **1d** (*ca*. 1.2 equiv.) (step 1), and 18 h at room temperature (step 2). The mixture was evaporated *in vacuo* (>200 mbar, 40 °C max). The crude was purified by flash chromatography (Et_2O in pentane 0 to 2%). Yield: 576mg, brown oil (59%). ^{19}F NMR yield: 81%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 4-C*H*), 6.72 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 57.2 Hz), 4.04 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.3 (d, OCF_3, $^{4}J_{F-H}$ = 5.4 Hz), -83.9 (s, CF_3), -110.7 (CF_2), -120.3 (dq, CH*F*OCF_3, $^{2}J_{F-H}$ = 57.2 Hz, $^{4}J_{F-H}$ = 5.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.2 (d, *C*CHFOCF_3, $^{2}J_{C-F}$ = 29.5 Hz), 131.6 (t, *C*C_2F_5, $^{2}J_{C-F}$ = 28.7 Hz), 121.1 (q, O*C*F_3, $^{1}J_{C-F}$ = 262 Hz), 118.6 (qt, *C*F_3, $^{1}J_{C-F}$ = 286.3 Hz, $^{2}J_{C-F}$ = 37.2 Hz), 109.9 (tq, *C*F_2, $^{1}J_{C-F}$ = 253.5 Hz, $^{2}J_{C-F}$ = 40 Hz), 107.4 (4-*C*H), 100.7 (dq, *C*HFOCF_3, $^{1}J_{C-F}$ = 227.4 Hz, $^{3}J_{C-F}$ = 4.3 Hz), 39.5 (N*C*H_3) ppm.
HRMS (ESI) calcd for $C_8H_6F_9N_2O$ [M+H]: 317.0331. Found: 317.0298.

Preparation of various *N*-substituted pyrazoles **II.64a-f**

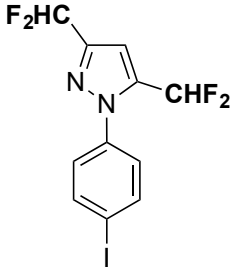
The synthesis of pyrazoles **II.64a** and **II.64b** was already reported:
F. Giornal, G. Landelle, N. Lui, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Proc. Res. Dev.* **2014**, *18*, 1002-1009.
II.64a was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.) after further treating the corresponding vinamidinium with a mixture of *tert*-butylhydrazine hydrochloride (1.5 equiv., 306 mg, 2.46 mmol) and Et_3N (1.54 equiv., 254 mg, 0.35 mL, 2.52 mmol) in DCM (5 mL) *via* syringe. After 1h, *tert*-butylhydrazine hydrochloride (0.735 equiv., 150 mg, 1.2 mmol) was further added. The mixture was stirred 1 h at room temperature. ^{19}F NMR yield: 90%.
II.64b was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.) after further treating the corresponding vinamidinium with phenyl hydrazine (1.5 equiv., 265 mg, 0.244 mL, 2.46 mmol), followed by cc H_2SO_4 (0.56 equiv., 92 mg, 0.05 mL, 0.91 mmol). After 2 h at room temperature, cc H_2SO_4 (0.556 equiv., 92 mg, 0.05 mL, 0.91 mmol) was added further, the mixture was stirred 18 h. ^{19}F NMR yield: 95%.

1-benzyl-3,5-bis(difluoromethyl)-1*H*-pyrazole (II.64c)



The corresponding vinamidinium was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.). After 1h at room temperature, a suspension of benzylhydrazine dihydrochloride (1.5 equiv., 479 mg, 2.46 mmol) and Et_3N (3.08 equiv., 509 mg, 0.7 mL, 5.04 mmol) in dry DCM (10 mL) was added *via* syringe. ^{19}F NMR yield: >99%. After concentration *in vacuo*, the crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 10%). Yield: 435 mg, colourless oil (99%).
^1H-NMR (400 MHz, $CDCl_3$): δ = 7.38 to 7.31 (m, 3H, 3',4',5'-C*H*Ph), 7.22 to 7.20 (m, 2H, 2',6'-C*H*Ph), 6.75 (s, 4-C*H*), 6.71 (t, 3-C*H*F_2, $^2J_{H-F}$ = 55 Hz), 6.58 (t, 5-C*H*F_2, $^2J_{H-F}$ = 54 Hz), 5.44 (s, CH_2Ph) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.9 (d, 3-CH*F*$_2$, $^2J_{F-H}$ = 55 Hz), -113.8 (d, 5-CH*F*$_2$, $^2J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.3 (t, *C*-3CHF_2, $^2J_{C-F}$ = 30 Hz), 137.0 (t, *C*-5CHF_2, $^2J_{C-F}$ = 27.5 Hz), 135.2, 129.0, 128.6, 127.6 (*C*$_6$H$_5$), 110.8 (t, 3-*C*HF_2, $^1J_{C-F}$ = 234.5 Hz), 108.3 (t, 5-*C*HF_2, $^1J_{C-F}$ = 237.6 Hz), 105.0 (4-*C*H), 55.3 (*C*H_2Ph) ppm.
HRMS (ESI) calcd for $C_{12}H_{11}F_4N_2$ [M+H]: 259.0853. Found: 259.0868.

3,5-bis(difluoromethyl)-1-(4-iodophenyl)-1*H*-pyrazole (II.64d)



Prepared according to **Method β** from **II.60A.b** (1 equiv., 200 mg, 0.76 mmol), 4-iodophenylhydrazine (1.24 equiv., 222 mg, 0.95 mmol) and conc. H_2SO_4 (1.19 equiv., 92 mg, 0.05 mL, 0.91 mmol) in Toluene/MeCN (4 mL/2 mL). The mixture was heated 30min at 120 °C and 30min at 140 °C in microwave apparatus. The mixture was filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 183 mg, brown oil (65%).

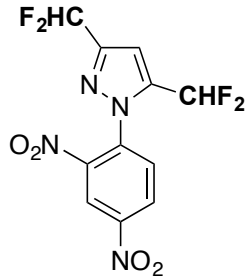
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, 2H, 3',5'-C*H*), 7.26 (d, 2H, 2',6'-C*H*), 6.97 (s, 4-C*H*), 6.75 (t, CHF_2, $^2J_{H-F}$ = 54.6 Hz), 6.63 (t, C*H*F_2, $^2J_{H-F}$ = 53.3 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -110.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.2 Hz), -112.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.8 (t, *C*CHF_2, $^2J_{C-F}$ = 30.6 Hz), 138.9 (3',5'-*C*H), 138.1 (1'-*C*), 137.8 (t, *C*CHF_2, $^2J_{C-F}$ = 30.0 Hz), 126.7 (2',6'-*C*H), 110.6 (t, *C*HF_2, $^1J_{C-F}$ = 235.1 Hz), 107.9 (t, *C*HF_2, $^1J_{C-F}$ = 236.7 Hz), 105.6 (4-*C*H), 95.2 (4'-*C*-I) ppm.

Anal. calcd for $C_{11}H_7F_4IN_2$: C, 35.70; H, 1.91; F, 20.53; I, 34.29; N, 7.57. Found: C, 35.96; H, 2.05; N, 7.46.

3,5-bis(difluoromethyl)-1-(2,4-dinitrophenyl)-1*H*-pyrazole (II.64e)



Prepared according to **Method β** from **II.60A.b** (1 equiv., 500 mg, 1.91 mmol), 2,4-dinitrophenylhydrazine (1.5 equiv., 569 mg, 2.87 mmol) and cc H_2SO_4 (2.1 equiv., 404 mg, 0.22 mL, 4.00 mmol) in Toluene (8 mL). The mixture was heated 60 min at 120 °C in microwave apparatus into a sealed vial. The yellow supernatant was separated from bottom dark gummy oil by pipetting and was evaporated *in vacuo*. This crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 10%). Yield: 420 mg, yellow thick oil (66%).

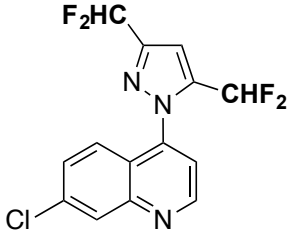
-NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, 3'-C*H*), 8.62 (dd, 5'-C*H*), 7.88 (d, 6'-C*H*), 6.99 (s, 4-C*H*), 6.74 and 6.67 (2 x t, 3,5-C*H*F_2, $^2J_{H-F}$ = 53.2 Hz and $^2J_{H-F}$ = 54.4 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.3 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.3 Hz), -113.3 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.4 (t, *C*CHF_2, $^2J_{C-F}$ = 30.3 Hz), 148.3 (*C*NO_2), 145.7 (1'-*C*), 138.9 (t, *C*CHF_2, $^2J_{C-F}$ = 27.4 Hz), 136.6 (*C*NO_2), 131.2 (6'-*C*), 128.2 (5'-*C*), 121.3 (3'-*C*), 110.0 (t, *C*HF_2, $^1J_{C-F}$ = 236.3 Hz), 107.8 (t, *C*HF_2, $^1J_{C-F}$ = 238.9 Hz), 107.1 (4-*C*H) ppm.

Anal. calcd for $C_{16}F_4N_4O_4$: C, 39.54; H, 1.81; F, 22.74; N, 16.77; O, 19.15. Found: C, 39.59; H, 1.92; N, 16.53.

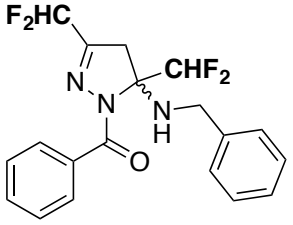
4-(3,5-bis(difluoromethyl)--pyrazol-1-yl)-7-chloroquinoline (II.64f)



Prepared according to **Method β** from **II.60A.b** (1 equiv., 200 mg, 0.76 mmol), 7-chloro-4-hydrazinylquinoline (1.5 equiv., 222 mg, 1.15 mmol) and conc. H_2SO_4 (1.19 equiv., 92 mg, 0.05 mL, 0.91 mmol) in Toluene/MeCN (8 mL/4 mL). The mixture was heated 30min at 140 °C under microwave irradiation into a sealed vial.
Conc. H_2SO_4 (1.19 equiv., 92 mg, 0.05 mL, 0.91 mmol) was added. After 30min at 140 °C under microwave irradiation, 7-chloro-4-hydrazinylquinoline (1.69 equiv., 250 mg, 1.29 mmol) and cc H_2SO_4 (1.19 equiv., 92 mg, 0.05 mL, 0.91 mmol) were added. The mixture was heated 60 min more at 140 °C under microwave irradiation. The very sluggish mixture was dissolved in MeOH/DCM (50 mL) using sonication. The solution was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 120 mg, colourless oil (48%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.04 (d, 2-C*H*), 8.21 (d, 3-C*H*), 7.55 to 7.41 (m, 1H + 2H, 5,6,8-C*H*), 7.07 (s, 4'-C*H*), 6.79 (t, C*H*F_2, $^2J_{H-F}$ = 54.4 Hz), 6.54 (t, C*H*F_2, $^2J_{H-F}$ = 53.4 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.4 (d, CHF_2, $^2J_{F-H}$ = 53.0 Hz), -112.5 (d, CHF_2, $^2J_{F-H}$ = 54.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.3 (2-*C*H), 150.1 (1-NC_{quat}), 148.7 (t, *C*CHF_2, $^2J_{C-F}$ = 30.8 Hz), 142.2 (4-*C*), 139.6 (t, *C*CHF_2, $^2J_{C-F}$ = 29.4 Hz), 137.1 (7-*C*-Cl), 129.7, 129.0, 124.1 (3,5,6-*C*H), 122.8 (1-N$C_{quat}C_{quat}$), 119.0 (8-*C*H), 110.4 (t, *C*HF_2, $^1J_{C-F}$ = 235.6 Hz), 107.6 (t, *C*HF_2, $^1J_{C-F}$ = 237.6 Hz), 105.6 (4-*C*H) ppm.
HRMS (ESI) calcd for $C_{14}H_9ClF_4N_3$ [M+H]: 330.0416 + 332.0389. Found: 330.0419 + 332.0387.

Preparation of *N*-substituted 3,5-bis(fluoroalkyl)pyrazolines **II.65-74**

(5-(benzylamino)-3,5-bis(difluoromethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.65A.b)



The corresponding vinamidinium was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.). After 1 h at room temperature, benzoyl hydrazine (1.5 equiv., 334 mg, 2.46 mmol) was added under argon flux, followed by cc H_2SO_4 (0.556 equiv., 92 mg, 0.05 mL, 0.91 mmol) *via* syringe. After 4h at room temperature, benzoyl hydrazine (1 equiv., 222 mg, 1.64 mmol) was added. The mixture was stirred 18 h more, and was then filtered through Na_2SO_4 layer and evaporated *in vacuo*. The yellow crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 310 mg, thick colourless oil (50%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (m, 2H, *o*-C*H*$_{Phenyl}$), 7.57 (tt, 1H, *p*-C*H*$_{Phenyl}$), 7.48 (t, 2H, *m*-C*H*$_{Phenyl}$), 7.34 (m, 5H, $CH_2C_6H_5$), 6.59 (dd, 5'-C*H*F_2, $^{2}J_{H-F}$ = 55.7, $^{2}J_{H-F}$ = 57.4 Hz), 6.36 (t, 3'-C*H*F_2, $^{2}J_{H-F}$ = 53.9 Hz), 3.79 to 3.60 (m, 2H, NHC*H*$_2$), 3.60 to 3.15 (m, 4-C*H*$_2$), 3.32 (br d, N*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.5 to -119.9 (m, 2F), -127.4 to -129.6 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.9 (*C*=O), 148.3 (t, *C*-3'CHF_2, $^{2}J_{C-F}$ = 31.9 Hz), 138.0, 133.0, 131.9, 129.8, 128.7, 128.2, 128.0, 127.8 (arom), 112.7 (dd, 5'-*C*HF_2, $^{1}J_{C-F}$ = 248.5 Hz, $^{1}J_{C-F}$ = 246.4 Hz), 110.6 (t, 3'-*C*HF_2, $^{1}J_{C-F}$ = 234.3 Hz), 86.6 (t, 5'C_{quat}, $^{2}J_{C-F}$ = 24.2 Hz), 46.1 (NH*C*H_2), 32.4 (4'-*C*H_2) ppm.
Anal. calcd for $C_{19}H_{17}F_4N_3O$: C, 60.16; H, 4.52; F, 20.03; N, 11.08; O, 4.22. Found: C, 59.97; H, 4.55; N, 11.06.

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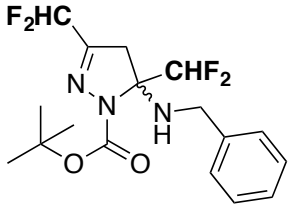
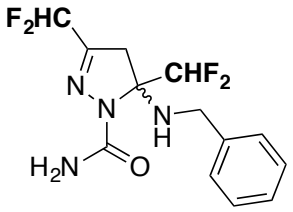
tert-butyl 5-(benzylamino)-3,5-bis(difluoromethyl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate (II.66A.b)



The corresponding vinamidinium was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.). After 1 h at room temperature, boc-hydrazide (1.5 equiv., 324 mg, 2.46 mmol) was added under argon flux, the mixture stirred for 1 h. ^{19}F NMR yield: 95%. After concentration *in vacuo*, the crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 384 mg, colourless solid (62%). M.p.: 106.5 - 107.2 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 to 7.21 (m, C_6H_5), 6.36 (t, 3-C*H*F_2, $^{2}J_{H-F}$ = 53.9 Hz), 6.19 (br t, 5-C*H*F_2, $^{2}J_{H-F}$ = 56.9 Hz), 3.63 to 3.00 (3 x m, 4H, NHC*H*$_2$Ph and 4-C*H*$_2$), 2.76 (br s, N*H*), 1.53 (s, C(C*H*$_3$)$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.5 to -119.9 (m, 2F), -127.4 to -130.4 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.3 (*C*=O), 146.2 (t, *C*-3CHF_2, $^{2}J_{C-F}$ = 31.8 Hz), 138.1, 128.7, 128.2, 127.7 (C_6H_5), 112.8 (t, 5-*C*HF_2, $^{1}J_{C-F}$ = 247.7 Hz), 110.9 (t, 3-*C*HF_2, $^{1}J_{C-F}$ = 233.4 Hz), 84.9 (t, 5*C*$_{quat}$, $^{2}J_{C-F}$ = 24.2 Hz), 83.6 (*C*(CH_3)$_3$), 45.9 (NH*C*H_2), 32.7 (4-*C*H_2), 28.2 (C(*C*H_3)$_3$) ppm.
Anal. calcd for $C_{17}H_{21}F_4N_3O_2$: C, 54.40; H, 5.64; F, 20.25; N, 11.19; O, 8.52. Found: C, 54.36; H, 5.69; N, 11.24.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in DCM/Et_2O.

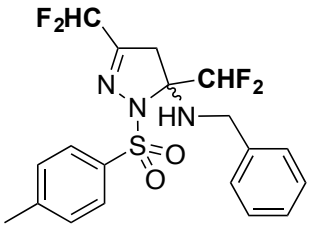
5-(benzylamino)-3,5-bis(difluoromethyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (II.67A.b)



The corresponding vinamidinium was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.) according to Method A (Scheme 2). After 1 h at room temperature, a white suspension of semicarbazide hydrochloride (1 equiv., 182 mg, 1.64 mmol) and Et_3N (1.54 equiv., 254 mg, 0.35 mL, 2.52 mmol) in dry MeCN (8 mL) was difficultly added under argon flux. After 4h, semicarbazide hydrochloride (1 equiv., 182 mg, 1.64 mmol) was added, the mixture 12 h more. After filtration through

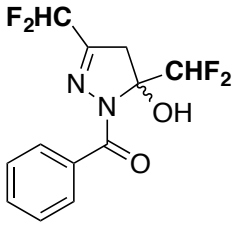
Na_2SO_4 layer and concentration *in vacuo*, the crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 100%). Yield: 280 mg, colourless solid (54%). M.p.: 151.0 - 151.7 °C.
^{1}H-NMR (400 MHz, CD_3CN): δ = 7.35 to 7.25 (m, C_6H_5), 6.47 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53.6 Hz), 6.40 (dd, 5-C*H*F_2, $^2J_{H-F}$ = 56.2 Hz, $^2J_{H-F}$ = 57.0 Hz), 5.79 (br s, NH_2), 3.57 (syst. AB, NHCH_2, Δν = 66.6 Hz, $^2J_{H-H}$ = 12.5 Hz), 3.45 to 3.10 (m, 2H, 4-CH_2), 3.06 (br s, N*H*) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -119.1 to -121.0 (m, 2F), -128.9 to -130.8 (m, 2F) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 155.7 (*C*=O), 145.8 (t, *C*-3CHF_2, $^2J_{C-F}$ = 30.2 Hz), 140.0, 129.5, 129.1, 128.3 (C_6H_5), 114.4 (dd, 5-*C*HF_2, $^1J_{C-F}$ = 244.6 Hz, $^1J_{C-F}$ = 246.6 Hz), 112.0 (t, 3-*C*HF_2, $^1J_{C-F}$ = 233.5 Hz), 85.6 (t, *C*-5CHF_2, $^2J_{C-F}$ = 23.9 Hz), 46.4 (NH*C*H_2), 34.1 (4-*C*H_2) ppm.
Anal. calcd for $C_{13}H_{14}F_4N_4O$: C, 49.06; H, 4.43; F, 23.88; N, 17.60; O, 5.03. Found: C, 49.04; H, 4.45; N, 17.57. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in DCM/Et_2O.

_N_-benzyl-3,5-bis(difluoromethyl)-1-tosyl-4,5-dihydro-1_H_-pyrazol-5-amine (II.69A.b)



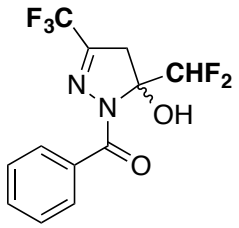
The corresponding vinamidinium was prepared from **II.59b** (1 equiv., 395 mg, 2.15 mmol) and **2A** (1.05 equiv.) according to general procedure. After 1 h at room temperature, 4-methylbenzenesulfonhydrazide (1.52 equiv., 610 mg, 3.27 mmol) was added under argon flux. After 1 h of stirring, the mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 1%). Pyrazole **II.79** was separated from minor 5-benzylaminopyrazoline **II.69A.b** (270mg, colourless oil, 29%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (m, 2H, *p*Tol), 7.36 to 7.28 (m, 5H + 2H, $CH_2C_6H_5$ and *p*Tol), 6.31 (t, 5-C*H*F_2, $^2J_{H-F}$ = 55.9 Hz), 6.29 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 3.74 to 3.61 (m, NHCH_2), 3.40 to 3.04 (m, 4-CH_2), 2.66 (dd, N*H*CH_2), 2.46 (s, CH_3, *p*Tol) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.2 to -119.6 (m, 2F), -124.1 to -127.7 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.7 (t, *C*-3CHF_2, $^2J_{C-F}$ = 32.4 Hz), 145.1, 138.0, 135.8, 130.0, 128.8, 128.4, 128.1, 127.8 (arom.), 113.1 (t, 5-*C*HF_2, $^1J_{C-F}$ = 247.4 Hz), 110.5 (t, 3-*C*HF2, $^1J_{C-F}$ = 234.2 Hz), 90.7 (t, *C*-5CHF_2, $^2J_{C-F}$ = 23.8 Hz), 46.3 (NH*C*H_2), 33.6 (4-*C*H_2), 21.8 (*C*H_3 *p*Tol) ppm.
Anal calcd for $C_{19}H_{19}F_4N_3O_2S$: C, 53.14; H, 4.46; F, 17.70; N, 9.79; O, 7.45; S, 7.47. Found: C, 53.21; H, 4.72; N, 9.46.

(3,5-bis(difluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70A.b)



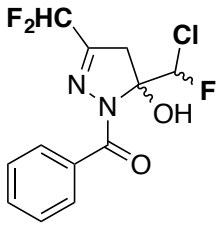
Prepared according to **Method δ** from **II.60A.b** (1 equiv., 450 mg, 1.72 mmol) and benzoyl hydrazide (1.88 equiv., 440 mg, 3.23 mmol) in HFIP (5 mL). The mixture was heated 60min at 120 °C in microwave apparatus into a sealed vial. Further benzoyl hydrazide (0.64 equiv., 150 mg, 1.10 mmol) was added. After 30min more, the mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 530 mg, white solid (99%). M.p.: 113.1 - 113.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, *o*-C*H*), 7.57 (tt, 1H, *p*-C*H*), 7.46 (t, *m*-C*H*), 6.50 (t, 5'-C*H*F$_2$, $^{2}J_{H-F}$ = 56.3 Hz), 6.37 (t, 3'-C*H*F$_2$, $^{2}J_{H-F}$ = 53.7 Hz), 5.17 (s, 5'-O*H*), 3.60 to 3.11 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -124.4 (m, 1F), -133.0 to -133.9 (m, 1F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5 (*C*(O)Ph), 150.1 (t, *C*-3'CHF$_2$, $^{2}J_{C-F}$ = 32.7 Hz), 132.9, 131.9, 130.2, 128.2 (*C*$_6$H$_5$), 111.6 (t, 5'-*C*HF$_2$, $^{1}J_{C-F}$ = 249 Hz), 110.2 (t, 3'-*C*HF$_2$, $^{1}J_{C-F}$ = 235.6 Hz), 93.6 (t, *C*-5'CHF$_2$, $^{2}J_{C-F}$ = 27.4 Hz), 36.7 (4'-*C*H$_2$) ppm.
Anal. calcd for $C_{12}H_{10}F_4N_2O_2$: C, 49.66; H, 3.47; F, 26.19; N, 9.65; O, 11.03. Found: C, 49.70; H, 3.50; N, 9.53.

(5-(difluoromethyl)-5-hydroxy-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70A.c)



Prepared according to **Method δ** from **II.60A.c** (1 equiv., 29 mg, 0.10 mmol) and benzoyl hydrazide (2.12 equiv., 30 mg, 0.22 mmol) in HFIP (0.6 mL). The mixture was heated 30min at 140 °C in microwave apparatus into a sealed vial and was concentrated *in vacuo*. The crude was purified by flash chromatography (DCM in cyclohexane 0 to 100%). Yield: 20 mg, white solid (62 %). M.p.: 143.7 - 143.9 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 2H, *o*-C*H*), 7,58 (tt, 1H, *p*-C*H*), 7.47 (t, 2H, *m*-C*H*), 6.51 (t, 5'-CHF$_2$, $^{2}J_{H-F}$ = 56.3 Hz), 5.18 (s, 5'-O*H*), 3.61 to 3.13 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -67.5 (s, C*F*$_3$), -124.3 to -125.2 (m, 2F), -132.9 to -133.8 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4 (*C*=O), 144.9 (q, *C*-3'CF$_3$, $^{2}J_{C-F}$ = 39.8 Hz), 133.1, 131.4, 130.5, 128.3 (*C*$_6$H$_5$), 119.4 (q, *C*F$_3$, $^{1}J_{C-F}$ = 271 Hz), 111.5 (t, 5'-*C*HF$_2$, $^{1}J_{C-F}$ = 249 Hz), 94.4 (t, *C*-5'CHF$_2$, $^{2}J_{C-F}$ = 27.6 Hz), 37.9 (4'-*C*H$_2$) ppm.
HRMS (ESI) calcd for $C_{12}H_{10}F_5N_2O_2$ [M+H]: 309.0657. Found: 309.0620.

(5-(chlorofluoromethyl)-3-(difluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70B.b)



Prepared according to **Method δ** from **II.60B.b** (1 equiv., 97 mg, 0.35 mmol) and benzoyl hydrazide (2.1 equiv., 100 mg, 0.73 mmol) in HFIP (2 mL). The mixture was heated 5,5h at 120 °C in microwave apparatus into a sealed vial and was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 15%). Yield: 108 mg, colourless solid (99%) (ca. 60/40 mixture of *syn*/*anti* diastereoisomers). M.p.: 104.2 - 105.5 °C.

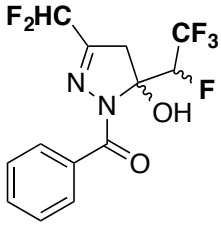
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 (t + t, *o*-C*H*), 7.56 (tt, p-CH), 7.45 (t, *m*-C*H*), 6.95 and 6.89 (d + d, 5'C*H*FCl, $^{2}J_{H-F}$ = 50.8 Hz and $^{2}J_{H-F}$ = 49.9 Hz), 6.37 and 6.35 (t + t, 3'C*H*F_2, $^{2}J_{H-F}$ = 53.9 Hz and $^{2}J_{H-F}$ = 53.6 Hz), 5.29 and 5.23 (br s, 5'-O*H*), 3.76 to 3.17 (2 x m, 4-CH_2) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.9 to -119.8 (m, 2F), -140.6 to -150.2 (m, 1F) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5 and 170.3 (*C*=O), 150.3 and 149.9 (2 x t, *C*-3'CHF_2, $^{2}J_{C-F}$ = 32.3 Hz), 132.8, 130.2, 130.0, 128.2 (C_6H_5), 110.3 and 110.2 (t + t, 3'*C*HF_2, $^{1}J_{C-F}$ = 236 Hz), 100.0 and 99.1 (2 x d, 5'*C*HFCl, $^{1}J_{C-F}$ = 250 Hz and $^{1}J_{C-F}$ = 249 Hz), 96.1 and 95.9 (d, *C*-5'CHFCl, $^{2}J_{C-F}$ = 24.3 Hz), 38.1 and 37.9 (4'-*C*H_2) ppm.

HRMS (ESI) calcd for $C_{12}H_{10}ClF_3N_2NaO_2$ [M+Na]: 329.0275 (+ 331.0249). Found: 329.0295 (+ 331.0220).

(3-(difluoromethyl)-5-hydroxy-5-(1,2,2,2-tetrafluoroethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70C.b-P1)



Prepared according to **Method δ** from *ca*. 65/35 mixture of **II.60C.b**/**II.61C.b** (1 equiv., 250 mg, 0.83 mmol) and benzoyl hydrazide (2.64 equiv., 300 mg, 2.20 mmol) in HFIP (3 mL). The mixture was heated 90min at 120 °C and 90min at 140 °C in microwave apparatus into a sealed vial and was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). **II.70C.b-P1** was separated from **II.70C.b-P2**. Yield: 166mg, colourless solid (58%). **II.70C.b-P1**/**II.70C.b-P2** were formed in a 68/31 ratio, and each product was a mixture of *syn*/*anti* diastereoisomers. Each product was repurified separately for data's. M.p.: 85.5 - 85.9 °C.

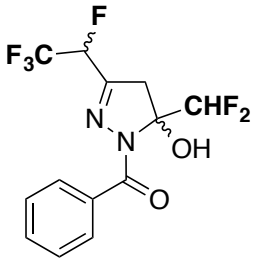
II.70C.b-P1 (major diasteroisomer):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *o*-C*H*), 7.58 (t, *p*-C*H*), 7.47 (t, *m*-C*H*), 6.37 (t, 3'-C*H*F_2, $^{2}J_{H-F}$ = 53.6 Hz), 5.68 (qd, 5'-C*H*FCF_3, $^{2}J_{H-F}$ = 44.9 Hz, $^{3}J_{H-F}$ = 6.8 Hz), 5.27 (s, 5'-O*H*), 3.69 to 3.19 (m, 2H, 4-CH_2) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -73.3 (dd, CHFC*F*$_3$, $^{3}J_{F-F}$ = 10.2 Hz, $^{3}J_{F-H}$ = 6.7 Hz), -119.0 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.7 Hz), -196.6 (dm, CH*F*CF_3, $^{2}J_{F-H}$ = 45 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1 (*C*=O), 150.4 (t, *C*-*3'*CHF_2, $^{2}J_{C-F}$ = 32.4 Hz), 133.0, 132.0, 130.3, 128.2 (C_6H_5), 121.7 (qd, 5'-CHF*C*F_3, $^{1}J_{C-F}$ = 282.5 Hz, $^{2}J_{C-F}$ = 25.2

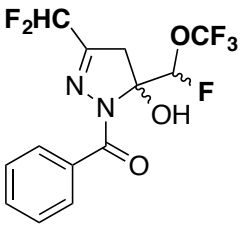
Hz), 110.2 (t, 3'*C*HF_2, $^1J_{C-F}$ = 235.2 Hz), 92.9 (d, *C*-5'$CHFCF_3$, $^2J_{C-F}$ = 23.1 Hz), 84.8 (qd, 5'*C*$HFCF_3$, $^1J_{C-F}$ = 194.7 Hz, $^2J_{C-F}$ = 32.2 Hz), 37.9 (4-*C*H_2) ppm.
Anal. calcd for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; F, 33.50; N, 8.23; O, 9.40. Found: C, 45.90; H, 3.03; N, 8.14.

(5-(difluoromethyl)-5-hydroxy-3-(1,2,2,2-tetrafluoroethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70C.b-P2)



Separated from **II.70C.b-P1** after flash chromatography. Yield: 77mg, colourless solid (27%) (ca.60/40 *syn*/*anti* mixture). M.p.: 108.5 - 109.6 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *o*-C*H*), 7.57 (t, *p*-C*H*), 7,46 (t, *m*-C*H*), 6.50 and 6.49 (2 x t, C*H*F_2, $^2J_{H-F}$ = 56.2 Hz), 5.47 (qd, C*H*FCF_3, $^2J_{H-F}$ = 45.1 Hz, $^3J_{H-F}$ = 6.0 Hz), 5.16 and 5.12 (5-O*H*), 3.62 to 3.07 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -73.8 and -77.0 (2 x dd, CHFCF_3, $^3J_{F-F}$ = 14.6 Hz, $^3J_{F-H}$ = 6 Hz), -124.6 to -134.0 (m, 2F), -201.6 and -202.2 (dqt and qdm, CH*F*CF_3, $^2J_{H-F}$ = 44.8 Hz, $^3J_{F-H}$ = 14.9 Hz, $^4J_{F-H}$ = 2.1 Hz and $^2J_{H-F}$ = 44.7 Hz, $^3J_{F-H}$ = 14.7 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4 (2 x d, *C*=O,), 147.6 (2 x d, *C*-3'$CHFCF_3$, $^2J_{C-F}$ = 27.6 Hz), 132.9, 131.8, 130.3, 128.2 (C_6H_5), 121.4 and 121.0 (2 x q, 3'$CHFCF_3$, $^1J_{C-F}$ = 282.6 Hz), 111.6 and 111.5 (2 x t, 5'*C*HF_2, $^1J_{C-F}$ = 248.6 Hz), 93.7 and 93.6 (2 x t, *C*-5'CHF_2, $^2J_{C-F}$ = 27.2 Hz), 85.0 and 84.6 (2 x dq, 3'*C*$HFCF_3$, $^1J_{C-F}$ = 185.8 Hz, $^2J_{C-F}$ = 18.6 Hz), 38.6 and 38.5 (2 x s, 4'-CH_2) ppm.

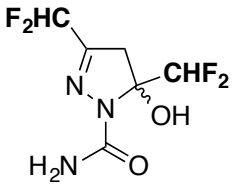
(3-(difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (II.70D.b)



Prepared according to **Method δ** from **II.60D.b** (1 equiv., 70 mg, 0.21 mmol) and benzoyl hydrazide (2.06 equiv., 60 mg, 0.44 mmol) in HFIP (1 mL). The mixture was heated 60min at 140 °C in microwave apparatus into a sealed vial and was concentrated *in vacuo*. The crude was purified by flash chromatography (DCM in cyclohexane 0 to 100%). Yield: 62mg, colourless oil (81%, purity ca.90wt.%), racemic mixture of *syn*/*anti* diastereoisomers.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 to 7.79 (m, 2H, *o*-C*H*), 7.59 to 7.55 (m, 1H, *p*-C*H*), 7.46 (t, 2H, *m*-C*H*), 6.58 and 6.56 (2 x d, C*H*$FOCF_3$, $^2J_{H-F}$ = 57.5 Hz and $^2J_{H-F}$ = 56.6 Hz), 6.37 and 6.36 (2 x t, C*H*$FOCF_3$, $^2J_{H-F}$ = 53.6 Hz), 5.34 and 5.28 (2 x br s, 5'-O*H*), 3.61 to 3.14 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.2 and -59.3 (2 x d, OCF_3, $^4J_{F-F}$ = 4 Hz), -118.9 and -119.0 (2 x d, CHF_2, $^2J_{F-H}$ = 53.9 Hz), -133.0 to -142.3 (m, 1F) ppm.

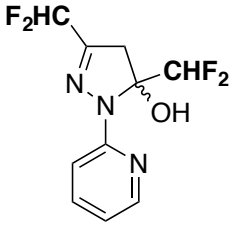
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5 and 170.4 (*C*=O), 150.3 and 150.1 (t, *C*CHF_2, $^2J_{C-F}$ = 32.3 Hz), 132.9, 132.8, 131.8, 131.7, 130.2, 130.0, 128.2 (C_6H*5*), 121.0 (qd, O*C*F_3, $^1J_{C-F}$ = 262 Hz, $^2J_{C-F}$ = 33 Hz), 110.2 (t, *C*HF_2, $^1J_{C-F}$ = 236 Hz), 102.3 and 102.2 (2 x dq, *C*HFOCF_3, $^1J_{C-F}$ = 240 Hz, $^3J_{C-H}$ = 3 Hz), 93.5 and 93.3 (2 x d, 5'-C_{quat}, $^2J_{C-F}$ = 29.1 Hz and $^2J_{C-F}$ = 27.3 Hz), 37.2 and 37.1 (4'-*C*H_2) ppm.
Anal. calcd for $C_{13}H_{10}F_6N_2O_3$: C, 43.83; H, 2.83; F, 32.00; N, 7.86; O, 13.47. Found: C, 44.13; H, 2.94; N, 7.74.

3,5-bis(difluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazole-1-carboxamide (II.72A.b)



Prepared according to **Method δ** from **II.60B.b** (1 equiv., 50 mg, 0.19 mmol) and semicarbazide hydrochloride (3.28 equiv., 70 mg, 0.63 mmol) in HFIP (1 mL). The mixture was heated 4h at 100 °C in microwave apparatus into a sealed vial and was concentrated *in vacuo*. ^{19}F NMR yield: 99%. Another crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 100%). Colourless solid. M.p.: 102.8 - 103.6 °C.
^{1}H-NMR (400 MHz, MeOD-d_4): δ = 6.56 (dd, 5-C*H*F_2, $^2J_{H-F}$ = 55.8 Hz, $^2J_{H-F}$ = 58.1 Hz), 6.54 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 4.85 (s, 3H, NH_2 + O*H*), 3.49 to 2.94 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, MeOD-d_4): δ = -119.5 to -121.5 (m, 2F), -127.9 to -134.1 (m, 2F) ppm.
^{13}C-NMR (100 MHz, MeOD-d_4): δ = 156.7 (*C*(O)NH_2), 147.1 (t, *C*-3CHF_2, $^2J_{C-F}$ = 31.2 Hz), 114.0 (t, 5-*C*HF_2, $^1J_{C-F}$ = 245.4 Hz), 112.2 (t, 3-*C*HF_2, $^1J_{C-F}$ = 233.1 Hz), 93.0 (t, *C*-5CHF_2, $^2J_{C-F}$ = 25.6 Hz), 38.8 (4-*C*H_2) ppm.
Anal. calcd for $C_6H_7F_4N_3O_2$: C, 31.45; H, 3.08; F, 33.17; N, 18.34; O, 13.96. Found: C, 31.55; H, 3.12; N, 18.03. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in DCM/Et_2O.

3,5-bis(difluoromethyl)-1-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazol-5-ol (II.73A.b)

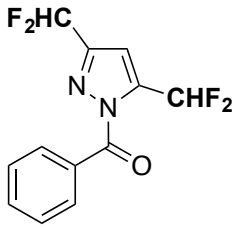


Prepared according to **Method δ** from **II.60B.b** (1 equiv., 500 mg, 1.91 mmol) and 2-hydrazinopyridine (3.28 equiv., 70 mg, 0.63 mmol) in HFIP (1 mL). The mixture was heated 30min at 140 °C and 30min at 160 °C in microwave apparatus into a sealed vial. 2-hydrazinopyridine (1.39 equiv., 290 mg, 2.66 mmol) and conc. H_2SO_4 (1.05 equiv., 202 mg, 0.11 mL, 2 mmol) were added. The mixture was heated 60min more at 140 °C and was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 437 mg, colourless solid (54%). M.p.: 71.9 - 72.3 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, 6'-C*H*), 7.67 (ddd, 4'-C*H*), 7.30 (d, 3'-C*H*), 6.90 (ddd, 5'-C*H*), 6.58 (t, 5-C*H*F_2, $^2J_{H-F}$ = 58.9 Hz), 6.44 (t, 3-C*H*F_2, $^2J_{H-F}$ = 54.1 Hz), 6.22 (s, 5-O*H*), 3.61 to 3.13 (m, 2H, 4-CH_2) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -116.8 to -118.7 (m, 2F), -124.0 to -134.8 (m, 2F) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.0 (N-*C*N), 146.6 (6'-*C*H), 145.4 (t, *C*-3CHF_2, $^2J_{C-F}$ = 31.2 Hz), 139.3 (4'-*C*H), 117.3 (3'-*C*H), 112.2 (t, 5-*C*HF_2, $^1J_{C-F}$ = 248.7 Hz), 111.0 (t, 3-*C*HF_2, $^1J_{C-F}$ = 233.2 Hz), 110.9 (5'-*C*H), 93.7 (dd, *C*-5CHF_2, $^2J_{C-F}$ = 28.0 Hz, $^2J_{C-F}$ = 25.3 Hz), 37.3 (4-*C*H_2) ppm.
Anal. calcd for $C_{10}H_9F_4N_3O$: C, 45.64; H, 3.45; F, 28.87; N, 15.97; O, 6.08. Found: C, 45.76; H, 3.53; N, 15.81. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in DCM/Et_2O.

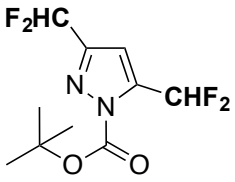
Preparation of 3,5-(bis)fluoroalkyl)-pyrazoles from pyrazolines or by protection

(3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl)(phenyl)methanone (II.75)



From **II.65A.b**: A solution of $SOCl_2$ (2.09 equiv., 65.6 mg, 0.04 mL, 0.551 mmol) in toluene (1 mL) was added to a solution of **II.65A.b** (1 equiv., 100 mg, 0.264 mmol) and dry pyridine (7.97 equiv., 166 mg, 0.17 mL, 2.1 mmol) in toluene (2 mL) at 0 °C. After raising the temperature to room temperature, the mixture was refluxed for 3h. ^{19}F NMR yield: 99%.
From **II.70A.b**: A solution of $SOCl_2$ (2 equiv., 82 mg, 0.05 mL, 0.689 mmol) in toluene (1 mL) was added dropwise to a solution of **II.70A.b** (1 equiv., 100 mg, 0.345 mmol) and dry pyridine (8.61 equiv., 234 mg, 0.24 mL, 2.97 mmol) in toluene (2 mL) at 0 °C. The solution was raised to room temperature over 1h, and was filtered. The filtrate was washed twice with water (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 86 mg, colourless oil (92%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *o*-C*H*), 7.68 (tt, *p*-C*H*), 7.53 (t, *m*-C*H*), 7.39 (t, C*H*F_2, $^2J_{H-F}$ = 54.3 Hz), 7.08 (s, 4'-C*H*), 6.70 (t, C*H*F_2, $^2J_{H-F}$ = 54.1 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.6 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.9 Hz), -115.0 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.9 (*C*=O), 149.5 (t, *C*-CHF_2, $^2J_{C-F}$ = 31 Hz), 142.5 (t, *C*-CHF_2, $^2J_{C-F}$ = 31 Hz), 134.2, 132.0, 130.3, 128.5 (*C*$_6$H$_5$), 110.1 and 108.3 (2 x t, 3,5-*C*HF_2, $^1J_{C-F}$ = 236 Hz and $^1J_{C-F}$ = 238.5 Hz), 107.7 (4'-*C*H) ppm.
Anal. calcd for $C_{12}H_8F_4N_2O$: C, 52.95; H, 2.96; F, 27.92; N, 10.29; O, 5.88. Found: C, 52.97; H, 3.04; N, 10.15.

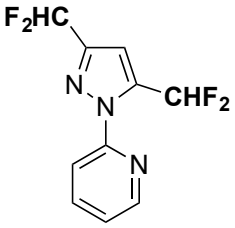
tert-butyl 3,5-bis(difluoromethyl)-1_H_-pyrazole-1-carboxylate (II.76)



A mixture of 3,5-bis(difluoromethyl)-1H-pyrazole (1 equiv., 1000 mg, 5.95 mmol), BOC anhydride (1.06 equiv., 1380 mg, 6.32 mmol) and DMAP (20.1 %, 146 mg, 1.2 mmol) was cooled to 0 °C and dissolved in dry MeCN (10 mL). Et_3N (1.09 equiv., 655 mg, 0.9 mL, 6.47 mmol) was added after 5 min, the mixture left to rise to room temperature over 1 h. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 1.27 g, colourless oil (80%). (Unstable)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 6.92 (s, 4-C*H*), 6.70 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 1.66 (s, 9H, C(C*H*$_3$)$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.6 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.3 Hz), -115.0 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.2 and 141.1 (2 x t, *C*-3CHF_2 and *C*-5CHF_2, $^2J_{C-F}$ = 31.2 Hz and $^2J_{C-F}$ = 31.5 Hz), 146.7 (*C*=O), 110.2 and 108.0 (2 x t, 3-*C*HF_2 and 5-*C*HF_2, $^1J_{C-F}$ = 236.0 Hz and $^1J_{C-F}$ = 238.5 Hz), 107.2 (4-*C*H), 88.3 (*C*(CH$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$) ppm.
HRMS (ESI) calcd. for $C_{10}H_{12}F_4N_2NaO_2$ [M+Na]: 291.0727. Found: 291.0745.

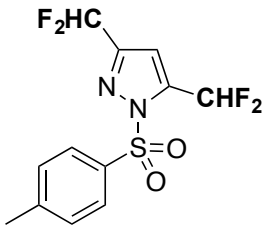
Ref: Maddaford, Adrian et al From PCT Int. Appl., 2008040995, 10 Apr 2008.

2-(3,5-bis(difluoromethyl)-1_H_-pyrazol-1-yl)pyridine (II.78)



Same procedure than **II.70A.b** starting from **II.73A.b** (1 equiv., 205 mg, 0.778 mmol). After 1 h at room temperature, the mixture was partitioned between water (5 mL) and DCM (5 mL). The organic layer was washed (brine), dried (Na_2SO_4), filtered, evaporated and dried *in vacuo* overnight. Yield: 202 mg, colourless solid (>99%). M.p.: 22-25 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.44 (dd, 6-C*H*), 7.97 (d, 3-C*H*), 7.87 (ddd, 4-C*H*), 7.78 (t, C*H*F_2, $^2J_{H-F}$ = 54.6 Hz), 7.29 (ddd, 5-C*H*), 7.00 (s, 4'-C*H*), 6.76 (t, C*H*F_2, $^2J_{H-F}$ = 54.8 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.9 (d, CH*F*$_2$, $^2J_{F-H}$ = 55.1 Hz), -114.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.5 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.8 (2-C_{quat}), 147.8 (6-*C*H), 147.7 (t, *C*CHF_2, $^2J_{C-F}$ = 30.3 Hz), 139.4 (t, *C*CHF_2, $^2J_{C-F}$ = 31.4 Hz), 139.2 (4-*C*H), 122.9 (5-*C*H), 114.8 (3-*C*H), 110.7 (t, *C*HF_2, $^1J_{C-F}$ = 235.4 Hz), 108.9 (t, *C*HF_2, $^2J_{C-F}$ = 237.7 Hz), 106.3 (4'-*C*H) ppm.
Anal. calcd for $C_{10}H_7F_4N_3$: C, 48.99; H, 2.88; F, 30.99; N, 17.14. Found: C, 48.88; H, 2.98; N, 16.85.

3,5-bis(difluoromethyl)-1-tosyl-1*H*-pyrazole (II.79)

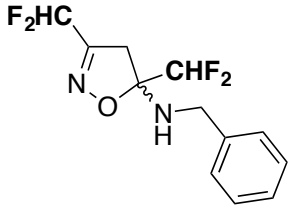


The corresponding vinamidinium was prepared from **II.59b** (1 equiv., 395 mg, 2.15 mmol) and **2A** (1.05 equiv.) according to general procedure. After 1 h at room temperature, 4-methylbenzenesulfonhydrazide (1.52 equiv., 610 mg, 3.27 mmol) was added under argon flux. After 1 h of stirring, the mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 1%). Pyrazole **II.79** was separated from minor 5-benzylaminopyrazoline **II.69A.b** (270mg, colourless oil). Yield: **II.79**, 375 mg, colourless oil (54%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (m, 2H, *p*Tol), 7.38 (m, 2H, *p*Tol), 7.27 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.9 Hz), 6.89 (s, 4-C*H*), 6.64 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.9 Hz), 2.45 (s, CH3, *p*Tol) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.5 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.8 Hz), -113.6 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.0 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 31.1 Hz), 147.4 (*C*CH$_3$ *p*Tol), 141.2 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 32.1 Hz), 133.0, 130.5, 128.9 (*p*Tol), 109.8 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 236.7 Hz), 107.6 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 238.6 Hz), 106.8 (4-*C*H), 21.9 (*C*H$_3$ *p*Tol) ppm.
HRMS (ESI) calcd for $C_{12}H_{10}F_4N_2NaO_2S$ [M+Na]: 345.0291. Found: 345.0313.

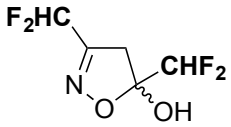
Preparation of 3,5-bis(fluoroalkyl)isoxazolines **II.80-81**

***N*-benzyl-3,5-bis(difluoromethyl)-4,5-dihydroisoxazol-5-amine (II.80A.b)**



The corresponding vinamidinium was prepared according to **Method α** from **II.59b** (1 equiv., 300 mg, 1.64 mmol) and **2A** (1.2 equiv.) according to general procedure. After 1 h at room temperature, hydroxylamine 50wt.% in H_2O (1.49 equiv., 161 mg, 0.15 mL, 2.45 mmol) was added *via* syringe. The mixture was stirred for 30min, diluted in DCM (4 mL) and washed with HCl 1N aq. (3 x 2 mL). The organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 358 mg, colourless oil (79 %).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, C_6H_5), 6.43 (t, 3-C*H*F_2, $^{2}J_{H-F}$ = 53.6 Hz), 5.87 (t, 5-C*H*F_2, $^{2}J_{H-F}$ = 55.0 Hz), 3.87 to 3.77 (m, 2H, NHCH_2), 3.19 (syst. AB, 4-CH_2, Δν = 62 Hz, $^{2}J_{H-H}$ = 18.9 Hz), 2.52 (br s, N*H*CH_2Ph) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.5 to -120.1 (m, 2F), -131.2 to -133.0 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.9 (t, *C*-3CHF$_2$, $^{2}J_{C-F}$ = 31.1 Hz), 138.3, 128.8, 128.2, 127.9 (C_6H_5), 112.7 (t, 5-*C*HF$_2$, $^{1}J_{C-F}$ = 249.3 Hz), 109.7 (t, 3-*C*HF$_2$, $^{1}J_{C-F}$ = 237.2 Hz), 100.8 (t, *C*-5CHF$_2$, $^{2}J_{C-F}$ = 22.8 Hz), 45.1 (NH*C*H$_2$Ph), 32.9 (4-*C*H$_2$) ppm.
HRMS (ESI) calcd for $C_{12}H_{11}F_4NNaO$ [M+Na]: 284.0669. Found: 284.0693.

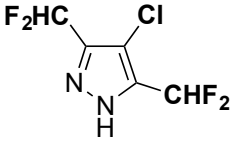
3,5-bis(difluoromethyl)-4,5-dihydroisoxazol-5-ol (II.81A.b)



Prepared according to **Method δ** from **II.60B.b** (1 equiv., 250 mg, 0.96 mmol) and hydroxylamine hydrochloride (2.41 equiv., 160 mg, 2.30 mmol) in HFIP (3 mL). The mixture was heated 30min at 120 °C and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O in cyclohexane 0 to 40%). Yield: 118 mg, colourless oil (66%). ^{19}F NMR yield: 99%.
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.48 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53.5 Hz), 5.87 (t, 5-C*H*F_2, $^2J_{H-F}$ = 54.8 Hz), 4.15 (br s, 5-O*H*), 3.29 (syst. AB, 4-CH_2, Δν = 99.6 Hz, $^2J_{H-H}$ = 18.8 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.6 to -120.2 (m, 2F), -130.1 to -133.0 (m, 2F) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 153.6 (t, *C*-3CHF_2, $^2J_{C-F}$ = 31.5 Hz), 111.6 (t, 5-CHF2, $^1J_{C-F}$ = 248 Hz), 109.0 (t, 3-*C*HF_2, $^1J_{C-F}$ = 236 Hz), 105.7 (t, 5-C_{quat}, $^2J_{C-F}$ = 26 Hz), 37.9 (4-*C*H_2) ppm.
Anal. calcd for $C_5H_5F_4NO_2$: C, 32.10; H, 2.69; F, 40.62; N, 7.49; O, 17.10. Found: C, 31.85; H, 3.17; N, 7.19.

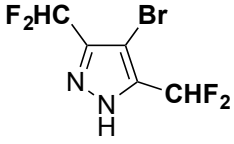
Functionalization of the position 4

4-chloro-3,5-bis(difluoromethyl)-1*H*-pyrazole (II.84a)



NaOCl aq. 13% solution (2.51 equiv., 8562 mg, 7.1 mL, 15 mmol) was added to a solution of 3,5-bis(difluoromethyl)-1H-pyrazole (**II.58A.b**) (1 equiv., 1.00 g, 5.95 mmol) in glacial AcOH (15 mL) at 0 °C. The mixture was stirred 18 h at room temperature, and was then quenched with sat. NH_4Cl aq. solution (100mL), pH was adjusted with sodium bicarbonate saturated solution (50 mL) until pH 5-6. The solution was extracted with Et_2O (3 x 100 mL). The organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by fc (Et_2O in pentane 0 to 50%). Yield: 987mg, pale solid (82%). The product was sublimed under reduced pressure (75-80 °C, <10 mbar) for spectral datas. M.p.: 59.5 - 60.0 °C.
^1H-NMR (400 MHz, $CDCl_3$): δ = 11.10 (br s, N*H*), 6.76 (t, 2 x C*H*F_2, $^2J_{H-F}$ = 53.3 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -116.0 (d, 2 x CH*F*$_2$, $^2J_{F-H}$ = 53.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.2 (t, 3,5-*C*CHF_2, $^2J_{C-F}$ = 27.1 Hz), 109.6 (quint., 4-*C*-Cl, $^3J_{C-F}$ = 3.6 Hz), 108.3 (t, 3,5-*C*HF_2, $^1J_{C-F}$ = 237.5 Hz) ppm.
HRMS (ESI) calcd for $C_5H_4ClF_4N_2$ [M+H]: 202.9994 + 204.9965. Found: 203.0008 + 204.9981.

4-bromo-3,5-bis(difluoromethyl)-1*H*-pyrazole (II.84b)



Fe (0.497 equiv., 33 mg, 0.591 mmol) was added to a solution of 3,5-bis(difluoromethyl)-1H-pyrazole (**II.58A.b**) (1 equiv., 200 mg, 1.19 mmol) and bromine (2.7 equiv., 52 mg, 0.17 mL, 3.21 mmol) at 0°C under stirring. After the addition, the ice bath was removed and the mixture stirred 1 h at 100°C. The mixture was diluted with Et2O (2 mL), washed with saturated thiosulfate solution (2 mL), extracted with Et_2O (2 x 5mL). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 10%). Yield: 220mg, white solid (90%). M.p.: 76.7 - 77.0 °C.

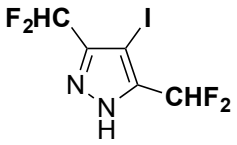
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.67 (s br, 1H, NH) , 6.75 (t, 2 x C*H*F_2, $^2J_{H-F}$ = 53.3Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.5 (d, 2 x CH*F*$_2$, $^2J_{F-H}$ = 53.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.9 (m, 2 x *C*CHF_2), 108.9 (t, 2 x C*H*F_2, $^1J_{C-F}$ = 237.5Hz), 93.1 (4-*C*Br) ppm.

Anal. calcd for $C_5H_3BrF_4N_2$: C, 24.31; H, 1.22; Br, 32.35; F, 30.77; N, 11.34. Found: C, 24.72; H, 1.50; N, 11.22.

3,5-bis(difluoromethyl)-4-iodo-1*H*-pyrazole (II.84c)



To a solution of 3,5-bis(difluoromethyl)-1H-pyrazole (**II.58A.b**) (1 equiv., 2 g, 11.9 mmol) in DCM (25 mL) at -15°C was added silver trifluoroacetate (1.05 equiv., 2.76 g, 12.5 mmol) followed by solid iodine (1.08 equiv., 3.25 g, 12.8 mmol). The mixture was raised to room temperature and stirred 2 h, and then was filtered. The filtrate was washed with saturated sodium thiosulfate solution (10 mL). The organic layer was washed (brine), dried ($MgSO_4$), filtered and evaporated *in vacuo*. Yield: 3.42g (crude), white solid (98%). The product was purified by flash chromatography (Et_2O in pentane 0 to 15%) for data's. M.p.: 91.5 - 92.3 °C.

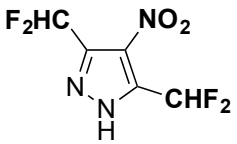
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.21 (br s, N*H*), 6.72 (t, 2 x C*H*F_2, $^2J_{H-F}$ = 53.3Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -114.9 (d, 2 x CH*F*$_2$, $^2J_{F-H}$ = 53.1 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.8 (t, 2 x *C*CHF_2, $^2J_{C-F}$ = 26.3Hz), 109.6 (t, 2 x *C*HF_2, $^1J_{C-F}$ = 237.5Hz), 56.5 (quint., *C*-I, $^3J_{C-F}$ = 3.6 Hz) ppm.

Anal. calcd for $C_5H_3F_4IN_2$: C, 20,42; H, 1,03; F, 25,85; I, 43,17 N, 9,53 . Found: C, 20,82; H, 1,32; N, 9,03.

3,5-bis(difluoromethyl)-4-nitro-1*H*-pyrazole (II.84d)

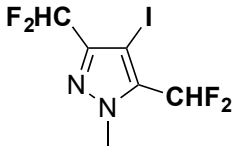


Fuming HNO_3 (4.98 equiv., 4.8 g, 3.2 mL, 53.3 mmol) was carefully added to a solution of 3,5-bis(difluoromethyl)-1H-pyrazole (**II.58A.b**) (1 equiv., 2 g, 10.7 mmol) in conc. H_2SO_4 (5 mL) into a sealed tube and heated at 115°C for 20min under microwave irradiation. The mixture was poured onto ice (200 mL), then basified with NaOH 2M (50 mL) and left to precipitate for 1 h. The suspension was filtered through a Buchner funnel, and the resulting white solid was dried in vacuo (1.3g). The aqueous was extracted with Et2O (2 x 75 mL), the organic layer was separated, washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo* to provide 1.0g of additional material. Yield: 2.3g, white solid (99%). The product was purified by flash chromatography (Et_2O in pentane 0 to 40%) for data's. M.p.: 95.0 - 96.2 °C.

^{1}H-NMR (400 MHz, MeOD-d_4): δ = 7.26 (t, 2 x C*H*F_2, $^2J_{H-F}$ = 52.9Hz) , 4.86 (s br., N*H*) ppm.

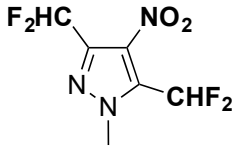
^{19}F-NMR (376 MHz, MeOD-d_4): δ = -119.8 (d, 2 x CHF_2, $^2J_{F-H}$ = 53.2Hz) ppm.
^{13}C-NMR (100 MHz, MeOD-d_4): δ = 140.6 (t, 2 x CCHF$_2$, $^2J_{C-F}$ = 26.1Hz), 132.1 (CNO$_2$), 109.6 (t, 2 x CHF$_2$, $^1J_{C-F}$ = 237.7Hz) ppm.
HRMS (ESI) calcd for $C_5H_2F_4N_3O_2$ [M-H]: 212.0089. Found: 212.0069.
Crystals of the crude compound suitable for X-ray crystallographic analysis were obtained by slow evaporation in DCM/MeOH (as ½hydrate). The compound was amorphous after chromatography.

3,5-bis(difluoromethyl)-4-iodo-1-methyl-1*H*-pyrazole (II.85c)



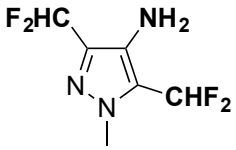
3,5-bis(difluoromethyl)-4-iodo-1H-pyrazole (**II.84c**) (1 equiv., 464 mg, 1.58 mmol) was dissolved in DCM (6 mL) and treated with MeI (1.22 equiv., 273 mg, 0.12 mL, 1.93 mmol) and Et$_3$N (1.5 equiv., 240 mg, 0.33 mL, 2.37 mmol). The mixture was stirred for 1 h. MeI (1.22 equiv., 273 mg, 0.12 mL, 1.93 mmol) was added, the mixture stirred 18 h more. Et$_3$N (1.5 equiv., 240 mg, 0.33 mL, 2.37 mmol) and MeI (1.12 equiv., 250 mg, 0.11 mL, 1.77 mmol) were added *via* syringe. After 1 h more, the mixture was evaporated *in vacuo*. Yield: 251mg, colourless solid (52%). M.p.: 57.0 - 57.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.75 (t, 5-CHF$_2$, $^2J_{H-F}$ = 52.1 Hz), 6.63 (t, 3-CHF$_2$, $^2J_{H-F}$ = 53.6 Hz), 4.08 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -114.0 (d, 3-CHF_2, $^2J_{F-H}$ = 54.0 Hz), -114.5 (d, 5-CHF_2, $^2J_{F-H}$ = 51.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.1 (t, C-3CHF$_2$, $^2J_{C-F}$ = 27.5 Hz), 136.8 (t, C-5CHF$_2$, $^2J_{C-F}$ = 24.4 Hz), 110.8 (t, 3-CHF$_2$, $^1J_{C-F}$ = 236.3 Hz), 109.1 (t, 5-CHF$_2$, $^1J_{C-F}$ = 236.3 Hz), 58.7 (t, 4-C-I, $^3J_{C-F}$ = 6.5 Hz), 39.5 (NCH$_3$) ppm.
Anal. calcd for $C_6H_5F_4IN_2$: C, 23.40; H, 1.64; F, 24.67; I, 41.20; N, 9.09. Found: C, 23.58; H, 1.75; N, 8.88.

3,5-bis(difluoromethyl)-1-methyl-4-nitro-1*H*-pyrazole (II.85d)



3,5-bis(difluoromethyl)-4-nitro-1H-pyrazole (**II.84d**) (1 equiv., 800 mg, 3.75 mmol) was dissolved in DCM (17 mL) and treated with MeI (1.88 equiv., 1.0 g, 0.44 mL, 7.06 mmol) and Et$_3$N (1.38 equiv., 524 mg, 0.72 mL, 5.18 mmol). The mixture was stirred at room temperature for 18 h, and was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 874mg, colourless oil (>99%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44 (t, 5-CHF$_2$, $^2J_{H-F}$ = 52.1 Hz), 7.03 (t, 3-CHF$_2$, $^2J_{H-F}$ = 53.2 Hz), 4.15 (s, NCH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.4 (dd, 5-CHF_2, $^2J_{F-H}$ = 51.7 Hz, $^5J_{F-H}$ = 1.4 Hz), -118.7 (dd, 3-CHF$_2$, $^2J_{F-H}$ = 53.2 Hz, $^5J_{F-H}$ = 2.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.6 (t, C-3CHF$_2$, $^2J_{C-F}$ = 26.5 Hz), 134.1 (t, C-5CHF$_2$, $^2J_{C-F}$ = 25.9 Hz), 131.6 (CNO$_2$), 108.1 (t, CHF$_2$, $^1J_{C-F}$ = 239.3 Hz), 106.4 (t, CHF$_2$, $^1J_{C-F}$ = 239.3 Hz), 40.8 (NCH$_3$) ppm.
Anal. calcd for $C_6H_5F_4N_3O_2$: C, 31.73; H, 2.22; F, 33.46; N, 18.50; O, 14.09. Found: C, 31.52; H, 2.20; N, 18.33.

3,5-bis(difluoromethyl)-1-methyl-1*H*-pyrazol-4-amine (II.85e)



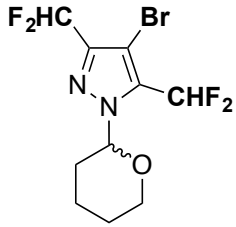
A mixture of 3,5-bis(difluoromethyl)-1-methyl-4-nitro-1H-pyrazole (**II.85d**) (1 equiv., 485 mg, 2.14 mmol) and Pd/C 10% (5.02 %, 114 mg, 0.107 mmol) in EtOH abs. (4 mL) was submitted to H_2 atmosphere for 1 h at room temperature. The mixture was filtered through Celite and evaporated *in vacuo*. Yield: 363mg, colourless oil (86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.74 (t, 5-C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 6.64 (t, 3-C*H*F_2, $^2J_{H-F}$ = 54.3 Hz), 3.83 (s, NC*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -113.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.9 Hz), -114.6 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.9 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.6 (t, *C*-3CHF_2, $^2J_{C-F}$ = 29.1 Hz), 128.9 (t, *C*NH_2, $^3J_{C-F}$ = 2.9 Hz), 122.0 (t, *C*-5CHF_2, $^2J_{C-F}$ = 26.9 Hz), 112.7 (t, 3-*C*HF_2, $^1J_{C-F}$ = 231.7 Hz), 109.0 (t, 5-*C*HF_2, $^1J_{C-F}$ = 234.8 Hz), 38.5 (N*C*H_3) ppm. HRMS (ESI) calcd for $C_6H_8F_4N_3$ [M+H]: 198.0649. Found: 198.0640.

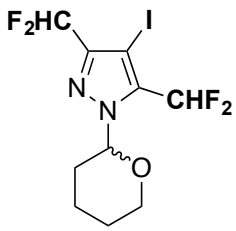
4-bromo-3,5-bis(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (II.86b)



A mixture of 4-bromo-3,5-bis(difluoromethyl)-1H-pyrazole (**II.84b**) (1 equiv., 1.51 g, 4.15 mmol), DHP (2.9 equiv., 1.02 g, 1.11 mL, 12.2 mmol) and cat. *p*-TsOH•H_2O (6.71 %, 0.08 g, 0.41 mmol) were heated at 50 °C in DCM (8 mL) for 18 h. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 1.31g, orange oil (95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.89 (t, 3-C*H*F_2, $^2J_{H-F}$ = 52.3Hz), 6.69 (t, 5-C*H*F_2, $^2J_{H-F}$ = 53.2 Hz), 5.60 (dd, 2'-C*H*), 3.68 and 4.03 (2 x m, 6'-CH_2), 2.32 (m, 1H, 3'-C*H*), 2.07 (m, 1H), 1.96 (m, 1H), 1.73 to 1.59 (m, 3H) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -114.4 (dd, 1F, $^2J_{F-F}$ = 315 Hz, $^2J_{F-H}$ = 52 Hz), 114.6 (dd, 1F, $^2J_{F-F}$ = 316 Hz, $^2J_{F-H}$ = 52 Hz), 114.6 (dd, 1F, $^2J_{F-F}$ = 315 Hz, $^2J_{F-H}$ = 52.2 Hz), -114.6 (dd, 1F, $^2J_{F-F}$ = 315 Hz, $^2J_{F-H}$ = 52.9 Hz), -115.2 (dd, 1F, $^2J_{F-F}$ = 315 Hz, $^2J_{F-H}$ = 52.9 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 143.9 (t, *C*-3CHF_2, $^2J_{C-H}$ = 28.1Hz) , 134.6 (t, C-5CHF_2, $^2J_{C-H}$ = 26.2 Hz), 110.5 (t, 3-*C*HF_2, $^1J_{C-H}$ = 236.3Hz), 107.7 (t, 5-*C*HF_2, $^1J_{C-H}$ = 236.8Hz), 94.6 (t, *C*-Br, $^3J_{C-H}$ = 5.4Hz), 68.1 (2'-*C*H), 29.5 (5'-*C*H_2), 24.7 (4'-*C*H_2), 22.1 (3'-*C*H_2) ppm. HRMS calcd for $C_{10}H_{11}BrF_4N_2NaO$ [M+Na]: 352.9883 + 354.9896. Found: 352.9882 + 354.9861.

3,5-bis(difluoromethyl)-4-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (II.86c)



A solution of 3,5-bis(difluoromethyl)-4-iodo-1H-pyrazole (**II.84c**) (1 equiv., 3.42 g, 11.6 mmol), DHP (3.1 equiv., 3.04 g, 3.3 mL, 36.1 mmol) and cat. *p*-TsOH•H_2O (5.42 %, 0.12 g, 0.631 mmol) in DCM (20 mL) was stirred at room temperature for 18 h, was filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in cyclohexane 0 to 20%). Yield: 3.93 g, colourless solid (89%). M.p.: 71.8 - 73.0 °C.

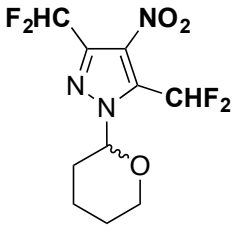
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.87 (t, 5-C*H*F_2, $^2J_{H-F}$ = 52 Hz), 6.73 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53 Hz), 5.62 (dd, 2'-C*H*), 4.03 and 3.66 (6'-CH_2), 2.33 (m, 1H), 2.06 (m, 1H), 1.95 (dd, 1H), 1.68 (m, 2H), 1.59 (m, 1H) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = 113.3 (dd, 1F, $^2J_{F-F}$ = 314 Hz, $^2J_{F-H}$ = 52.2 Hz), 113.7 (dd, 1F, $^2J_{F-F}$ = 315 Hz, $^2J_{F-H}$ = 52.2 Hz), 113.8 (dd, 1F, $^2J_{F-F}$ = 314 Hz, $^2J_{F-H}$ = 53.9 Hz), 114.4 (dd, 1F, $^2J_{F-F}$ = 314 Hz, $^2J_{F-H}$ = 53.3 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.7 (t, *C*-3CHF_2, $^2J_{C-F}$ = 27.5 Hz), 137.2 (t, *C*-5CHF_2, $^2J_{C-F}$ = 26 Hz), 111.0 (t, 3-*C*HF_2, $^1J_{C-F}$ = 236 Hz), 108.9 (t, 5-*C*HF2, $^1J_{C-F}$ = 237 Hz), 86.9 (2'-*C*H), 68.0 (6'-*C*H_2), 58.6 (t, *C*-I, $^3J_{C-F}$ = 5.5 Hz), 29.5, 24.6, 22.1 (5',4',3'-*C*H_2) ppm.

HRMS (ESI) calcd for $C_{10}H_{11}F_4IN_2NaO$ [M+Na]: 400.9744. Found: 400.9742.

3,5-bis(difluoromethyl)-4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (II.86d)



3,5-bis(difluoromethyl)-4-nitro-1H-pyrazole hydrate (**II.84d**) (1 equiv., 1.9 g, 8.22 mmol), DHP (2.66 equiv., 1.84 g, 2 mL, 21.9 mmol) and cat. *p*-TsOH•H_2O (7.03 %, 0.11 g, 0.578 mmol) were stirred in DCM (20 mL) for 18 h at room temperature. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (DCM in cyclohexane 0 to 50%). Yield: 1.11 g, colourless oil solidifying upon storage (45%). M.p.: 54.7 - 55.4 °C.

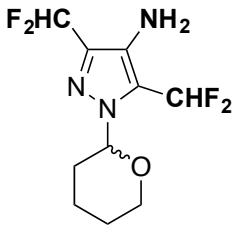
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47 (t, 5-C*H*F_2, $^2J_{H-F}$ = 52 Hz), 7.01 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53 Hz), 5.72 (dd, 2'-C*H*), 4.05 and 3.69 (6'-CH_2), 2.38 (m, 1H), 2.10 (m, 1H), 1.96 (dd, 1H), 1.84 to 1.48 (m, 3H) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.2 (dd, 1F, $^2J_{F-F}$ = 324 Hz, $^2J_{F-H}$ = 52 Hz), -116.0 (dd, 1F, $^2J_{F-F}$ = 324 Hz, $^2J_{F-H}$ = 52 Hz), -118.0 (dd, 1F, $^2J_{F-F}$ = 314 Hz, $^2J_{F-H}$ = 53 Hz), -118.8 (dd, 1F, $^2J_{F-F}$ = 314 Hz, $^2J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.9 (t, *C*-3CHF_2, $^2J_{C-F}$ = 26 Hz), 134.3 (t, *C*-5CHF_2, $^2J_{C-F}$ = 26.5 Hz), 131.8 (*C*NO_2), 108.3 (t, 5-*C*HF_2, $^1J_{C-F}$ = 240 Hz), 106.2 (t, 3-*C*HF_2, $^1J_{C-F}$ = 240 Hz), 94.6 (2'-*C*H), 68.2 (6'-*C*H_2), 29.2, 24.4, 21.8 (5',4',3'-*C*H_2) ppm.

Anal. calcd for $C_{10}H_{11}F_4N_3O_3$: C, 40.41; H, 3.73; F, 25.57; N, 14.14; O, 16.15. Found: C, 40.52; H, 3.78; N, 14.14. Crystals of the crude compound suitable for X-ray crystallographic analysis were obtained by slow evaporation in DCM/Et_2O.

3,5-bis(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-amine (II.86e)



A solution of 3,5-bis(difluoromethyl)-4-nitro-1-(oxan-2-yl)-1H-pyrazole (**II.86d**) (1 equiv., 405 mg, 1.36 mmol) in EtOH abs. (3 mL) was bubbled with hydrogen for 18 h at 50 °C in presence of Palladium on carbon 10% wt. (0.0621 equiv., 90 mg, 0.0846 mmol) under inert atmosphere. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 297mg, colourless oil (82%, 95wt. purity).

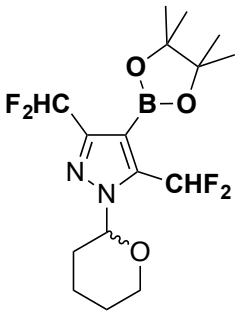
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.98 (dd, 5-C*H*F_2, $^{2}J_{H-F}$ = 53.8 Hz, $^{2}J_{H-F}$ = 55.7 Hz), 6.66 (t, 3-C*H*F_2, $^{2}J_{H-F}$ = 54.2 Hz), 5.35 (dd, 2'-C*H*), 3.90 (dd, 6'-CH_xH_y), 3.73 (br s, NH_2), 3.62 (m, 6'-CH_xH_y), 2.22 (m, 1H), 2.00 (m, 2H), 1.61 (m, 3H) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.8 (dd, 1F, $^{2}J_{F-F}$ = 311 Hz, $^{2}J_{F-H}$ = 55 Hz), -113.4 (dd, 1F, $^{2}J_{F-F}$ = 312 Hz, $^{2}J_{F-H}$ = 54 Hz), -114.4 (dd, 1F, $^{2}J_{F-F}$ = 310 Hz, $^{2}J_{F-H}$ = 54 Hz), -118.3 (dd, 1F, $^{2}J_{F-F}$ = 311 Hz, $^{2}J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 133.9 (t, *C*-3CHF_2, $^{2}J_{C-F}$ = 29.5 Hz), 129.5 (*C*NH_2), 120.9 (t, *C*-5CHF_2, $^{2}J_{C-F}$ = 29 Hz), 112.8 (t, 3-*C*HF_2, $^{1}J_{C-F}$ = 232 Hz), 110.0 (t, 5-*C*HF_2, $^{1}J_{C-F}$ = 234 Hz), 86.6 (2'-*C*H), 67.0 (6'-*C*H_2), 28.9, 24.7, 21.6 (5',4',3'-*C*H_2) ppm.

HRMS (ESI) calcd for $C_{10}H_{13}F_4N_3NaO$ [M+Na]: 290.0887. Found: 290.0889.

3,5-bis(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (II.86f)



A solution of 3,5-bis(difluoromethyl)-4-iodo-1-(oxan-2-yl)-1H-pyrazole (**II.86c**) (1 equiv., 207 mg, 0.55 mmol) in distilled THF (2 mL) was cooled to -30 °C and the turbo Grignard reagent 1.3M in THF (2.97 equiv., 1.3 M, 1.25 mL, 1.62 mmol) was added *via* syringe, the mixture was stirred at -30 °C for 1 h. 3-isopropoxycarbonylphenylboronic acid (1.52 equiv., 155 mg, 0.17 mL, 0.833 mmol) in distilled THF (1 mL) was added *via* syringe. The mixture allowed to reach room temperature over 1 h was then diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 210mg, colourless oil (99%).

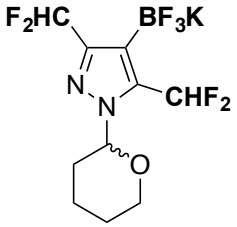
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, 3-C*H*F_2, $^{2}J_{H-F}$ = 52.8 Hz), 6.89 (t, 5-C*H*F_2, $^{2}J_{H-F}$ = 54.1 Hz), 5.66 (dd, 2'-C*H*), 4.10 and 3.68 (m and td, 2H, 6'-CH_xH_y), 2.41 (m, 1H), 2.08 (m, 1H), 1.92 (dd, 1H), 1.72 (m, 2H), 1.58 (1H), 1.31 (s, 12H, pinacol) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.4 (dd, 1F, $^{2}J_{F-F}$ = 315 Hz, $^{2}J_{F-H}$ = 53 Hz), -113.1 (dd, 1F, $^{2}J_{F-F}$ = 311 Hz, $^{2}J_{F-H}$ = 54 Hz), -113.3 (dd, 1F, $^{2}J_{F-F}$ = 315 Hz, $^{2}J_{F-H}$ = 52 Hz), -113.7 (dd, 1F, $^{2}J_{F-F}$ = 311 Hz, $^{2}J_{F-H}$ = 54 Hz) ppm.

^{11}B-NMR (128MHz, $CDCl_3$): δ = 28.9 (br s, *B*(pin)) ppm.

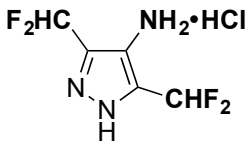
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.0 (t, *C*-3CHF_2, $^2J_{C\text{-}F}$ = 25.5 Hz), 142.2 (t, *C*-5CHF_2, $^2J_{C\text{-}F}$ = 23.9 Hz), 110.4 (t, 5-*C*HF_2, $^1J_{C\text{-}F}$ = 235.9 Hz), 108.4 (t, 3-*C*HF_2, $^1J_{C\text{-}F}$ = 235.9 Hz), 86.5 (2'-*C*H), 84.4 (2 x C_{quat} pinacol), 68.4 (6'-*C*H_2), 30.1, 27.0, 22.5 (5',4',3'-*C*H_2), 24.7 (m, 4 x *C*H_3, pinacol) ppm.
Anal. calcd for $C_{16}H_{23}BF_4N_2O_3$: C, 50.82; H, 6.13; B, 2.86; F, 20.09; N, 7.41; O, 12.69. Found: C, 51.00; H, 6.21; N, 7.54.

3,5-bis(difluoromethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-4-(trifluoro-λ⁴-boranyl)-1*H*-pyrazole, potassium salt (II.86g)



A solution of 3,5-bis(difluoromethyl)-1-(oxan-2-yl)-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (**II.86f**) (1 equiv., 200 mg, 0.529 mmol) in MeOH (3 mL) was treated with potassium a solution of bifluoride 2N aq. (4.54 equiv., 2 M, 1.2 mL, 2.4 mmol) for 30min at room temperature. The mixture was evaporated *in vacuo*, and then triturated in MeOH/water (1:1) 3 times with solvent removal by vacuum each time. The solid residue was triturated in cyclohexane, the supernatant pipetted out, and the residual solid was dried in high vacuum overnight. Yield: 188mg, colourless solid (99%). M.p.: >270 °C.
^{1}H-NMR (400 MHz, DMSO-d^6): δ = 7.06 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 53.6 Hz), 6.83 (t, CHF2, $^2J_{H\text{-}F}$ = 54.7 Hz), 5.48 (dd, 2'-C*H*), 3.95 and 3.56 (2 x dt, 6'-CH_xH_y), 2.26 (qd, 1H), 1.97 and 1.80 (dt and dq, 2H), 1.65 (m, 1H), 1.52 (m, 2H) ppm.
^{19}F-NMR (376 MHz, DMSO-d^6): δ = -109.1 (ddq, 1F, $^2J_{F\text{-}F}$ = 315 Hz, $^2J_{F\text{-}H}$ = 53 Hz, $^5J_{F\text{-}B}$ = 2 Hz), -110.7 (ddq, 1F, $^2J_{F\text{-}F}$ = 315 Hz, $^2J_{F\text{-}H}$ = 53 Hz, $^5J_{F\text{-}B}$ = 2 Hz), -110.8 (ddq, 1F, $^2J_{F\text{-}F}$ = 302 Hz, $^2J_{F\text{-}H}$ = 54 Hz, $^5J_{F\text{-}B}$ = 1.8 Hz), -111.3 (ddq, 1F, $^2J_{F\text{-}F}$ = 302 Hz, $^2J_{F\text{-}H}$ = 54 Hz, $^5J_{F\text{-}B}$ = 1.8 Hz), -132.3 (br s, B*F*$_3$K) ppm.
^{11}B-NMR (128 MHz, DMSO-d^6): δ = 0.62 (q, BF_3K, $^1J_{B\text{-}F}$ = 18.2 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d^6): δ = 147.4 (t, *C*-3CHF_2, $^2J_{C\text{-}F}$ = 21.7 Hz), 136.1 (t, *C*-5CHF_2, $^2J_{C\text{-}F}$ = 21.7 Hz), 111.2 (t, 5-*C*HF_2, $^1J_{C\text{-}F}$ = 233 Hz), 109.7 (t, 3-*C*HF_2, $^1J_{C\text{-}F}$ = 231 Hz), 85.2 (2'-*C*H), 67.3 (6'-*C*H_2), 29.6, 24.6, 22.3 (3',4',5'-*C*H_2) ppm.
HRMS (ESI neg) calcd for $C_{10}H_{11}BF_7N_2O$ [M-K]: (318.0883) + 319.0849 + (320.0878). Found: (318.0860) + 319.0847 + (320.0842).

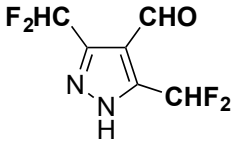
3,5-bis(difluoromethyl)-1*H*-pyrazol-4-amine hydrochloride (II.84e)



3,5-bis(difluoromethyl)-1-(oxan-2-yl)-1H-pyrazol-4-amine (**II.86e**) (1 equiv., 335 mg, 1.25 mmol) was treated with HCl 2N in Et_2O (3.03 equiv., 2 M, 1.9 mL, 3.8 mmol). The gummy mixture was diluted with Et_2O/DCM (3 mL/3 mL). The suspension was filtered on Büchner, the residual solid was dried *in vacuo* overnight. Yield: 126 mg, orange solid (46%). M.p.: degradation > 156-170 °C.
^{1}H-NMR (400 MHz, MeOD-d$_4$): δ = 7.15 (t, 2 x *C*HF_2, $^2J_{H\text{-}F}$ = 53.7 Hz), 5.37 (br s, 4*H*) ppm.
^{19}F-NMR (376 MHz, MeOD-d$_4$): δ = -115.8 (d, 2 x CH*F*$_2$, $^2J_{F\text{-}H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, MeOD-d_4): δ = 137.9 (t, 2 x *C*CHF$_2$, $^2J_{C-F}$ = 28.5 Hz), 110.9 (t, 2 x *C*HF$_2$, $^1J_{C-F}$ = 236 Hz), 110.5 (*C*NH$_2$•HCl) ppm.
HRMS (ESI) calcd for $C_5H_6F_4N_3$ [M+H]: 184.0492. Found: 184.0489.

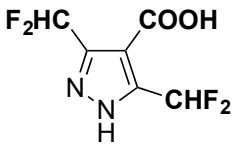
3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carbaldehyde (II.84f)



Same procedure than **II.86f** for iodine/magnesium exchange from 3,5-bis(difluoromethyl)-4-iodo-1-(oxan-2-yl)-1H-pyrazole (**II.86c**) (1 equiv., 500 mg, 1.32 mmol). After 1 h at -30 °C, anhydrous DMF (24.4 equiv., 2.36 g, 2.5 mL, 32.3 mmol) was added *via* syringe, the mixture was allowed to reach room temperature over 1 h. The residue was partitioned between Et_2O (10 mL) and water (10 mL). The aqueous was extracted with Et_2O (2 x 10 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was dissolved in EtOH (6 mL) and HCl aq. (3.63 equiv., 12 M, 0.4 mL, 4.8 mmol) was added. The mixture was stirred for 72 h, and then was partitioned between Et_2O (10 mL) and water (10 mL). Similar work up was achieved. The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%). Yield: 140mg, colourless solid (54%). M.p.: 76.7 - 77.2 °C.
^{1}H-NMR (400 MHz, CD_3CN): δ = 12.1 (br s, N*H*), 10.0 (s, C*H*O), 7.13 (t, 2 x CHF_2, $^2J_{H-F}$ = 53.5 Hz) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -115.2 (br d, 2 x CH*F*$_2$, $^2J_{F-H}$ = 54.0 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 185.0 (*C*HO), 144.6 (br s, 2 x *C*CHF$_2$), 119.5 (*C*CHO), 110.5 (t, 2 x *C*HF$_2$, $^1J_{C-F}$ = 235.6 Hz) ppm.
HRMS (ESI) calcd for $C_6H_3F_4N_2O$ [M-H]: 195.0176. Found: 195.0189.

The **THP-pyrazole carboxaldehyde** was isolated from 3,5-bis(difluoromethyl)-4-iodo-1-(oxan-2-yl)-1H-pyrazole (**II.86c**) (1 equiv., 500 mg, 1.32 mmol) after purification of the 1st crude by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 205mg, colourless oil (55%), unstable upon storage.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.15 (C*H*O), 7.43 (t, 5-C*H*F$_2$, $^2J_{H-F}$ = 52.5 Hz), 6.90 (t, 3-C*H*F$_2$, $^2J_{H-F}$ = 53.4 Hz), 5.67 (dd, 2'-C*H*), 4.07 and 3.70 (6'-CH_xH_y), 2.30 (m, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.70 (m, 2H), 1.62 (m, 1H) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -110.7 (dd, 1F, $^2J_{F-F}$ = 316 Hz, $^2J_{F-H}$ = 54 Hz), -111.5 (dd, 1F, $^2J_{F-F}$ = 316 Hz, $^2J_{F-H}$ = 54 Hz), -113.4 (dd, 1F, $^2J_{F-F}$ = 321 Hz, $^2J_{F-H}$ = 53 Hz), -114.4 (dd, 1F, $^2J_{F-F}$ = 321 Hz, $^2J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 184.6 (*C*HO), 146.9 (*C*CHF$_2$, $^2J_{C-F}$ = 30 Hz), 138.6 (*C*CHF$_2$, $^2J_{C-F}$ = 26.4 Hz), 119.8 (*C*CHO), 110.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 236 Hz), 107.3 (t, *C*HF$_2$, $^1J_{C-F}$ = 238 Hz), 87.6 (2'-*C*H), 68.3 (6'-CH_xH_y), 29.9, 24.6, 22.0 (3',4',5'-*C*H$_2$) ppm.

3,5-bis(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid (II.84g)



Same procedure than **II.86f** for iodine/magnesium exchange from 3,5-bis(difluoromethyl)-4-iodo-1-(oxan-2-yl)-1H-pyrazole (**II.86c**) (1 equiv., 1 g, 2.64 mmol). After 1 h at -30 °C, the mixture was canulated onto solid CO_2 covered with 4mL of distilled THF, and raised from -30°C to room temperature over 1 h. The solvent was removed in vacuo, and HCl 1N (1.97 equiv., 1 M, 5.2 mL, 5.2 mmol) was slowly added. The

layers were separated, and the aqueous acidified with HCl 1N (3mL) and extracted with Et_2O (3 x 5 mL). The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (MeOH in AcOEt 0 to 20%). Yield: (THP-pyrazole carboxylic acid) 3,5-bis(difluoromethyl)-1-(oxan-2-yl)-1H-pyrazole-4-carboxylic acid, 472 mg, thick colourless oil (60%). Quick decomposition observed upon storage (<1 h). No fraction could be kept pure enough for data, but spectral data's are presented below.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.14 (COO*H*), 7.53 (t, 5-C*H*F_2, $^2J_{H-F}$ = 52.5 Hz), 7.03 (t, 3-C*H*F_2, $^2J_{H-F}$ = 53.5 Hz), 5.73 (dd, 2'-C*H*), 4.11 and 3.70 (6'-CH_xH_y), 2.43 (m, 1H), 2.10 (m, 1H), 1.95 (m, 1H), 1.72 (m, 2H), 1.59 (m, 1H) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -114.1 (dd, 1F, $^2J_{F-F}$ = 321 Hz, $^2J_{F-H}$ = 52 Hz), -115.8 (dd, 1F, $^2J_{F-F}$ = 321 Hz, $^2J_{F-H}$ = 52 Hz), -116.5 (dd, 1F, $^2J_{F-F}$ = 312 Hz, $^2J_{F-H}$ = 53 Hz), -117.4 (dd, 1F, $^2J_{F-F}$ = 312 Hz, $^2J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.9 (*C*OOH), 146.8 (t, *C*-3CHF_2, $^2J_{C-F}$ = 25.7 Hz), 139.4 (t, *C*-5CHF_2, $^2J_{C-F}$ = 24.5 Hz), 112.0 (*C*COOH), 109.2 and 107.0 (2 x t, 2 x *C*HF_2, $^1J_{C-F}$ = 237 and 238 Hz), 87.1 (2'-*C*H), 68.4 (6'-*C*H_2), 29.8, 24.6, 22.3 (3',4',5'-*C*H_2) ppm.

HRMS calcd for $C_{11}H_{12}F_4N_2NaO_3$ [M+Na]: 319.0676. Found: 319.0660.

The THP-intermediate (289mg, partially decomposed) was taken up in MeOH (2 mL) and cat. conc. HCl was added. After 1 h at room temperature, the solvent was removed *in vacuo,* the product was crystallized from water. Yield: 80 mg, colourless solid (39%). Overall yield: 23% (2 steps). M.p.: 264.5 - 265.7 °C.

II.84g:

^{1}H-NMR (400 MHz, MeOD-d_4): δ = 7.24 (t, 2x C*H*F_2, $^2J_{H-F}$ = 53.6 Hz), 4.97 (br s, 2H, COO*H* + N*H*) ppm.

^{19}F-NMR (376 MHz, MeOD-d_4): δ = -117.8 (br d, CHF2, $^2J_{F-H}$ = 44.5 Hz) ppm.

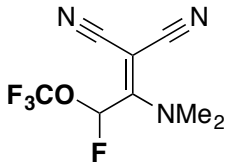
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.1 (*C*OOH), 145.0 (m, 2 x *C*CHF_2), 113.0 (q, *C*COOH, $^3J_{C-F}$ = 4 Hz), 110.1 (t, 2 x *C*HF_2, $^1J_{C-F}$ = 236 Hz) ppm.

Anal. calc for $C_6H_6F_4N_2O_2$: C, 33.98; H, 1.90; F, 35.83; N, 13.21; O, 15.09. Found: C, 34.04; H, 1.83; N, 13.19.

Application of the new FAR for innovative ($CHFOCF_3$)-Heterocycles

Preparation of key adducts **II.91-92**

2-(1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene)malononitrile (6a)



Solid activated FAR **2D** (1.22 equiv., 930 mg, 3.33 mmol) was taken up in dry MeCN (4 mL) at room temperature before solution of malononitrile (1 equiv., 180 mg, 2.72 mmol) was added *via* syringe. After placing a water-bath, Et_3N (1.51 equiv., 414 mg, 0.57 mL, 4.1 mmol) was carefully added *via* syringe. The mixture was stirred 1 h at room temperature. Internal standard: fluorobenzene (1.17 equiv., 306 mg, 0.3 mL, 3.18 mmol). ^{19}F NMR yield: 53%. An excess of Al_2O_3 was added and the mixture was concentrated *in vacuo*. The cake was washed twice with cyclohexane and the combined filtrate was evaporated *in vacuo*, to yield 290mg of orange oil (45%).

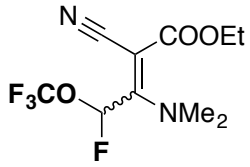
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.76 d, C*H*FOCF$_3$, $^2J_{H-F}$ = 53.5 Hz), 3.40 (s, N(CH_3)$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (d, OC*F*$_3$, $^4J_{F-F}$ = 4.8 Hz), -127.6 (d, CH*F*OCF$_3$, $^2J_{F-H}$ = 53.1 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.8 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 23.1 Hz), 120.8 (q, O*C*F$_3$, $^1J_{C-F}$ = 265.2 Hz), 114.3 and 114.0 (2 x *C*N), 101.1 (dq, *C*HFOCF$_3$, $^1J_{C-F}$ = 239.5 Hz, $^4J_{C-F}$ = 3.7 Hz), 55.7 (d, *C*(CN)$_2$, $^3J_{C-F}$ = 6.3 Hz), 44.2 (s br, N(*C*H$_3$)$_2$) ppm.

HRMS (ESI) calcd for $C_8H_7F_4N_3NaO$ $[M+Na]^+$: 260.0417. Found: 260.0432.

ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (6b)



Same procedure than **2D** (1.22 equiv., 930 mg, 3.33 mmol), ethyl cyanoacetate (1 equiv., 307 mg, 0.27 mL, 2.72 mmol) and DIPEA (2 equiv., 703 mg, 0.9 mL, 5.45 mmol). The Al_2O_3 cake was washed twice with cyclohexane and the combined filtrate was evaporated *in vacuo*, to yield 815mg of orange oil (95wt.%, 39%). Clean data's after purification by flash chromatography (AcOEt in cyclohexane 0 to 30%).

Major isomer:

^1H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 54.1 Hz), 4.20 (q, OCH_2CH$_3$), 3.33 (s, N(CH_3)$_2$), 1.28 (t, OCH$_2$CH_3) ppm.

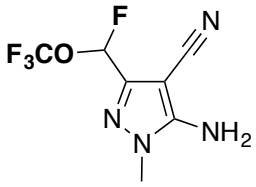
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.5 (d, OC*F*$_3$, $^4J_{F-F}$ = 4.1 Hz), -132.0 (d, CH*F*OCF$_3$, $^2J_{F-H}$ = 54.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.3 (*C*=O), 161.5 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 21.8 Hz), 120.9 (q, O*C*F$_3$, $^1J_{C-F}$ = 263.4 Hz), 117.3 (*C*N), 98.6 (qd, *C*HFOCF$_3$, $^1J_{C-F}$ = 235.3 Hz, $^4J_{C-F}$ = 3.8 Hz), 75.9 (d, *C*CN, $^3J_{C-F}$ = 5.2 Hz), 61.6 (O*C*H$_2$CH$_3$), 44.7 (s br, N(*C*H$_3$)$_2$), 14.2 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{10}H_{12}F_4N_2NaO_3$ $[M + Na]^+$: 307.0676. Found: 307.0670.

Regioselective preparation of 3-(CHFOCF$_3$)-5-amino pyrazoles carbonitrile and carboxylates

5-amino-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carbonitrile (II.89)



A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile (1 equiv., 462 mg, 1.95 mmol) in dry MeCN (5 mL) was treated with methyl hydrazine (1.63 equiv., 146 mg, 0.17 mL, 3.17 mmol) at room temperature. The mixture was stirred for 30min. The mixture was concentrated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 50%) to yield 416mg of yellow solid (90%). M.p.: 95.0 - 96.4 °C.

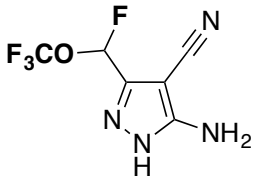
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.58 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 56 Hz), 4.68 (s br, NH_2), 3.66 (NCH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.3 (d, OC*F*$_3$, $^4J_{F-F}$ = 4.8 Hz), -122.5 (qd, CH*F*OCF$_3$, $^2J_{F-H}$ = 56.5 Hz, $^4J_{F-F}$ = 5.2 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.6 (*C*NH$_2$), 144.6 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 28.8 Hz), 121.0 (q, O*C*F$_3$, $^1J_{C-F}$ = 260.6 Hz), 112.5 (*C*N), 100.6 (qd, *C*HFOCF$_3$, $^1J_{C-F}$ = 228.0 Hz, $^3J_{C-F}$ = 3.8 Hz), 73.7 (*C*CN), 35.1 (N*C*H$_3$) ppm.

Anal. calcd for $C_7H_6F_4N_4O$: C, 35.30; H, 2.54; F, 31.91; N, 23.53; O, 6.72. Found: C, 35.59; H, 2.63; N, 23.56.

5-amino-3-(fluoro(trifluoromethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (II.90)



A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile (1 equiv., 400 mg, 1.69 mmol) and boc-hydrazide (1.5 equiv., 335 mg, 2.53 mmol) in dry MeCN (4 mL) was heated at 50 °C for 18 h and 2 h more at 70 °C. The mixture was concentrated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 50%), to yield 245mg of colourless solid (99%).

M.p.: 141.6 - 142.1 °C.

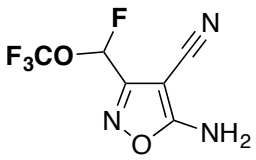
^{1}H-NMR (400 MHz, CD_3CN): δ = 10.55 (s br, N*H*), 6.80 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 55.5 Hz), 5.36 (s br, NH_2) ppm.

^{19}F-NMR (376 MHz, CD_3CN): δ = -59.9 (d, CHFOC*F*$_3$, $^4J_{F-F}$ = 5.5 Hz), -124.0 (dq, CH*F*OCF$_3$, $^2J_{F-H}$ = 55.4 Hz, $^4J_{F-F}$ = 4.7 Hz) ppm.

^{13}C-NMR (100 MHz, CD_3CN): δ = 155.0 (*C*NH$_2$), 146.7 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 28 Hz), 121.9 (q, O*C*F$_3$, $^1J_{C-F}$ = 260 Hz), 113.4 (*C*N), 102.5 (dq, *C*HFOCF$_3$, $^1J_{C-F}$ = 225 Hz, $^3J_{C-F}$ = 3 Hz) ppm.

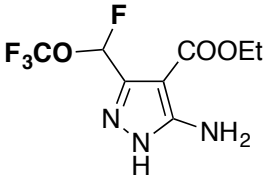
Anal. calcd for $C_6H_4F_4N_4O$: C, 32.16; H, 1.80; F, 33.91; N, 25.00; O, 7.14. Found: C, 32.28; H, 1.99; N, 24.57.

5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carbonitrile (II.91)



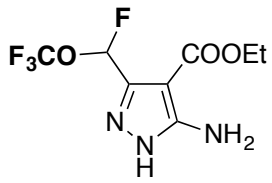
A solution of 2-[1-(dimethylamino)-2-fluoro-2-(trifluoromethoxy)ethylidene]propanedinitrile (1 equiv., 50 mg, 0.21 mmol) in dry MeCN (4 mL) was treated with hydroxylamine 50wt.% aqueous (1.55 equiv., 22 mg, 0.02 mL, 0.32 mmol) at room temperature. The mixture was stirred for 15min. Internal standard: fluorobenzene (1 equiv., 20 mg, 0.02 mL, 0.21 mmol). ^{19}F NMR yield: 99%.
The desired product was isolated after purification by flash chromatography (Et_2O in pentane 0 to 50%), to yield a pale solid (after trituration in pentane). M.p.: 110.3 - 110.9 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.88 (s br, NH_2), 7.53 (d, C*H*FOCF_3, $^2J_{H-F}$ = 53.3 Hz) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -58.0 (m, OCF_3), -129.8 (dq, CHFOCF_3, $^2J_{F-H}$ = 52.9 Hz, $^4J_{F-F}$ = 4.5 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 173.5 (O*C*NH_2), 157.1 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 27 Hz), 120.4 (q, O*C*F_3, $^1J_{C-F}$ = 263 Hz), 111.0 (*C*N), 99.5 (d, *C*HFOCF_3, $^1J_{C-F}$ = 229 Hz), 61.9 (*C*-CN) ppm.
Anal. calcd for $C_6H_3F_4N_3O_2$: C, 32.01; H, 1.34; F, 33.76; N, 18.67; O, 14.21. Found: C, 31.94; H, 1.58; N, 18.13.

ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)-1*H*-pyrazole-4-carboxylate (II.93)



Same procedure than **7a**. The mixture was stirred over 1 h. The mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 50%) to yield a yellow solid after trituration in pentane (160mg, 39%).
M.p.: 96.0 - 99.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.5 (s br, N*H*), 7.25 (d, C*H*FOCF_3, $^2J_{H-F}$ = 56.5 Hz), 5.44 (s br, NH_2), 4.32 (q, OCH_2), 1.35 (t, OCH_2CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.1 (d, OCF_3, $^4J_{F-F}$ = 5 Hz), -129.3 (d, C*H*FOCF_3, $^2J_{F-H}$ = 56.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.4 (*C*=O), 152.3 (N*C*-NH_2), 143.8 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 22 Hz), 121.1 (q, O*C*F_3, $^1J_{C-F}$ = 262 Hz), 100.8 (dq, *C*HFOCF_3, $^1J_{C-F}$ = 225 Hz, $^3J_{C-F}$ = 3 Hz), 93.2 (d, *C*COOEt, $^3J_{C-F}$ = 3.7 Hz), 60.5 (O*C*H_2), 14.4 (OCH_2*C*H_3) ppm.
HRMS (ESI) calcd for $C_8H_{10}F_4N_3O_3$ $[M+H]^+$: 272.0653. Found: 272.0671.

ethyl 5-amino-3-(fluoro(trifluoromethoxy)methyl)isoxazole-4-carboxylate (II.94)



A solution of ethyl 2-cyano-3-(dimethylamino)-4-fluoro-4-(trifluoromethoxy)but-2-enoate (1 equiv., 410 mg, 1.30 mmol) in dry MeCN (4 mL) was treated with hydroxylamine hydrochloride (1.66 equiv., 150 mg, 2.16 mmol), followed after 1 h without reaction by Et_3N (1.0 equiv., 131 mg, 0.18 mL, 1.3 mmol). After 1 h at room temperature, the mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%) to yield a white solid (353mg, 99%) after trituration in pentane. M.p.: 119.6 - 119.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 55.2 Hz), 6.23 (s br, NH_2), 4.32 (m, OCH_2), 1.34 (t, OCH$_2$CH_3) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.3 (d, OC*F*$_3$, $^4J_{F-F}$ = 5.5 Hz), -131.4 (qd, CH*F*OCF$_3$, $^2J_{F-H}$ = 55.3 Hz, $^4J_{F-F}$ = 5.1 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.3 (*C*NH$_2$), 162.3 (*C*=O), 155.7 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 24.8 Hz), 121.0 (q, O*C*F$_3$, $^1J_{C-F}$ = 262 Hz), 99.1 (dq, *C*HFOCF$_3$, $^1J_{C-F}$ = 233 Hz, $^3J_{C-F}$ = 4 Hz), 85.4 (*C*COOEt), 61.0 (O*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$) ppm.

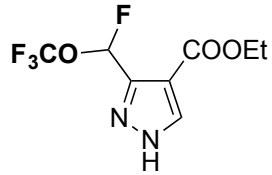
Anal. calcd for $C_8H_8F_4N_2O_4$: C, 35.31; H, 2.96; F, 27.92; N, 10.29; O, 23.51. Found: C, 35.31; H, 3.06; N, 10.34.

Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow evaporation of a concentrated solution in Et_2O/DCM.

Preparation of Bixafen analogues

General procedure adapted from:
Pazenok, S.; Norbert, L.; Neeff, A., *WO2008022777* (Bayer CropScience, filed 25.08.2006).

ethyl 3-(fluoro(trifluoromethoxy)methyl)-1*H*-pyrazole-4-carboxylate (II.95a)

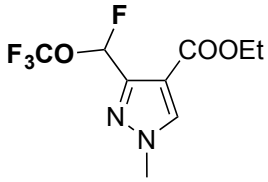


The required amount of 1,1,2-trifluoro-2-(trifluoromethoxy)ethene (1.2 equiv., 1.5 g, 1 mL, 9.03 mmol) was condensed at -78°C into a Schlenk vessel under inert atmosphere, then was treated with dimethylamine 2M in THF (1.2 equiv., 2 M, 4.52 mL, 9.04 mmol). After 5min at -78 °C, the Schlenk was placed into a water bath. BF_3•Et_2O (1.2 equiv., 1.29 g, 1.15 mL, 9.08 mmol) was carefully added *via* syringe, the mixture was stirred 15min. A solution of ethyl 3-(dimethylamino)prop-2-enoate (1 equiv., 1.08 g, 7.54 mmol) in dry MeCN (10 mL) was prepared under inert atmosphere into a Schlenk vessel. The first solution was added *via* syringe to the second, the resulting mixture was stirred 2 h at room temperature. A solution of hydrazine hydrate (1.51 equiv., 0.571 g, 0.56 mL, 11.4 mmol) in dry MeCN (5 mL) was then added. After 1 h more, the reaction mixture was evaporated *in vacuo*. The crude was purified by silica gel chromatography (Et_2O in pentane 0 to 50%), to yield a beige solid (1.53g, 79%). M.p.: 105.7 - 106.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.7 (s br, N*H*), 8.17 (d, 5-C*H*, $^4J_{F-F}$ = 1.7 Hz), 7.45 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 56 Hz), 4.37 (q, OCH_2), 1.38 (t, OCH$_2$CH_3), ppm.

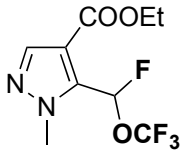
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.1 (d, OC*F*$_3$, J = 4.8 Hz), -127.0 (d, CH*F*OCF$_3$, $^2J_{F-H}$ = 56 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.0 (*C*=O), 145.1 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 22.4 Hz), 134.3 (5-*C*H$_{arom}$), 121.1 (q, O*C*F$_3$, $^1J_{C-F}$ = 262 Hz), 113.0 (d, *C*COOEt, $^3J_{C-F}$ = 3.6 Hz), 99.9 (qd, *C*HFOCF$_3$, $^1J_{C-F}$ = 228 Hz, $^3J_{C-F}$ = 3.7 Hz), 61.2 (O*C*H$_2$), 14.3 (OCH$_2$*C*H$_3$), ppm.
Anal calcd for $C_8H_8F_4N_2O_3$: C, 37.51; H, 3.15; F, 29.67; N, 10.94; O, 18.74. Found: C, 37.86; H, 3.14; N, 11.03.

ethyl 3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylate (II.95b)



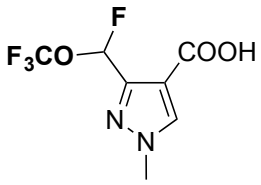
Same procedure using methyl hydrazine. After reaction complete, the mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 40%), and both regioisomers (ca. 75/25) were separated (**II.95c** eluted first, followed by **II.95b**).
II.95b: 1.15g (56%), colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (5-C*H*), 7.24 (d, C*H*FOCF$_3$, $^2J_{H-F}$ = 55.7 Hz), 4.29 (q, OC*H*$_2$), 3.94 (NC*H*$_3$), 1.32 (OCH$_2$C*H*$_3$), ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.2 (d, OC*F*$_3$, $^4J_{F-F}$ = 5.5 Hz), -125.3 (qd, CH*F*OCF$_3$, $^2J_{H-F}$ = 55.8 Hz, $^4J_{F-F}$ = 5.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.8 (*C*=O), 145.2 (d, *C*CHFOCF$_3$, $^2J_{C-F}$ = 23.8 Hz), 135.0 (5-*C*H), 121.1 (q, O*C*F$_3$, $^1J_{C-F}$ = 262 Hz), 113.2 (d, *C*COOEt, $^3J_{C-F}$ = 2.9 Hz), 99.5 (qd, *C*HFOCF$_3$, $^1J_{C-F}$ = 229.4 Hz, $^3J_{C-F}$ = 3.9 Hz), 60.9 (O*C*H$_2$), 39.8 (N*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$), ppm.
HRMS (ESI) calcd for $C_9H_{10}F_4N_2NaO$ $[M+Na]^+$: 293.0520. Found: 293.0497.

ethyl 5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylate (II.95c)



Separated from **II.95b** by chromatography**.** 392mg (19%), colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, CH3), 4.02 (d, NCH3, J = 1 Hz), 4.28 (m, OCH2), 7.64 (d, CHFOCF3, J = 54.3 Hz), 7.81 (d, CH, J = 0.7 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.8 (d, OCF3, J = 4.8 Hz), -126.7 (qd, CHFOCF3, J = 54.5 Hz, J = 5.2 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH3), 39.1 (d, CH3, J = 3 Hz), 60.9 (OCH2), 97.8 (qd, CHFOCF3, J = 226 Hz, J = 4 Hz), 114.4 (d, CCOOEt, J = 4.4 Hz), 120.1 (q, OCF3, J = 262.5 Hz), 135.8 (d, CCHFOCF3, J = 23.7 Hz), 140.3 (CH), 162.3 (C=O) ppm.
HRMS (ESI) calcd for $C_9H_{11}F_4N_2O_3$ $[M+H]^+$: 271.0700. Found: 271.0696.

3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (II.96b)



A solution of **II.95b** (1 equiv., 810 mg, 3 mmol) in EtOH (6 mL) was treated with NaOH 12.5M (3.04 equiv., 12.5 M, 0.73 mL, 9.13 mmol) and stirred at room temperature for 18 h. The mixture was partitioned between DCM and aq. HCl 1N. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The oily residue was triturated in pentane and dried *in vacuo*. Yield: 725mg of white solid (99%). M.p.: 117.2 - 117.6 °C.

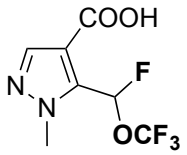
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.3 (br s, COO*H*), 7.98 (CH_{arom}), 7.26 (d, C*H*FOCF_3, $^2J_{H-F}$ = 55.9 Hz), 4.00 (s, CH_3), ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.2 (d, OCF_3, $^4J_{F-F}$ = 5.4 Hz), -125.3 (qd, CH*F*OCF_3, $^2J_{F-H}$ = 55.8 Hz, $^4J_{F-F}$ = 5.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.2 (*C*OOH), 146.2 (*C*CHFOCF_3, $^2J_{C-F}$ = 24 Hz), 136.0 (*C*H$_{arom}$), 121.1 (q, O*C*F_3, $^1J_{C-F}$ = 261 Hz), 112.1 (d, *C*COOH, $^3J_{C-F}$ = 2.7 Hz), 99.2 (qd, CHFO*C*F_3, $^1J_{C-F}$ = 230 Hz, $^3J_{C-F}$ = 4 Hz), 40.1 (*C*H$_3$), ppm.

Anal. calcd for $C_7H_6F_4N_2O_3$: C, 34.72; H, 2.50; F, 31.39; N, 11.57; O, 19.82. Found: C, 35.05; H, 2.27; N, 11.66.

5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (II.96c)



Same procedure as **II.96b**. White solid (177 mg, 99 %). M.p.: 140.5 - 141.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.9 (br s, COO*H*), 7.97 (s, CH_{arom}), 7.64 (d, C*H*FOCF_3, $^2J_{H-F}$ = 54.3 Hz), 4.11 (s, CH_3) ppm.

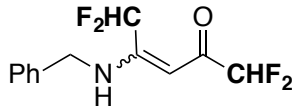
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (d, OCF_3, $^4J_{F-F}$ = 4.8 Hz), -126.6 (qd, CH*F*OCF_3, $^2J_{F-H}$ = 54.5 Hz, $^4J_{F-F}$ = 5.2 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.6 (*C*OOH), 141.3 (*C*H$_{arom}$), 136.8 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 24 Hz), 120.9 (q, OCF_3, $^1J_{C-F}$ = 263 Hz), 113.4 (d, *C*COOH, $^3J_{C-F}$ = 4.3 Hz), 97.5 (qd, CHFOCF_3, $^1J_{C-F}$ = 226 Hz, $^3J_{C-F}$ = 3.6 Hz), 39.5 (d, CH_3, $^4J_{C-F}$ = 2.8 Hz), ppm.

Anal. calcd for $C_7H_6F_4N_2O_3$: C, 34.72; H, 2.50; F, 31.39; N, 11.57; O, 19.82. Found: C, 35.01; H, 2.77; N, 10.39.

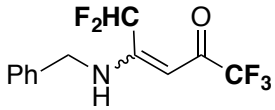
Access to mono- and bis-fluoroalkyl heterocycles without FARs

4-(benzylamino)-1,1,5,5-tetrafluoropent-3-en-2-one (II.60A.b)



Prepared quantitatively using the procedure described below (using 2,2-difluoroacetic anhydride). Data's already given in this experimental section.

4-(benzylamino)-1,1,1,5,5-pentafluoropent-3-en-2-one (II.60E.b)



A solution of **II.59b** (3 g, 15.6 mmol) in DCM (20 mL) was cooled to -5 °C and pyridine (1.99 equiv., 2.44 g, 2.5 mL, 30.9 mmol) was added. After 10min, a solution of TFAA (1.49 equiv., 4.98 g, 3.3 mL, 23.3 mmol) in DCM (10 mL) was added dropwise over 10min at -5 °C. The mixture was stirred from -5 °C to room temperature over 18 h. Same procedure with benzyl(1,1,1-trifluoropropan-2-ylidene)amine. Crystallization of the crude was exothermic, to give an orange solid (99%). Ratio E/Z of 88:12. M.p.: 107.8 - 108.2 °C.

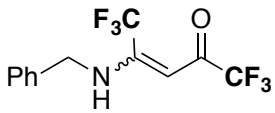
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.66 (s br, N*H*), 7.43 to 7.29 (m, 5H, Ph), 6.21 (t, C*H*F_2, $^{2}J_{H-F}$ = 53 Hz), 5.70 (s, 1H, C*H*CO), 4.67 (d, NHC*H*$_2$Ph) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -77.3 (s, C*F*$_3$), -119.8 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179/7 (q, *C*CF_3, $^{2}J_{C-F}$ = 34.6 Hz), 158.2 (t, *C*CHF_2, $^{2}J_{C-F}$ = 22 Hz), 135.6, 129.4, 128.7, 127.4 (Phenyl), 116.8 (q, *C*F_3, $^{1}J_{C-F}$ = 288 Hz), 110.7 (t, *C*HF_2, $^{1}J_{C-F}$ = 245 Hz), 87.2 (t, *C*HCO, $^{3}J_{C-F}$ = 7 Hz), 48.4 (CH_2NH) ppm.

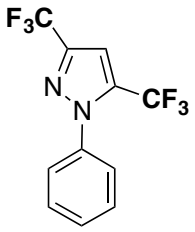
Anal. calcd for $C_{12}H_{10}F_5NO$: C, 51.62; H, 3.61; F, 34.02; N, 5.02; O, 5.73. Found: C, 51.61; H, 3.70; N, 5.12.

4-(benzylamino)-1,1,1,5,5,5-hexafluoropent-3-en-2-one (II.60E.c)



Same procedure from **II.59c**. Yield 2.9g of clean oil (98%). The crude was purified by flash chromatography (Et_2O in pentane 0 to 10%) for data's. This compound previously reported: H. Ohkura et al., *Tetrahedron* 59 (2003) 1647–1656.

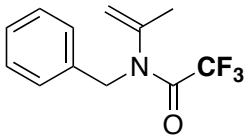
1-phenyl-3,5-bis(trifluoromethyl)-1*H*-pyrazole (II.97)



A solution II.60E.c (1 equiv., 400 mg, 1.346 mmol) in MeCN (4 mL) was treated with phenyl hydrazine (1.5 equiv., 218 mg, 0.2 mL, 2.02 mmol) rapidly followed by conc. H_2SO_4 (0.54 equiv., 73 mg, 0.04 mL, 0.73 mmol) under inert atmosphere at room temperature. After 1 h at reflux, the mixture was cooled to room temperature and pyridine (7.99 equiv., 850 mg, 0.87 mL, 10.8 mmol) was added. After 5min, $SOCl_2$ (2.05 equiv., 328 mg, 0.2 mL, 2.76 mmol) was added very carefully. After 1 h more at room temperature, NMR showed full conversion.
^{19}F NMR yield: 99%.

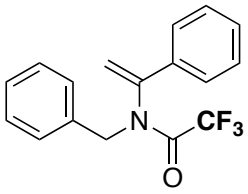
Ref: J.C. Sloop et al. / Journal of Fluorine Chemistry 118 (2002) 135–147.

***N*-benzyl-2,2,2-trifluoro-*N*-(prop-1-en-2-yl)acetamide (II.98a)**



A solution of benzyl(propan-2-ylidene)amine (1 equiv., 520 mg, 3.53 mmol) in DCM (8 mL) was cooled to -5 °C and pyridine (1.93 equiv., 537 mg, 0.55 mL, 6.8 mmol) was added. After 10min, TFAA (1.06 equiv., 785 mg, 0.52 mL, 3.74 mmol) was added dropwise over 10min at -5 °C. The mixture was stirred from -5 °C to room temperature over 18 h. The mixture was diluted with DCM, filtered and evaporated *in vacuo*. An azeotropic distillation using toluene was performed to remove the residual pyridine. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 690mg of colourless oil (80%).
E/Z ratio: *ca*. 92/8
Major isomer:
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 to 7.28 (m, 5H, Phenyl), 5.07 (q, NCC*H*H, $^{4}J_{H-H}$ = 1 Hz), 4.70 (s, NCCH*H*), 4.68 (s, $PhCH_2N$), 1.91 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -67.6 (s, CF_3) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.6 (q, $COCF_3$, $^{2}J_{C-F}$ = 36 Hz), 140.5 (N*C*CHH), 135.7, 128.9, 128.6, 128.0 (Phenyl), 117.8 (NC*C*HH), 116.7 (q, CF_3, $^{1}J_{C-F}$ = 288 Hz), 50.5 ($PhCH_2N$), 20.3 (CH_3) ppm.
HRMS (ESI) calcd for $C_{12}H_{12}F_3NNaO$ [M+Na]: 266.0763. Found: 266.0769.

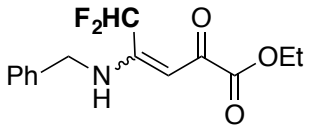
_N_-benzyl-2,2,2-trifluoro-_N_-(1-phenylvinyl)acetamide (II.98b)



Same procedure from benzyl(1-phenylethylidene)amine (1 equiv., 710 mg, 3.39 mmol). The mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 872mg of colourless oil (84%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 5H, $NCH_2C_6\mathit{H}_5$), 7.32 to 7.22 (m, $NCC_6\mathit{H}_5$), 5.67 (s, NCC*H*H), 5.38 (br s, PhC*H*HN), 4.87 (s, NCCH*H*), 3.90 (PhCH*H*N) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.6 (s, $C\mathit{F}_3$) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 157.8 (q, *C*OCF_3, $^{2}J_{C\text{-}F}$ = 36 Hz), 142.8 (N*C*CHH), 135.4, 134.1, 129.6, 129.5, 129.1, 128.6, 128.2, 126.4 (2 x Phenyl), 116.7 (q, *C*F_3, $^{1}J_{C\text{-}F}$ = 289 Hz), 116.0 (NC*C*HH), 51.2 (Ph*C*H_2N), 27.0 (*C*H_3) ppm.
Anal calcd. for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; F, 18.67; N, 4.59; O, 5.24. Found: C, 66.95; H, 4.71; N, 4.66.

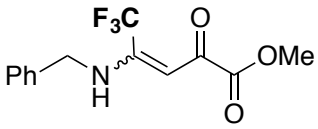
Preparation of mono(fluoroalkyl)-vinamides – prepared from alkyl oxalyl chlorides and Rf-ketimines

ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (II.99b)



A solution of **II.59b** (1 equiv., 250 mg, 1.30 mmol) in DCM (2 mL) was cooled to -20 °C. Pyridine (1.05 equiv., 108 mg, 0.11 mL, 1.36 mmol) was added, followed after 10 min by a solution of ethyl oxalyl monochloride (1.03 equiv., 183 mg, 0.15 mL, 1.34 mmol) in DCM (1 mL). The mixture was stirred from -20 °C to room temperature over 18 h. The mixture was taken up in DCM (5 mL) followed by Et_2O (10 mL). The resulting precipitate was filtered off, the filtrate concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 15%). Yield: 224 mg (61 %) of orange oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.91 (s br, N*H*), 7.39 to 7.28 (m, 5*H*, Phenyl), 6.18 (t, C*H*F_2, $^{2}J_{H\text{-}F}$ = 53 Hz), 6.17 (s, C*H*CO), 4.66 (d, CH_2NH), 4.31 (q, OCH_2), 1.36 (t, OCH_2CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -118.9 (d, CHF_2, $^{2}J_{F\text{-}H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.2 (*C*(O)COOEt), 162.6 (*C*(O)OEt), 156.8 (t, *C*CHF_2, $^{2}J_{C\text{-}F}$ = 22 Hz), 136.2, 129.2, 128.3, 127.3 (C_{Phenyl}), 111.4 (t, *C*HF_2, $^{1}J_{C\text{-}F}$ = 245 Hz), 91.4 (t, *C*HCO, $^{3}J_{C\text{-}F}$ = 7 Hz), 62.2 (OCH_2), 48.2 (*C*H_2NH), 14.1 (OCH_2CH_3) ppm.
Anal. calcd for $C_{14}H_{15}F_2NO_3$: C, 59.36; H, 5.34; F, 13.41; N, 4.94; O, 16.94. Found: C, 59.16; H, 5.36; N, 4.95.

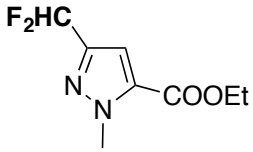
methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (II.101c)



A solution of **II.59c** (1000 mg, 4.82 mmol) in DCM (10 mL) was cooled to -20 °C. Pyridine (1.03 equiv., 391 mg, 0.4 mL, 4.95 mmol) was added, followed after 10 min by a solution of methyl oxalyl chloride (1.06 equiv., 625 mg, 0.47 mL, 5.1 mmol) in DCM (6 mL). The mixture was stirred from -20 °C to room temperature over 18 h, and was then concentrated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 10%).
Yield: 680 mg (49 %) of colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.02 (s br, N*H*), 7.40 to 7.28 (m, 5*H*, Phenyl), 6.40 (s, C*H*CO), 4.64 (d, C*H*$_2$NH), 3.87 (s, COOC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.6 (s, C*F*$_3$) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.3 (CH*C*O), 162.7 (*C*OOMe), 152.6 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 32.5 Hz), 135.8, 129.3, 128.5, 127.4 (C_{Phenyl}), 119.6 (q, *C*F$_3$, $^{1}J_{C-F}$ = 278 Hz), 90.4 (q, *C*HCO, $^{3}J_{C-F}$ = 5 Hz), 53.1 (COO*C*H$_3$), 49.0 (*C*H$_2$NH) ppm.
HRMS (ESI) calcd for $C_{13}H_{12}F_3NNaO_3$ [M+Na]: 310.0661. Found: 310.0635.

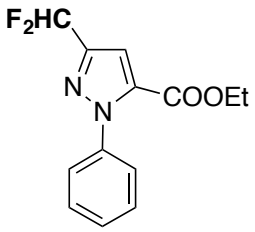
Preparation of 3-Rf-pyrazoles-5-carboxylates and carboxylic acids from mono(fluoroalkyl)vinamides

ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (II.103b)



A solution of **II.99b** (1 equiv., 520 mg, 1.78 mmol) in MeCN (4 mL) was treated with methyl hydrazine (1.57 equiv., 129 mg, 0.15 mL, 2.8 mmol) rapidly followed by conc. H_2SO_4 (0.511 equiv., 92 mg, 0.05 mL, 0.91 mmol) under inert atmosphere at room temperature. The mixture was stirred 1 h and then was diluted with DCM, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 40%).
Yield: 230mg of colourless oil (63%). (11% of the intermediate pyrazoline were isolated)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, 4-C*H*, $^{4}J_{H-F}$ = 1 Hz), 6.66 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 55 Hz), 4.36 (q, OC*H*$_2$), 4.19 (s, C*H*$_3$), 1.38 (t, OCH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.1 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 55 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.4 (*C*=O), 145.1 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 29.8 Hz), 134.0 (*C*COOEt), 110.8 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 234 Hz), 108.7 (4-*C*H), 61.5 (O*C*H$_2$), 40.1 (N*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_8H_{11}F_2N_2O_2$ [M+H]: 205.0783. Found: 205.0782.

ethyl 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (II.105b)



A solution of ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (1 equiv., 420 mg, 1.44 mmol) in MeCN (4 mL) was treated with phenyl hydrazine (1.47 equiv., 228 mg, 0.21 mL, 2.12 mmol) rapidly followed by conc. H_2SO_4 (0.506 equiv., 73.6 mg, 0.04 mL, 0.728 mmol) under inert atmosphere. The mixture was refluxed overnight. DCM (20 mL) was added, the mixture filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 310mg of orange oil (81%).

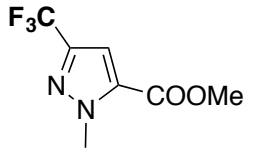
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 to 7.41 (m, 5*H*, Phenyl), 7.24 (s, 4-C*H*), 6.76 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 54.9 Hz), 4.26 (q, OC*H*$_2$), 1.26 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.2 (d, CH*F*$_2$, $^2J_{F\text{-}H}$ = 54.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.4 (*C*=O), 146.8 (t, *C*CHF$_2$, $^2J_{C\text{-}F}$ = 30 Hz), 139.8 (N*C*$_{Phenyl}$), 135.0 (*C*COOEt), 129.2, 128.7, 126.0 (*C*$_{Phenyl}$), 110.7 (t, *C*HF$_2$, $^1J_{C\text{-}F}$ = 234 Hz), 109.6 (4-*C*H), 61.6 (O*C*H$_2$), 13.9 (OCH$_2$*C*H$_3$) ppm.

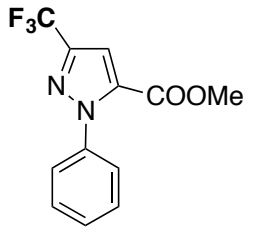
HRMS (ESI) calcd for $C_{13}H_{13}F_2N_2O_2$ [M+H]: 267.0940. Found: 267.0918.

methyl 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (II.107c)



A solution of **II.101c** (1 equiv., 150 mg, 0.47 mmol) in MeCN (1 mL) was treated with methyl hydrazine (1.59 equiv., 34.4 mg, 40 µL, 0.747 mmol) rapidly followed by conc. H_2SO_4 (0.503 equiv., 23.9 mg, 13 µL, 0.237 mmol) under inert atmosphere at room temperature. The mixture was stirred at 90 °C for 1 h and removed from the oil bath for 5 min. Pyridine (8.02 equiv., 298 mg, 305 µL, 3.77 mmol) was added, followed after 5 min by $SOCl_2$ (2.05 equiv., 114 mg, 70 µL, 0.965 mmol). The mixture was stirred 30 min at room temperature. ^{19}F NMR yield: >99%. No NMR characterization, ^{19}F reference of ethyl carboxylate used.

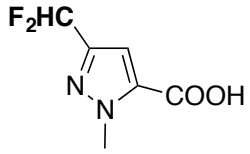
methyl 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (II.105c)



A solution of **II.101c** (1 equiv., 500 mg, 1.74 mmol) in MeCN (5 mL) was treated with phenylhydrazine (1.51 equiv., 283 mg, 0.26 mL, 2.62 mmol) rapidly followed by conc. H_2SO_4 (0.523 equiv., 92 mg, 0.05 mL, 0.91 mmol) under inert atmosphere at room temperature. The mixture was refluxed for 2 days and cooled to room temperature. Pyridine (7.81 equiv., 1075 mg, 1.1 mL, 13.6 mmol) was added, followed by a very slow addition of $SOCl_2$ (1.98 equiv., 410 mg, 0.25 mL, 3.45 mmol) *via* syringe. The mixture was stirred 30 min, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%).
Yield: 370mg (*ca*. 80wt.%) of red solid (64%). HRMS (ESI) calcd for $C_{12}H_{10}F_3N_2O_2$ [M+H]: 271.0689. Found: 271.0697.

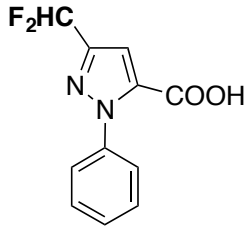
Ref: Muthuppalaniappan, Peyyappan et al, PCT Int. Appl., 2011042797, 14 Apr 2011.

3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (II.104b)



A mixture of **II.103b** (1 equiv., 185 mg, 0.906 mmol) and NaOH 2N (2.01 equiv., 2 M, 0.912 mL, 1.82 mmol) in EtOH (2.61 mL) was stirred at room temperature for 1 h. The mixture was treated with HCl 1N until pH 2-3, then was extracted with DCM. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Yield: 160mg of white solid (99%) after trituration in pentane. M.p.: 179.8 – 180.2 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.7 (s br, COO*H*), 7.02 (s, 4-C*H*), 7.01 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 54.4 Hz), 4.11 (s, NC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -111.6 (d, CH*F*$_2$, $^2J_{F\text{-}H}$ = 54.5 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 160.1 (*C*=O), 144.0 (t, *C*CHF$_2$, $^2J_{C\text{-}F}$ = 28.5 Hz), 134.6 (*C*COOH), 110.9 (t, *C*HF$_2$, $^1J_{C\text{-}F}$ = 232 Hz), 108.4 (4-*C*H), 39.7 (N*C*H$_3$) ppm.
Anal. calcd for $C_6H_6F_2N_2O_2$: C, 40.92; H, 3.43; F, 21.57; N, 15.91; O, 18.17. Found: C, 41.10; H, 3.57; N, 15.63.

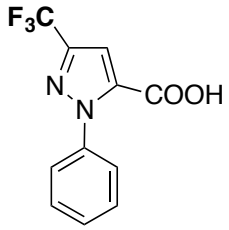
3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylic acid (II.106b)



A mixture of **II.105b** (1 equiv., 160 mg, 0.601 mmol) and NaOH 2N (1.83 equiv., 2 M, 0.55 mL, 1.1 mmol) in EtOH (1 mL) was stirred at room temperature for 1 h. The mixture was treated with HCl 1N until pH 2-3, then was extracted with DCM. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a brown solid (160mg) after trituration in pentane. M.p.: 132.7 - 133.5 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.6 (*C*OOH), 7.50 (m, 5*H*, C_{Phenyl}), 7.25 (s, 4-C*H*), 7.13 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 54 Hz) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -112.2 (d, CH*F*$_2$, $^2J_{F\text{-}H}$ = 53.7 Hz) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 159.3 (*C*OOH), 146.0 (t, *C*CHF$_2$, $^{2}J_{C\text{-}F}$ = 29 Hz), 139.7 (N*C*$_{Phenyl}$), 135.9 (*C*COOH), 128.9, 128.7, 125.9 (*C*$_{Phenyl}$), 110.9 (t, *C*HF$_2$, $^{1}J_{C\text{-}F}$ = 233 Hz), 109.5 (4-*C*H) ppm.
Anal. calcd for $C_{11}H_8F_2N_2O_2$: C, 55.47; H, 3.39; F, 15.95; N, 11.76; O, 13.43. Found: C, 55.97; H, 3.54; N, 11.61.

1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid (II.106c)



A mixture of **II.105c** (1 equiv., 170 mg, 0.503 mmol) and NaOH 2N (2.19 equiv., 2 M, 0.55 mL, 1.1 mmol) in EtOH (1 mL) was stirred at room temperature for 1 h. The mixture was treated with HCl 1N until pH 2-3, then was extracted with DCM. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a brown solid. M.p.: 155 - 165 °C (degradation observed).
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.7 (s br, COO*H*), 7.52 (m, 5H, C*H*$_{Phenyl}$), 7.50 (4-C*H*) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -60.9 (s, C*F*$_3$) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 158.9 (*C*OOH), 141.0 (q, *C*CF$_3$, $^{2}J_{C\text{-}F}$ = 38 Hz), 139.4 (N-1*C*$_{Phenyl}$), 136.4 (*C*COOH), 129.3, 128.7, 126.0 (2-6*C*$_{Phenyl}$), 120.9 (q, *C*F$_3$, $^{1}J_{C\text{-}F}$ = 269 Hz), 110.1 (4-*C*H) ppm.
HRMS (ESI) calcd for $C_{11}H_8F_3N_2O_2$ [M+H]: 257.0532. Found: 257.0536.

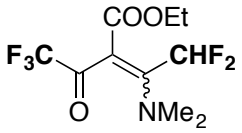
Chapter III

Preparation of key intermediates

Preparation of key enamine-ketone carboxylates – example of **III.2A.a**

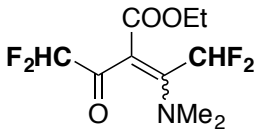
TFEDMA (1.03 equiv., 5.33 g, 4.3 mL, 34.9 mmol) was activated in anhydrous MeCN (25 mL) with BF_3⋅Et_2O (1.05 equiv., 5.04 g, 4.5 mL, 35.5 mmol) *via* syringe under inert atmosphere into a Teflon flask. After 15min, the solution was cooled to -30 °C. A solution of ethyl 4,4,4-trifluoroacetoacetate (1 equiv., 6.25 g, 5 mL, 33.9 mmol) and pyridine (3.02 equiv., 8.12 g, 8.3 mL, 102 mmol) in MeCN (40 mL) was cooled to -30 °C and canulated into the first flask. The mixture was allowed to reach room temperature over 18 h. The mixture was concentrated under high vacuum, taken up in DCM and filtered through Celite. The filtrate was evaporated *in vacuo*. The resulting oil was taken up in toluene and was filtered once more through Celite. The second filtrate was submitted to an azeotropic distillation (<100 mbar, 55-60 °C). Yield: 9g (95wt.%) of orange oil (92%).

ethyl 3-(dimethylamino)-4,4-difluoro-2-(2,2,2-trifluoroacetyl)but-2-enoate (III.2A.a)



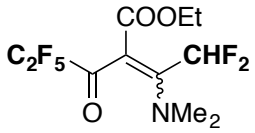
Orange oil. Yield: 92%. Purity: 95wt.%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.56 (t, C*H*F_2, $^2J_{H-F}$ = 52.4 Hz), 4.13 (q, 2H, OC*H*$_2$CH$_3$), 3.14 (s, 6H, N(C*H*$_3$)$_2$), 1.20 (t, 3H, OCH_2C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -72.2 (s, C*F*$_3$), -116.7 (d, CH*F*$_2$, $^2J_{F-H}$ = 52 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.1 (q, *C*(O)CF_3, $^2J_{C-F}$ = 34.6 Hz), 165.8 (*C*OOEt), 163.2 (t, *C*CHF_2, $^2J_{C-F}$ = 21 Hz), 116.8 (q, *C*F_3, $^1J_{C-F}$ = 290 Hz), 110.0 (t, *C*HF_2, $^1J_{C-F}$ = 248 Hz), 100.0 (*C*COOEt), 61.5 (O*C*H_2CH_3), 45.3 (N(*C*H_3)$_2$), 13.6 (OCH_2*C*H_3) ppm.
HRMS (ESI) calcd for $C_{10}H_{13}F_5NO_3$ $[M+H]^+$: 290.0810. Found: 290.0795.

ethyl 2-(2,2-difluoroacetyl)-3-(dimethylamino)-4,4-difluorobut-2-enoate (III.2A.b)



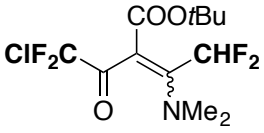
Yield: 3.32g (60wt.% by GCMS) of orange oil (72%). No clean analysis was achieved due to low purity and the oil was used in state in the pyrimidine synthesis.

ethyl 2-(1-(dimethylamino)-2,2-difluoroethylidene)-4,4,5,5,5-pentafluoro-3-oxopentanoate (III.2A.c)



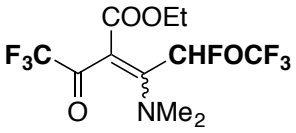
Yellow oil. Yield: 89%. Purity: 95wt.%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.49 (t, C*H*F_2, $^{2}J_{H-F}$ = 52.3 Hz), 4.20 (q, OC*H*$_2$), 3.17 (s, 6H, N(C*H*$_3$)$_2$), 1.28 (t, OCH_2CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -80.7 (CF_2CF_3), -115.9 (CF_2), -116.0 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 52.6 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.6 (t, *C*(O)C_2F_5, $^{2}J_{C-F}$ = 25.7 Hz), 165.8 (*C*=O), 162.9 (t, *C*CHF_2, $^{2}J_{C-F}$ = 21 Hz), 118.8 (qt, *C*F_3CF_2, $^{1}J_{C-F}$ = 287 Hz, $^{3}J_{C-F}$ = 36 Hz), 110.1 (t, CHF_2, $^{1}J_{C-F}$ = 248 Hz), 108.0 (tq, *C*F_2CF_3, $^{1}J_{C-F}$ = 271 Hz, $^{3}J_{C-F}$ = 36 Hz), 102.0 (*C*COOEt), 61.8 (OCH_2), 45.3 (N(*C*H_3)$_2$), 13.8 (CH_2CH_3) ppm.
HRMS (ESI) calcd for $C_{11}H_{13}F_7NO_3$ $[M+H]^+$: 340.0778. Found: 340.0772.

***tert*-butyl 2-(2-chloro-2,2-difluoroacetyl)-3-(dimethylamino)-4,4-difluorobut-2-enoate (III.2A.d)**



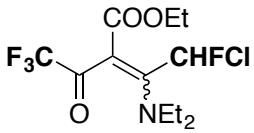
Orange oil. Yield: 99%. Purity: 93wt.%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.55 (t, C*H*F_2, $^{2}J_{H-F}$ = 52.5 Hz), 3.14 (s, N(C*H*$_3$)$_2$), 1.48 (s, 9H, C(C*H*$_3$)$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -58.7 (s, C*F*$_2$Cl), -115.9 (d, C*H*F_2, $^{2}J_{F-H}$ = 52.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.3 (t, *C*(O)CF_2Cl, $^{2}J_{C-F}$ = 28.9 Hz), 165.0 (*C*OOtBu), 161.9 (t, *C*CHF_2, $^{2}J_{C-F}$ = 20.9 Hz), 121.4 (t, *C*F_2Cl, $^{1}J_{C-F}$ = 306 Hz), 110.3 (t, *C*HF_2, $^{1}J_{C-F}$ = 247 Hz), 102.2 (t, *C*$COCF_2Cl$, $^{3}J_{C-F}$ = 5.4 Hz), 82.6 (C(CH_3)$_3$), 45.1 (N(*C*H_3)$_2$), 27.9 (C(*C*H_3)$_3$) ppm.
HRMS (ESI) calcd for $C_{12}H_{17}ClF_4NO_3$ $[M+H]^+$: 334.0828 + 336.0802. Found: 334.0784 + 336.0758.

ethyl 3-(dimethylamino)-4-fluoro-2-(2,2,2-trifluoroacetyl)-4-(trifluoromethoxy)but-2-enoate (III.2D.a)



Red oil. Yield: 80%. Purity: 95wt.%.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, $CHFOCF_3$, $^{2}J_{H-F}$ = 53.7 Hz), 4.22 (q, OCH_2CH_3), 3.16 (s, N(CH_3)$_2$), 1.29 (t, OCH_2CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.8 (m, C*F*$_3$), -72.4 (s, OC*F*$_3$), -127.9 (d, CH*F*OCF_3, $^{2}J_{F-H}$ = 54.1 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.8 (q, *C*(O)CF_3, $^{2}J_{C-F}$ = 35 Hz), 165.9 (*C*=O), 161.7 (d, *C*$CHFOCF_3$, $^{2}J_{C-F}$ = 22 Hz), 120.8 (q, O*C*F_3, $^{1}J_{C-F}$ = 263 Hz), 116.7 (q, *C*F_3, $^{1}J_{C-F}$ = 290 Hz), 100.0 (dq, *C*$HFOCF_3$, $^{1}J_{C-F}$ = 238.2 Hz, $^{3}J_{C-F}$ = 3.5 Hz), 100.1 (d, *C*COOEt, $^{3}J_{C-F}$ = 4.4 Hz), 61.7 (O*C*H_2CH_3), 45.4 (N(*C*H_3)$_2$), 13.7 (OCH_2CH_3) ppm.
HRMS (ESI) calcd for $C_{11}H_{13}F_7NO_4$ $[M+H]^+$: 356.0727. Found: 356.0725.

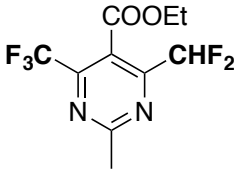
ethyl 4-chloro-3-(diethylamino)-4-fluoro-2-(2,2,2-trifluoroacetyl)but-2-enoate (III.2B.a)



Dark oil. Yield: 75%. Purity: 75wt.%. Spectra not provided due to low purity.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, C*H*FCl, $^{2}J_{H-F}$ = 48.6 Hz), 4.17 (qd, OCH_2), 3.65 to 3.52 (m, N(CH_2CH$_3$)$_2$), 1.27 (m, N(CH$_2$CH_3)$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -72.0 (s, CF_3), -138.1 (d, CH*F*Cl, $^{2}J_{F-H}$ = 48.3 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.7 (q, *C*(O)CF$_3$, $^{2}J_{C-F}$ = 34.6 Hz), 166.8 (d, *C*CHFCl, $^{2}J_{C-F}$ = 18.7 Hz), 165.8 (*C*=O), 117.0 (q, *C*F$_3$, $^{1}J_{C-F}$ = 290 Hz), 98.3 (d, *C*COOEt, $^{3}J_{C-F}$ = 3 Hz), 93.9 (d, *C*HFCl, $^{1}J_{C-F}$ = 256 Hz), 61.3 (O*C*H$_2$), 48.0 (d, N(*C*H$_2$CH$_3$)$_2$, $^{3}J_{C-F}$ = 3.4 Hz), 13.8 (OCH$_2$*C*H$_3$), 12.6 (N(CH$_2$*C*H$_3$)$_2$) ppm.
HRMS (ESI) calcd for $C_{12}H_{17}ClF_4NO_3$ [M+H]$^{+}$: 334.0828 + 336.0802. Found: 334.0800 + 336.0770.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow evaporation of a concentrated solution in Et_2O/DCM.

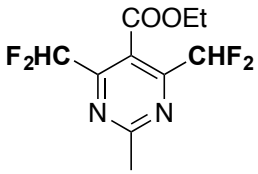
Preparation of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylates

ethyl 4-(difluoromethyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.5A.a)



A mixture of **III.2A.a** (1 equiv., 100 mg, 0.311 mmol), acetamidine hydrochloride (2.04 equiv., 60 mg, 0.635 mmol) and Et_3N (3.01 equiv., 94.6 mg, 0.13 mL, 0.935 mmol) in MeCN (0.5 mL) was heated at 70 °C for 15min in the micro-wave (High). ^{19}F NMR yield: 91%. The mixture was partitioned between Et_2O and water. The aqueous was extracted with Et_2O twice. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in cyclohexane 0 to 20%), to yield a colourless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.72 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 53.6 Hz), 4.46 (q, OCH_2), 2.90 (s, CH_3), 1.39 (t, CH$_2$CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.4 (s, CF_3), -118.6 (d, CHF_2, $^{2}J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9 (N*C*N), 163.1 (*C*=O), 159.1 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 26 Hz), 153.9 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 36.3 Hz), 120.7 (*C*COOEt), 120.1 (q, *C*F$_3$, $^{1}J_{C-F}$ = 277 Hz), 112.0 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 244.5 Hz), 63.6 (O*C*H$_2$), 25.9 (*C*H$_3$), 13.9 (CH$_2$*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{10}H_{10}F_5N_2O_2$ [M+H]$^{+}$: 285.0657. Found: 285.0677.

ethyl 4,6-bis(difluoromethyl)-2-methylpyrimidine-5-carboxylate (III.5A.b)



A mixture of **III.2A.b** (60wt.%, 1 equiv., 2600 mg, 5.75 mmol), acetamidine hydrochloride (2 equiv., 1090 mg, 11.5 mmol) and Et_3N (3 equiv., 1747 mg, 2.4 mL, 17.3 mmol) in MeCN (12 mL) was heated at 70 °C for 15min in the μ-wave (High). Additional 45min and 60min at 70 °C were achieved. The mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%), to give 180mg of colourless oil (12%).

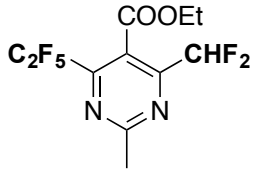
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.79 (t, 2 x C*H*F_2, $^2J_{H-F}$ = 54 Hz), 4.46 (q, OC*H*$_2$), 2.89 (s, CC*H*$_3$), 1.40 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -119.0 (d, 2 x CH*F*$_2$, $^2J_{F-H}$ = 54 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9 (N*C*N), 163.6 (*C*=O), 158.8 (t, 2 x *C*CHF$_2$, $^2J_{C-F}$ = 25 Hz), 120.7 (*C*COOEt), 111.7 (t, 2 x *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 63.3 (O*C*H$_2$), 26.0 (CH$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{10}H_{11}F_4N_2O_2$ $[M+H]^+$: 267.0751. Found: 267.0765.

ethyl 4-(difluoromethyl)-2-methyl-6-(perfluoroethyl)pyrimidine-5-carboxylate (III.5A.c)



Same procedure than **III.5A.a** starting from ethyl 2-[1-(dimethylamino)-2,2-difluoroethylidene]-4,4,5,5,5-pentafluoro-3-oxopentanoate (95wt.%, 1.4 mmol, 500mg) in MeCN (3 mL). ^{19}F NMR yield: 85%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 3%), to give 296mg of colourless oil (63%).

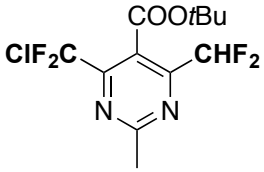
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.68 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 4.44 (q, OC*H*$_2$), 2.87 (CC*H*$_3$), 1.37 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.5 (C*F*$_3$CF$_2$), -113.7 (C*F*$_2$CF$_3$), -118.4 (t, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5 (N*C*N), 163.0 (*C*=O), 159.0 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 153.9 (t, *C*C$_2$F$_5$, $^2J_{C-F}$ = 26.6 Hz), 122.2 (*C*COOEt), 118.4 (qt, *C*F$_3$CF$_2$, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 35.5 Hz), 112.2 (t, *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 111.0 (tq, *C*F$_2$CF$_3$, $^1J_{C-F}$ = 259 Hz, $^2J_{C-F}$ = 38.7 Hz), 63.5 (O*C*H$_2$CH$_3$), 25.8 (C*C*H$_3$), 13.8 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{11}H_{10}F_7N_2O_2$ $[M+H]^+$: 335.0625. Found: 335.0655.

tert-butyl 4-(chlorodifluoromethyl)-6-(difluoromethyl)-2-methylpyrimidine-5-carboxylate (III.5A.d)



Same procedure than **III.5A.a** starting from **III.2A.d** (93wt.%, 2.78 mmol, 1000mg) in MeCN (4 mL). Additional 45min and 60min at 70 °C were achieved. ^{19}F NMR yield: 58%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 5%). Yield: 230mg of colourless oil (25%).

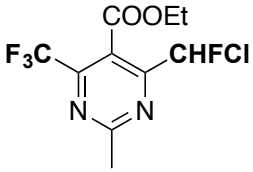
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.70 (t, C*H*F$_2$, $^2J_{H-F}$ = 54 Hz), 2.87 (s, 3H, CC*H*$_3$), 1.58 (s, 9H, C(C*H*$_3$)$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -55.9 (s, C*F*$_2$Cl), -118.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 54 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.2 (N*C*N), 162.0 (*C*=O), 158.9 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.4 Hz), 157.4 (t, *C*CF$_2$Cl, $^2J_{C-F}$ = 30.1 Hz), 122.9 (t, *C*F$_2$Cl, $^1J_{C-F}$ = 292 Hz), 120.3 (*C*COO*t*Bu), 112.2 (t, *C*HF$_2$, $^1J_{C-F}$ = 246 Hz), 85.8 (*C*(CH$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$), 25.9 (C*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{12}H_{13}ClF_4N_2NaO$ [M+Na]$^+$: 351.0494 (+ 353.0468). Found: 351.0468 (+ 353.0446).

ethyl 4-(chlorofluoromethyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.5B.a)



Same procedure than **III.5A.a** in abs. EtOH starting from **III.2B.a** (75wt.%, 1 equiv., 1000 mg, 2.25 mmol) with 30min heating in microwave. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%), to give 240mg of brown oil (36%).

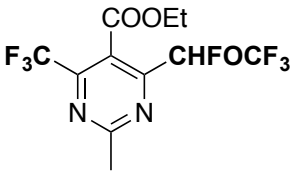
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, C*H*FCl, $^2J_{H-F}$ = 49.6 Hz), 4.46 (q, OC*H*$_2$CH$_3$), 2.89 (s, C*H*$_3$), 1.40 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.3 (s, C*F*$_3$), -143.7 (d, CH*F*Cl, $^2J_{F-H}$ = 49.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9 (N*C*N), 163.2 (*C*=O), 162.1 (d, *C*CHFCl, $^2J_{C-F}$ = 24 Hz), 154.0 (q, *C*CF$_3$, $^2J_{C-F}$ = 36 Hz), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 119.6 (*C*COOEt), 96.6 (d, *C*HFCl, $^1J_{C-F}$ = 248 Hz), 63.6 (O*C*H$_2$CH$_3$), 26.0 (C*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

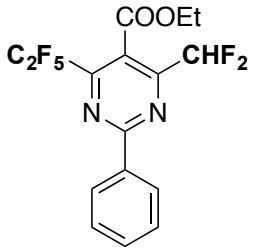
HRMS (ESI) calcd for $C_{10}H_{10}ClF_4N_2O_2$ [M+H]$^+$: 301.0361 (+ 303.0335). Found: 301.0351 (+ 303.0468).

ethyl 4-(fluoro(trifluoromethoxy)methyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.



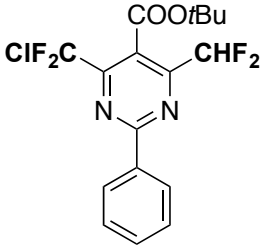
Same procedure than **III.5A.a** in abs. EtOH starting from **III.2D.a** (1 equiv., 2 g, 5.35 mmol). ^{19}F NMR yield: 80%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%), to give 910mg of colourless oil (49%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 56.1 Hz), 4.43 (q, OC*H*$_2$CH$_3$), 2.90 (s, CC*H*$_3$), 1.37 (t, OCH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (d, CHFOC*F*$_3$, $^{4}J_{F-F}$ = 4.8 Hz), -66.5 (s, C*F*$_3$), -130.4 (dq, CH*F*OCF$_3$, $^{2}J_{F-H}$ = 55.9 Hz, $^{4}J_{F-F}$ = 4.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.1 (N*C*N), 163.0 (*C*=O), 158.4 (d, *C*CHFOCF$_3$, $^{2}J_{C-F}$ = 26.3 Hz), 154.0 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 36.3 Hz), 121.0 (q, OCF$_3$, $^{1}J_{C-F}$ = 263.1 Hz), 120.9 (*C*COOEt), 120.1 (q, *C*F$_3$, $^{1}J_{C-F}$ = 277.2 Hz), 102.5 (dq, *C*HFOCF$_3$, $^{1}J_{C-F}$ = 236.8 Hz, $^{3}J_{C-F}$ = 3.5 Hz), 63.6 (O*C*H$_2$CH$_3$), 25.9 (C*C*H$_3$), 13.7 (OCH$_2$*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{11}H_{10}F_7N_2O_2$ [M+H]$^+$: 351.0574. Found: 351.0562.

ethyl 4-(perfluoroethyl)-2-phenyl-6-(difluoromethyl)pyrimidine-5-carboxylate (III.7A.c)



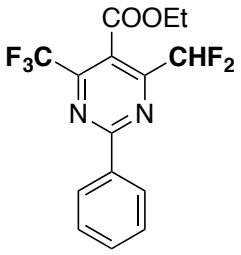
Same procedure than **III.5A.a** starting from **III.2A.a** (1 equiv., 480 mg, 1.34 mmol), benzamidine (2.2 equiv., 355 mg, 2.96 mmol) and Et_3N (3.3 equiv., 451 mg, 0.62 mL, 4.46 mmol) in MeCN (4 mL). ^{19}F NMR yield: >99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 3%). Yield: 463mg of colourless solid (87%). M.p.: 52.8 - 53.2 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, 2',6'-C*H*), 7.61 to 7.51 (m, 3',4',5'-C*H*), 6.80 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 54 Hz), 4.48 (q, OC*H*$_2$), 1.41 (t, CH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.1 (s, C*F*$_3$CF$_2$), -113.3 (s, CF$_2$CF$_3$), -118.3 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.8 and 163.2 (N*C*N and *C*=O), 159.6 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25.7 Hz), 154.4 (t, *C*CF$_2$CF$_3$, $^{2}J_{C-F}$ = 27.3 Hz), 134.5, 133.0, 129.3, 129.2 (*C*$_{arom.}$), 122.1 (*C*COOEt), 118.6 (qt, *C*F$_3$CF$_2$, $^{1}J_{C-F}$ = 288 Hz, $^{2}J_{C-F}$ = 35 Hz), 112.5 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 245.8 Hz), 111.2 (tq, *C*F$_2$CF$_3$, $^{1}J_{C-F}$ = 259.4 Hz, $^{2}J_{C-F}$ = 39.6 Hz), 63.5 (O*C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.
Anal. calcd for $C_{16}H_{11}F_7N_2O_2$: C, 48.50; H, 2.80; F, 33.56; N, 7.07; O, 8.07. Found: C, 48.79; H, 2.78; N, 7.26.

***tert*-butyl 4-(chlorodifluoromethyl)-2-phenyl-6-(difluoromethyl)pyrimidine-5-carboxylate (III.7A.d)**



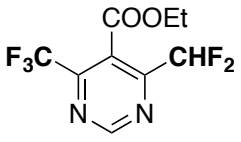
Same procedure than **III.5A.a** starting from **III.2A.d** (93wt.%, 1 equiv., 403 mg, 1.12 mmol), benzamidine (2.67 equiv., 360 mg, 3.00 mmol) and Et_3N (4 equiv., 451 mg, 0.62 mL, 4.46 mmol) in MeCN (4 mL). ^{19}F NMR yield: >99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 3%), to give 410mg of colourless solid (93%). M.p.: 150.4 - 151.0 °C.
^1H-NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, 2',6'-C*H*), 7.55 (m, 3',4',5'-C*H*), 6.81 (d, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 1.62 (s, 9H, C(CH_3)$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -55.5 (s, CF_2Cl), -118.0 (d, CHF_2, $^2J_{F-H}$ = 53.8 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7 and 162.2 (N*C*N and *C*=O), 159.3 (*C*CHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 157.8 (t, *C*CF$_2$Cl, $^2J_{C-F}$ = 30.3 Hz), 134.9, 132.8, 129.2, 129.0 ($C_{arom.}$), 123.2 (t, *C*F$_2$Cl, $^1J_{C-F}$ = 292.5 Hz), 120.4 (*C*COO*t*Bu), 112.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.8 Hz), 85.8 (*C*(CH$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$) ppm.
Anal. calcd for $C_{17}H_{15}ClF_4N_2O_2$: C, 52.25; H, 3.87; Cl, 9.07; F, 19.45; N, 7.17; O, 8.19. Found: C, 52.43; H, 3.81; N, 7.39.

ethyl 4-(difluoromethyl)-2-phenyl-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.7A.a)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 507 mg, 1.58 mmol), benzamidine (1.97 equiv., 374 mg, 3.11 mmol) and Et_3N (2.96 equiv., 473 mg, 0.65 mL, 4.68 mmol) in abs. EtOH (2 mL) after 30min in the microwave.
^{19}F NMR yield: >99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 4%), to give 428 mg of colourless solid (78%). M.p.: 69.3 - 69.6 °C.
^1H-NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, 2H, 2',6'-C*H*), 7.55 (m, 3H, 3',4',5'-C*H*), 6.82 (t, C*H*F_2, $^2J_{H-F}$ = 54 Hz), 4.49 (q, OCH_2CH$_3$), 1.42 (t, OCH$_2$CH_3) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.5 (s, CF_3), -118.5 (d, CHF_2, $^2J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.3 (N*C*N), 163.2 (*C*=O), 159.6 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.7 Hz), 154.4 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.7 Hz), 134.6 (1'-*C*), 133.0 (4'-*C*), 129.3 and 129.1 (2',3',5',6'-*C*), 120.7 (*C*COOEt), 120.2 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 112.3 (t, *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 63.5 (O*C*H$_2$), 13.9 (CH$_2$*C*H$_3$) ppm.
Anal calcd for $C_{15}H_{11}F_5N_2O_2$: C, 52.03; H, 3.20; F, 27.43; N, 8.09; O, 9.24. Found: C, 52.07; H, 3.19; N, 8.13.

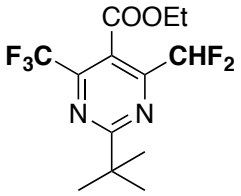
ethyl 4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.9)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 507 mg, 1.58 mmol), formamidine hydrochloride (1.97 equiv., 250 mg, 3.1 mmol) and Et_3N (2.96 equiv., 473 mg, 0.65 mL, 4.68 mmol) in abs. EtOH (2 mL). (30min in the micro-wave (High)). ^{19}F NMR yield: 35%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%), to give 138mg of colourless oil (32%).
^1H-NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, NC*H*N), 6.78 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz), 4.49 (q, OCH_2CH$_3$), 1.41 (t, OCH$_2$CH_3) ppm.

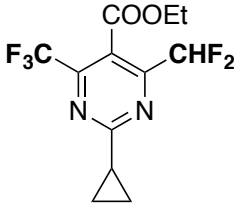
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.3 (s, CF_3), -118.6 (d, CHF_2, $^2J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.4 (*C*=O), 159.2 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26 Hz), 158.8 (N*C*HN), 153.9 (q, *C*CF$_3$, $^2J_{C-F}$ = 37 Hz), 123.8 (*C*COOEt), 120.0 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 111.8 (t, *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 63.8 (O*C*H$_2$CH$_3$), 13.8 (OCH$_2$*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_9H_7F_5N_2NaO$ [M+Na]$^+$: 293.0320. Found: 293.0307.

ethyl 2-(*tert*-butyl)-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.11)



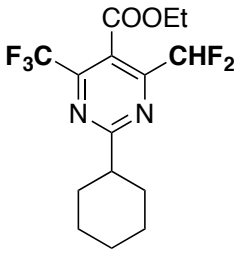
Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1.16 g, 3.61 mmol), *tert*-butylcarbamidine hydrochloride (2.15 equiv., 1.08 g, 7.75 mmol), Et_3N (2.99 equiv., 1.09 g, 1.5 mL, 10.8 mmol) in MeCN (8 mL). Internal standard: fluorobenzene (1.47 equiv., 0.51 g, 0.5 mL, 5.31 mmol). ^{19}F NMR yield: 99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%), to give 930 mg of colourless oil (79%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.71 (t, C*H*F$_2$, $^2J_{H-F}$ = 54.0 Hz), 4.46 (q, OC*H*$_2$CH$_3$), 1.44 (s, 9H, *t*Bu), 1.39 (t, OCH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.5 (s, CF_3), -118.0 (d, CHF_2, $^2J_{F-H}$ = 54.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179.2 (N*C*N), 163.4 (*C*=O), 158.7 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.7 Hz), 153.6 (q, *C*CF$_3$, $^2J_{C-F}$ = 36 Hz), 120.3 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 120.2 (*C*COOEt), 112.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 246 Hz), 63.4 (O*C*H$_2$CH$_3$), 40.3 (*C*(CH$_3$)$_3$), 29.2 (C(*C*H$_3$)$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{13}H_{16}F_5N_2O_2$ [M+H]$^+$: 327.1126. Found: 327.1150.

ethyl 2-cyclopropyl-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.13)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1.3 g, 4.05 mmol), cyclopropane-1-carboximidamide hydrochloride (2.01 equiv., 0.98 g, 8.13 mmol), Et_3N (3.02 equiv., 1.24 g, 1.7 mL, 12.2 mmol) in abs. EtOH (8 mL). ^{19}F NMR yield: 99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 10%), to give 750mg of colourless oil (60%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.65 (t, C*H*F$_2$, $^2J_{H-F}$ = 53.9 Hz), 4.39 (q, OCH$_2$CH$_3$), 2.40 (m, CC*H*), 1.33 (t, OCH$_2$CH$_3$), 1.22 (m, 4H, CH$_2$C*H*$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.8 (s, CF_3), -118.9 (d, CHF_2, $^2J_{F-H}$ = 54.0 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.4 (N*C*N), 163.3 (*C*=O), 159.0 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 153.7 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.4 Hz), 120.2 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 119.9 (*C*COOEt), 112.1 (t, *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 63.3 (O*C*H$_2$CH$_3$), 18.7 (*C*H), 13.7 (O*C*H$_2$CH$_3$), 13.0 (*C*H$_2$*C*H$_2$) ppm.
HRMS (ESI) calcd for $C_{12}H_{12}F_5N_2O_2$ [M+H]$^+$: 311.0813. Found: 311.0784.

ethyl 2-cyclohexyl-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.15)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 2 g, 6.22 mmol), cyclohexanecarboximidamide hydrochloride (1.98 equiv., 2 g, 12.3 mmol) and Et_3N (3.01 equiv., 1.89 g, 2.6 mL, 18.7 mmol) in abs. EtOH (12 mL). ^{19}F NMR yield: 18%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 10%), to give 320mg of colourless oil (15%).

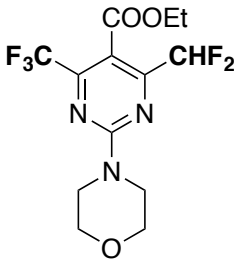
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.64 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 4.38 (q, OC*H*$_2$CH$_3$), 2.99 (tt, 1'-C*H*), 1.95 and 1.59 (d and qd, 2H + 2H, 2',6'-C*H*$_2$, ax/eq), 1.79 and 1.37 (d and m, 2H + 2H, 3',5'-C*H*$_2$, ax/eq), 1.69 and 1.25 (d and tt, 2H, 4'-C*H*$_2$, ax/eq), 1.32 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.4 (s, C*F*$_3$), -118.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 54 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.3 (N*C*N), 163.3 (CO), 159.0 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.7 Hz), 153.8 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.0 Hz), 120.6 (*C*COOEt), 120.2 (q, *C*F$_3$, $^1J_{C-F}$ = 277.4 Hz), 112.4 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.2 Hz), 63.5 (O*C*H$_2$CH$_3$), 47.2 (1'-*C*H), 31.6 (2',6,-*C*H$_2$), 26.0 (3',5'-*C*H$_2$), 25.8 (4'-*C*H$_2$), 13.9 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{15}H_{17}F_5N_2NaO_2$ $[M+Na]^+$: 375.1102. Found: 375.1098.

ethyl 4-(difluoromethyl)-2-morpholino-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.17)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1 g, 3.28 mmol), 4-morpholinecarboximidamide,hydriodide (1:1) (1.18 equiv., 1 g, 3.89 mmol) and Et_3N (2.85 equiv., 0.946 g, 1.3 mL, 9.35 mmol) in abs. EtOH (8 mL). Additional 15min and 15min at 70 °C were achieved. ^{19}F NMR yield: 83%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%), to give 350 mg of colourless solid (30%). M.p.: 78.5 - 79.0 °C.

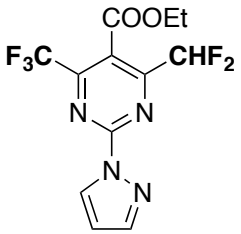
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.65 (t, C*H*F_2, $^2J_{H-F}$ = 54.1 Hz), 4.36 (q, OC*H*$_2$CH$_3$), 3.93 (m, 4H, C*H*$_2$OC*H*$_2$), 3.77 (m, C*H*$_2$NC*H*$_2$), 1.35 (OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -67.0 (s, C*F*$_3$), -120.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.9 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.2 (*C*=O), 160.9 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24.4 Hz), 160.0 (N*C*N), 155.5 (q, *C*CF$_3$, $^2J_{C-F}$ = 35.9 Hz), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 277.4 Hz), 111.4 (t, *C*HF$_2$, $^1J_{C-F}$ = 244.4 Hz), 111.1 (*C*COOEt), 66.7 (*C*H$_2$O*C*H$_2$), 62.7 (O*C*H$_2$CH$_3$), 44.5 (*C*H$_2$N*C*H$_2$), 13.8 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{13}H_{14}F_5N_3O_3$: C, 43.95; H, 3.97; F, 26.74; N, 11.83; O, 13.51. Found: C, 43.98; H, 4.01; N, 11.89.

ethyl 4-(difluoromethyl)-2-(1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.19)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1.1 g, 3.42 mmol), 1H-pyrazole-1-carboxamidine hydrochloride (2 equiv., 1 g, 6.82 mmol) and Et_3N (3.04 equiv., 1.05 g, 1.44 mL, 10.4 mmol) in abs. EtOH (8 mL). ^{19}F NMR yield: 65%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in cyclohexane 0 to 20%), to give 285mg of electrostatic colourless solid (25%) after trituration in pentane. M.p.: 93.3 - 93.7 °C.

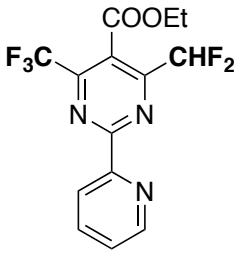
^1H-NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, 5'-C*H*), 7.93 (d, 3'-C*H*), 6.83 (t, CHF_2, $^2J_{H-F}$ = 53.5 Hz), 6.59 (dd, 4'-C*H*), 4.47 (q, OC*H*$_2$CH$_3$), 1.40 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.4 (s, C*F*$_3$), -118.5 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.0 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.3 (*C*=O), 162.1 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26.5 Hz), 156.3 (q, *C*CF$_3$, $^2J_{C-F}$ = 37.5 Hz), 155.1 (N*C*N), 146.1 (3'-*C*), 130.5 (5'-*C*), 120.4 (*C*COOEt), 119.7 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 111.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 246.5 Hz), 110.7 (4'-*C*), 63.8 (O*C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{12}H_9F_5N_4O_2$: C, 42.87; H, 2.70; F, 28.25; N, 16.66; O, 9.52. Found: C, 42.97; H, 2.81; N, 16.51.

ethyl 4-(difluoromethyl)-2-(pyridin-2-yl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.20)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1000 mg, 3.11 mmol), pyridine-2-carboximidamide hydrochloride (1.2 equiv., 590 mg, 3.74 mmol) and Et_3N (3.01 equiv., 946 mg, 1.3 mL, 9.35 mmol) in abs. EtOH (8 mL). ^{19}F NMR yield: 99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%), to give 890mg of greenish solid (82%). M.p.: 100.0 - 100.5 °C.

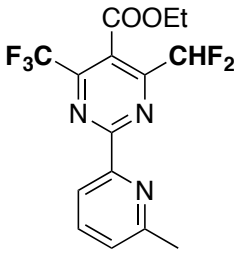
^1H-NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, 6'-C*H*), 8.63 (d, 3'-C*H*), 7.95 (td, 4'-C*H*), 7.52 (ddd, 5'-C*H*), 6.93 (t, C*H*F$_2$, $^2J_{H-F}$ = 53.6 Hz), 4.50 (q, OC*H*$_2$CH$_3$), 1.42 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.2 (s, C*F*$_3$), -117.5 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.9 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.0 and 162.7 (N*C*N and *C*=O), 160.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26.5 Hz), 154.7 (q, *C*CF$_3$, $^2J_{C-F}$ = 37 Hz), 152.0 (2'-*C*), 150.9 (6'-*C*H), 137.5, 126.5, 125.2 (3',4',5'-*C*H), 122.2 (*C*COOEt), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 277.6 Hz), 112.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.5 Hz), 63.7 (O*C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{14}H_{10}F_5N_3O_2$: C, 48.43; H, 2.90; F, 27.36; N, 12.10; O, 9.21. Found: C, 48.62; H, 3.00; N, 12.16.

ethyl 4-(difluoromethyl)-2-(6-methylpyridin-2-yl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.22)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 500 mg, 1.64 mmol), 6-methylpyridine-2-carboximidamide hydrochloride (1.14 equiv., 320 mg, 1.86 mmol) and Et_3N (2.85 equiv., 473 mg, 0.65 mL, 4.68 mmol) in abs. EtOH (2 mL). ^{19}F NMR yield: 89%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 25%), to give 562mg of green solid (95%). M.p.: 87.0 - 87.5 °C.

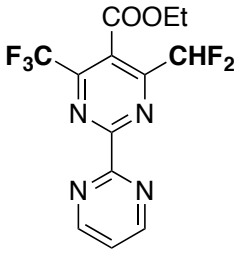
^1H-NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, 1H, 5'-C*H*), 7.79 (t, 1H, 4'-C*H*), 7.36 (d, 1H, 3'-C*H*), 6.92 (t, C*H*F_2, $^2J_{H-F}$ = 53.7 Hz), 4.48 (q, OC*H*$_2$CH$_3$), 2.72 (s, CH*3*), 1.40 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.1 (s, C*F*$_3$), -117.6 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.3 and 162.8 (N*C*N and *C*=O), 160.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 27 Hz), 160.0 (2'-*C*), 154.7 (q, *C*CF$_3$, $^2J_{C-F}$ = 37 Hz), 151.6 (6'-*C*), 137.5, 126.5, 122.6 (3',4',5'-*C*H), 122.1 (*C*COOEt), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 277.6 Hz), 112.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.5 Hz), 63.6 (O*C*H$_2$CH$_3$), 25.0 (*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{15}H_{12}F_5N_3O_2$: C, 49.87; H, 3.35; F, 26.29; N, 11.63; O, 8.86. Found: C, 50.01; H, 3.43; N, 11.52.

ethyl 4-(difluoromethyl)-6-(trifluoromethyl)-[2,2'-bipyrimidine]-5-carboxylate (III.24)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1 g, 3.11 mmol), Et_3N (3.01 equiv., 0.946 g, 1.3 mL, 9.35 mmol) and pyrimidine-2-carboximidamide hydrochloride (2.03 equiv., 1 g, 6.31 mmol) in abs. EtOH (8 mL). ^{19}F NMR yield: 99%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in cyclohexane 0 to 100%), to give 720mg of a colourless solid (66%). M.p.: 165.6 - 166.5 °C.

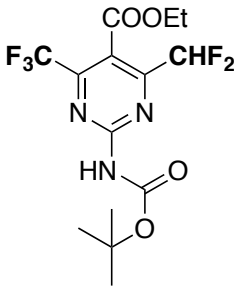
^1H-NMR (400 MHz, $CDCl_3$): δ = 9.08 (d, 4',6'-C*H*), 7.53 (t, 5'-C*H*), 6.95 (t, C*H*F_2, $^2J_{H-F}$ = 53.5 Hz), 4.52 (q, OC*H*$_2$CH$_3$), 1.42 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -65.9 (s, C*F*$_3$), -117.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.3 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.8 and 162.5 (N*C*N and N'*C*'N'), 160.6 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26.6 Hz), 160.5 (*C*=O), 158.5 (4',6'-*C*), 155.3 (q, *C*CF$_3$, $^2J_{C-F}$ = 37.4 Hz), 123.5 (*C*COOEt), 122.5 (5'-*C*), 120.0 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 112.5 (t, *C*HF$_2$, $^1J_{C-F}$ = 246 Hz), 63.9 (O*C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{13}H_9F_5N_4O_2$: C, 44.84; H, 2.61; F, 27.28; N, 16.09; O, 9.19. Found: C, 44.89; H, 2.68; N, 16.12.

ethyl 2-((*tert*-butoxycarbonyl)amino)-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.26)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 2 g, 6.22 mmol), Et_3N (3.04 equiv., 1.89 g, 2.6 mL, 18.7 mmol) and *tert*-butyl N-(diaminomethylidene)carbamate (2.02 equiv., 2 g, 12.56 mmol) in abs. EtOH (4 mL). The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 15%), to give 1.35g of colourless oil (56%).

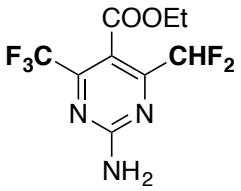
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, N*H*), 6.70 (t, C*H*F_2, $^2J_{H-F}$ = 53.7 Hz), 4.40 (q, OC*H*$_2$CH$_3$), 1.52 (s, 9H, *t*Bu), 1.35 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.7 (s, C*F*$_3$), -119.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.9 (*C*=O), 161.2 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 157.5 (N*C*N), 155.5 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.9 Hz), 149.5 (NH*C*=O), 119.8 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 117.6 (*C*COOEt), 116.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.5 Hz), 83.2 (*C*(CH$_3$)$_3$), 63.4 (O*C*H$_2$CH$_3$), 28.1 (C(*C*H$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{14}H_{16}F_5N_3NaO_4$ $[M+Na]^+$: 408.0953. Found: 408.0904.

ethyl 2-amino-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.27)



A solution of **III.26** (1 equiv., 440 mg, 1.14 mmol) and cat. TFA (few drops) in DCM (5 mL) was stirred at room temperature for 18 h. The mixture was evaporated *in vacuo*, to yield the pure product as a colourless solid (325mg, 99%). M.p.: 82.5 - 82.8 °C.

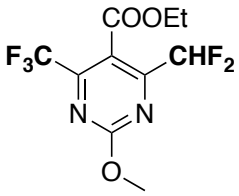
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.70 (t, C*H*F_2, $^2J_{H-F}$ = 54.0 Hz), 6.16 (s br, N*H*$_2$), 4.39 (q, OC*H*$_2$CH$_3$), 1.36 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.9 (s, C*F*$_3$), -120.5 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.9 and 162.2 (N*C*N and *C*=O), 161.5 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24.1 Hz), 156.0 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.3 Hz), 120.0 (q, *C*F$_3$, $^1J_{C-F}$ = 277.3 Hz), 113.4 (*C*COOEt), 110.8 (t, *C*HF$_2$, $^1J_{C-F}$ = 244.6 Hz), 63.1 (O*C*H$_2$CH$_3$), 13.8 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_9H_8F_5N_3O_3$: C, 37.91; H, 2.83; F, 33.31; N, 14.74; O, 11.22. Found: C, 37.76; H, 2.86; N, 14.75.

ethyl 4-(difluoromethyl)-2-methoxy-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.28)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 500 mg, 1.73 mmol), *O*-Methylisourea hydrochloride (1.8 equiv., 344 mg, 3.11 mmol) and Et_3N (2.7 equiv., 473 mg, 0.65 mL, 4.68 mmol) in MeCN (4 mL). ^{19}F NMR yield: 90%. The mixture was concentrated *in vacuo*. The crude purified by flash chromatography (AcOEt in cyclohexane 0 to 2%), to give 400mg of colourless oil (77%).

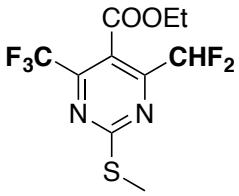
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.68 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 4.41 (q, OC*H*$_2$), 4.13 (s, C*H*$_3$), 1.35 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.8 (s, C*F*$_3$), -119.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.0 (N*C*N), 163.0 (*C*=O), 162.5 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.7 Hz), 156.7 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.8 Hz), 119.7 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 117.4 (*C*COOEt), 111.4 (t, *C*HF$_2$, $^1J_{C-F}$ = 245 Hz), 63.4 (OCH$_2$), 56.5 (O*C*H$_3$), 13.7 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_{10}H_9F_5N_2O_3$: C, 40.01; H, 3.02; F, 31.64; N, 9.33; O, 15.99. Found: C, 39.57; H, 3.07; N, 9.45.

ethyl 4-(difluoromethyl)-2-(methylthio)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.29)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 500 mg, 1.56 mmol), Et_3N (3.01 equiv., 473 mg, 0.65 mL, 4.68 mmol) and 2-methyl-2-thiopseudourea sulfate (1.19 equiv., 516 mg, 1.85 mmol) in abs. EtOH (2 mL). ^{19}F NMR yield: 79%. The mixture was filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 20%), to give 157mg of colourless oil (32%).

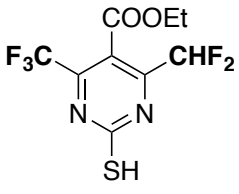
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.69 (t, C*H*F_2, $^2J_{H-F}$ = 53.9 Hz), 4.44 (q, 2H, OC*H*$_2$CH$_3$), 2.65 (s, SC*H*$_3$), 1.38 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.6 (s, C*F*$_3$), -119.0 (d, CH*F*$_2$, $^2J_{F-H}$ = 54 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.5 (N*C*N), 163.0 (*C*=O), 159.3 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.8 Hz), 154.0 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.6 Hz), 120.0 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 118.0 (*C*COOEt), 116.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 246 Hz), 63.5 (O*C*H$_2$CH$_3$), 14.6 (S*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{10}H_{10}F_5N_2O_2S$ $[M+H]^+$: 317.0378. Found: 317.0353.

ethyl 4-(difluoromethyl)-2-mercapto-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.30)



Same procedure than **III.5A.a** from **III.2A.a** (1 equiv., 1000 mg, 3.11 mmol), Et_3N (3 equiv., 946 mg, 1.3 mL, 9.35 mmol) and thiourea (2 equiv., 474 mg, 6.23 mmol) in MeCN (5 mL). ^{19}F NMR yield: 46%. The mixture was evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 100%, and secondly MeOH in DCM 0 to 2%), to give 70mg of brown residue (7%).

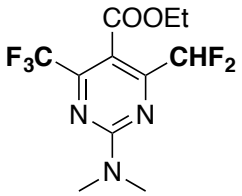
^1H-NMR (400 MHz, $CDCl_3$): δ = 6.66 (t, C*H*F_2, $^2J_{H-F}$ = 53.6 Hz), 4.88 (s br, S*H*), 4.44 (q, OC*H*$_2$CH$_3$), 1.38 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.6 (s, C*F*$_3$), -119.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.7 (N*C*(SH)N), 162.6 (*C*=O), 159.7 (t, *C*CHF$_2$, $^2J_{C-F}$ = 26.3 Hz), 154.2 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.4 Hz), 119.6 (q, *C*F$_3$, $^1J_{C-F}$ = 276.8 Hz), 119.0 (*C*COOEt), 111.2 (t, *C*HF$_2$, $^1J_{C-F}$ = 246.2 Hz), 63.5 (O*C*H$_2$CH$_3$), 13.7 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_9H_7F_5N_2NaO_2S$ $[M+Na]^+$: 325.0041. Found: 325.0026.

ethyl 4-(difluoromethyl)-2-(dimethylamino)-6-(trifluoromethyl)pyrimidine-5-carboxylate (III.33)



Isolated after separation from **III.29** by flash chromatography (**III.33** more polar).

^1H-NMR (400 MHz, $CDCl_3$): δ = 6.65 (t, C*H*F_2, $^2J_{H-F}$ = 54.2 Hz), 4.36 (q, OC*H*$_2$), 3.27 (s, N(C*H*$_3$)$_2$), 1.35 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -67.0 (s, C*F*$_3$), -120.0 (d, CH*F*$_2$, $^2J_{F-H}$ = 54.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.6 and 160.7 (N*C*N and *C*=O), 160.6 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24.6 Hz), 155.3 (q, *C*CF$_3$, $^2J_{C-F}$ = 35.7 Hz), 120.3 (q, *C*F$_3$, $^1J_{C-F}$ = 276 Hz), 111.7 (t, *C*HF$_2$, $^1J_{C-F}$ = 244 Hz), 110.0 (*C*COOEt), 62.6 (O*C*H$_2$), 37.2 (N(*C*H$_3$)$_2$), 13.9 (OCH$_2$*C*H$_3$) ppm.

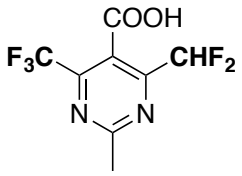
HRMS (ESI) calcd for $C_{11}H_{13}F_5N_3O_2$ [M+H]: 314.0922. Found: 314.0950.

Preparation of 4,6-bis(fluoroalkyl)pyrimidine-5-carboxylic acids

General procedure: Example of **5a**

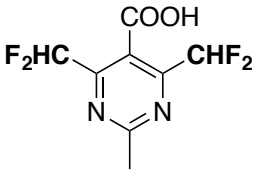
A solution of **III.5A.a** (1 equiv., 1305 mg, 4.59 mmol) was saponified in abs. EtOH (10 mL) in EtOH (10 mL) using NaOH 2N (3 equiv., 2 M, 7 mL, 14 mmol). The mixture was stirred for 18 h. The mixture was acidified with aq. HCl 2N solution until pH 2-3 and then extracted with DCM. The organic layer was evaporated *in vacuo*, to yield 4-(difluoromethyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (1.09 g, 4.26 mmol, 93 %) as a colourless solid after trituration in pentane.
All examples were saponified using the same conditions, starting from the corresponding esters.

4-(difluoromethyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.6A.a)



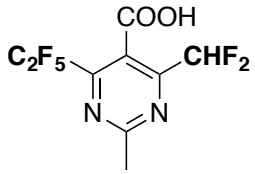
Colourless solid (1.09g, 93%). M.p.: 164.0 - 165.4 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.5 (COO*H*), 7.18 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 53.4 Hz), 2.82 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -65.4 (s, C*F*$_3$), -119.2 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 168.8 and 164.2 (N*C*N and *C*=O), 158.3 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 24.7 Hz), 151.7 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 35.4 Hz), 121.4 (*C*COOH), 120.1 (q, *C*F$_3$, $^{1}J_{C-F}$ = 277 Hz), 151.6 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243 Hz), 25.4 (*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_8H_6F_5N_2O_2$ [M+H]$^+$: 257.0344. Found: 257.0344.

4,6-bis(difluoromethyl)-2-methylpyrimidine-5-carboxylic acid (III.6A.b)



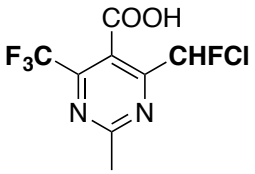
Colourless solid (180mg, 99%). M.p.: 137.4 - 139.6 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.4 (s br, COO*H*), 7.24 (t, 2 x C*H*F$_2$, $^{2}J_{H-F}$ = 53 Hz), 2.80 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -119.4 (d, 2 x CH*F*$_2$, $^{2}J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 168.9 (N*C*N), 164.5 (*C*=O), 158.2 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 23.7 Hz), 121.5 (m, *C*COOH), 111.0 (t, 2 x *C*HF$_2$, $^{1}J_{C-F}$ = 241 Hz), 25.6 (*C*H$_3$) ppm.
Anal. calcd for $C_8H_6F_4N_2O_2$: C, 40.35; H, 2.54; F, 31.91; N, 11.76; O, 13.44. Found: C, 40.68; H, 2.77; N, 11.30.

4-(difluoromethyl)-2-methyl-6-(perfluoroethyl)pyrimidine-5-carboxylic acid (III.6A.c)



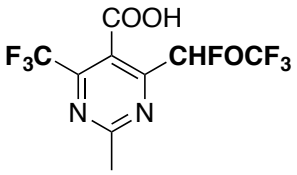
Colourless solid (154mg, 99%). M.p.: 159.9 - 160.5 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.6 (s.br, COO*H*), 7.16 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 53.4 Hz), 2.81 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -80.6 (s, C*F*$_3$), -112.8 (s, C*F*$_2$), -119.0 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.3 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 168.3 and 164.1 (N*C*N and *C*=O), 158.3 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25 Hz), 151.3 (t, *C*C$_2$F$_5$, $^{2}J_{C-F}$ = 26.5 Hz), 123.3 (*C*COOH), 118.1 (qt, *C*F$_3$CF$_2$, $^{1}J_{C-F}$ = 287 Hz, $^{2}J_{C-F}$ = 35.4 Hz), 111.7 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243.3 Hz), 110.8 (tq, *C*F$_2$CF$_3$, $^{1}J_{C-F}$ = 257.4 Hz, $^{2}J_{C-F}$ = 38.6 Hz), 25.5 (*C*H$_3$) ppm.
Anal. calcd for $C_9H_5F_7N_2O_2$: C, 35.31; H, 1.65; F, 43.44; N, 9.15; O, 10.45. Found: C, 35.30; H, 1.77; N, 9.06.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow evaporation of a concentrated solution in Et_2O/DCM.

4-(chlorofluoromethyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.6B.a)



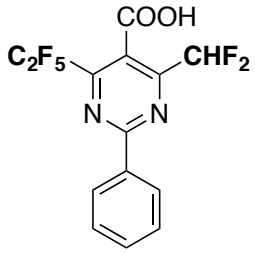
Colourless solid (125mg, 55%). M.p.: 163.4 - 165.5 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.4 (s br, COO*H*), 7.75 (d, C*H*FCl, $^{2}J_{H-F}$ = 47.8 Hz), 2.81 (s, C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -65.3 (s, C*F*$_3$), -142.3 (d, 2 x CH*F*$_2$, $^{2}J_{F-H}$ = 47.8 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 168.8 (N*C*N), 164.1 (*C*OOH), 161.3 (d, *C*CHFCl, $^{2}J_{C-F}$ = 23.4 Hz), 151.8 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 35.3 Hz), 120.3 (m, *C*COOH), 120.1 (q, *C*F$_3$, $^{1}J_{C-F}$ = 276 Hz), 96.7 (d, *C*HFCl, $^{1}J_{C-F}$ = 247 Hz), 25.5 (*C*H$_3$) ppm.
Anal. calcd for $C_8H_5ClF_4N_2O_2$: C, 35.25; H, 1.85; Cl, 13.01; F, 27.88; N, 10.28; O, 11.74. Found: C, 36.03; H, 2.07; N, 10.24.

4-(fluoro(trifluoromethoxy)methyl)-2-methyl-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.6D.a)



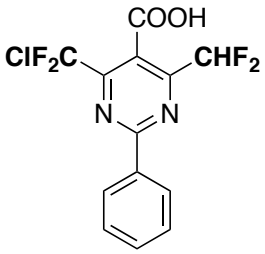
Colourless solid (408mg, 89%). M.p.: 107.3 - 108.8 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.30 (s.br, COO*H*), 7.41 (d, C*H*FOCF_3, $^{2}J_{H-F}$ = 54.7 Hz), 2.83 (s, CCH_3) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -58.1 (d, CHFOC*F*$_3$, $^{4}J_{F-F}$ = 4.7 Hz), -65.4 (s, *C*F$_3$), -132.2 (dq, CH*F*OCF$_3$, $^{2}J_{F-H}$ = 54.8 Hz, $^{4}J_{F-F}$ = 4.6 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 168.9 (N*C*N), 164.1 (*C*OOH), 157.6 (d, *C*CHFOCF3, $^{2}J_{C-F}$ = 24.8 Hz), 152.0 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 35.6 Hz), 121.6 (*C*COOH), 120.6 (q, O*C*F$_3$, $^{1}J_{C-F}$ = 261.5 Hz), 120.1 (q, *C*F$_3$, $^{1}J_{C-F}$ = 276.6 Hz), 102.2 (dq, *C*HFOCF$_3$, $^{1}J_{C-F}$ = 235.6 Hz, $^{5}J_{C-F}$ = 3.0 Hz), 25.5 (C*C*H$_3$) ppm.
Anal. calcd for $C_9H_5F_7N_2O_3$: C, 33.56; H, 1.56; F, 41.28; N, 8.70; O, 14.90. Found: C, 33.89; H, 1.73; N, 8.64.

4-(perfluoroethyl)-2-phenyl-6-(difluoromethyl)pyrimidine-5-carboxylic acid (III.8A.c)



Colourless solid (105mg, 77%). M.p.: 214.5 - 214.8 °C.
^{1}H-NMR (400 MHz, MeOD-d_4): δ = 8.50 (d, 2',6'-C*H*), 7.56 (m, 3',4',5'-C*H*), 7.02 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 53.5 Hz) ppm.
^{19}F-NMR (376 MHz, MeOD-d_4): δ = -82.7 (s, C*F*$_3$), -114.2 (s, C*F*$_2$), -120.5 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.1 Hz) ppm.
^{13}C-NMR (100 MHz, MeOD-d_4): δ = 166.0 and 165.7 (N*C*N and *C*OOH), 161.2 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25.2 Hz), 154.8 (t, *C*C$_2$F$_5$, $^{2}J_{C-F}$ = 26.9 Hz), 136.1, 134.0, 130.2, 130.0 (*C*$_{arom.}$), 124.5 (*C*COOH), 120.2 (qt, *C*F$_3$CF$_2$, $^{1}J_{C-F}$ = 286.6 Hz, $^{2}J_{C-F}$ = 35.9 Hz), 113.7 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243.8 Hz), 112.7 (tq, *C*F$_2$CF$_3$, $^{1}J_{C-F}$ = 257.9 Hz, $^{2}J_{C-F}$ = 38.0 Hz) ppm.
HRMS (ESI) calcd for $C_{14}H_8F_7N_2O_2$ $[M+H]^+$: 369.0469. Found: 369.0430.

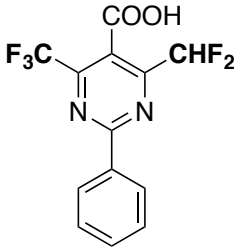
4-(chlorodifluoromethyl)-2-phenyl-6-(difluoromethyl)pyrimidine-5-carboxylic acid (III.8A.d)



A solution of *tert*-butyl 4-(chlorodifluoromethyl)-6-(difluoromethyl)-2-phenylpyrimidine-5-carboxylate (1 equiv., 150 mg, 0.384 mmol) in HCOOH (1 mL) was stirred 18 h at 50 °C. The solution was evaporated *in vacuo*, to 80mg of colourless solid (62%) after trituration in pentane. M.p.: 195.2 - 196.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.6 (s br, COO*H*), 8.47 (d, 2',6'-C*H*), 7.65 to 7.56 (m, 3',4',5'-C*H*), 6.98 (t, C*H*F$_2$, $^{2}J_{H-F}$ = 53.3 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.4 (s, C*F*$_2$Cl), -120.0 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 53.2 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.7 and 164.7 (N*C*N and *C*=O), 160.3 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25 Hz), 158.3 (t, *C*CF$_2$Cl, $^{2}J_{C-F}$ = 30 Hz), 135.9, 133.7, 130.1, 129.6 (*C*$_{Phenyl}$), 124.2 (t, *C*F$_2$Cl, $^{1}J_{C-F}$ = 291 Hz), 120.4 (*C*COOH), 113.1 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243 Hz) ppm.

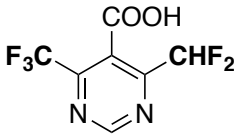
Anal. calcd for $C_{13}H_7ClF_4N_2O_2$: C, 46.66; H, 2.11; Cl, 10.59; F, 22.71; N, 8.37; O, 9.56. Found: C, 46.16; H, 2.18; N, 8.25.

4-(difluoromethyl)-2-phenyl-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.8A.a)



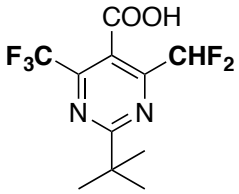
Colourless solid (240mg, 97%). M.p.: 262.5 - 263.0 °C.
^{1}H-NMR (400 MHz, CD_3CN): δ = 8.45 (m, 2H, 2',6'-C*H*), 8.16 (s.br, COO*H*), 7.63 to 7.54 (m, 3H, 3',4',5'-C*H*), 7.02 (t, C*H*F_2, $^2J_{H-F}$ = 53.5 Hz) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -67.2 (s, C*F*$_3$), -120.5 (d, CH*F*$_2$, $^2J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 166.0 (N*C*N), 165.1 (*C*OOH), 160.0 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24.3 Hz), 154.0 (*C*CF$_3$, $^2J_{C-F}$ = 36 Hz), 136.2 (1'-*C*), 133.5 (4'-*C*), 130.1 and 129.6 (2',3',5',6'-*C*), 124.6 (*C*COOH), 121.6 (q, *C*F$_3$, $^1J_{C-F}$ = 276 Hz), 112.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 243 Hz) ppm.
HRMS (ESI) calcd for $C_{13}H_8F_5N_2O_2$ $[M+H]^+$: 319.0500. Found: 319.0488.

4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.10)



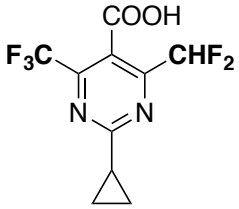
Yellow solid (110mg, 94%). M.p.: 141.0 - 142.5 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.7 (s br, COO*H*), 9.66 (2-C*H*), 7.22 (t, C*H*F_2, $^2J_{H-F}$ = 52.8 Hz) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -65.5 (s, C*F*$_3$), -119.4 (d, CH*F*$_2$, $^2J_{F-H}$ = 52.5 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 163.8 and 158.8 (N*C*N and *C*OOH), 158.2 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24.7 Hz), 151.6 (q, *C*CF$_3$, $^2J_{C-F}$ = 35.7 Hz), 124.3 (*C*COOH), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 276.4 Hz), 111.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 242.7 Hz) ppm.
HRMS (ESI) calcd for $C_7H_4F_5N_2O_2$ $[M+H]^+$: 243.0187. Found: 243.0199.

2-(*tert*-butyl)-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.12)



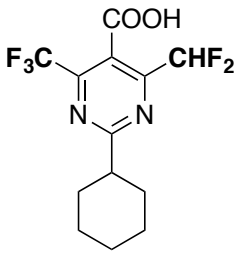
Colourless solid (259mg, 92%). M.p.: 101 - 102 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.45 (*s* br, COO*H*), 6.78 (t, C*H*F_2, $^{2}J_{H-F}$ = 54 Hz), 1.47 (s, 9H, C(C*H*$_3$)$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.3 (s, C*F*$_3$), -117.5 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179.9 (N*C*N), 169.2 (*C*OOH), 158.8 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 28.4 Hz), 153.7 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 36.6 Hz), 120.2 (q, *C*F$_3$, $^{1}J_{C-F}$ = 276.6 Hz), 118.8 (*C*COOH), 112.6 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 246.0 Hz), 40.5 (*C*(CH$_3$)$_3$), 29.3 (C(*C*H$_3$)$_3$) ppm.
Anal. calcd for $C_{11}H_{11}F_5N_2O_2$: C, 44.30; H, 3.72; F, 31.85; N, 9.39; O, 10.73. Found: C, 44.49; H, 3.90; N, 9.43.

2-cyclopropyl-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.14)



Colourless solid (351mg, 99%). M.p.: 107.0 - 108.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.7 (s br, COO*H*), 6.74 (t, C*H*F_2, $^{2}J_{H-F}$ = 54 Hz), 2.47 (m, CC*H*), 1.32 (m, 4H, C*H*$_2$C*H*$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.4 (s, C*F*$_3$), -118.3 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.1 (N*C*N), 168.4 (*C*=O), 159.0 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25.9 Hz), 154.0 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 36.4 Hz), 120.0 (q, *C*F$_3$, $^{1}J_{C-F}$ = 277 Hz), 118.6 (*C*COOH), 112.0 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 245 Hz), 18.9 (C*C*H), 13.7 (*C*H$_2$*C*H$_2$) ppm.
Anal. calcd for $C_{10}H_7F_5N_2O_2$: C, 42.57; H, 2.50; F, 33.66; N, 9.93; O, 11.34. Found: C, 42.80; H, 2.59; N, 9.84.

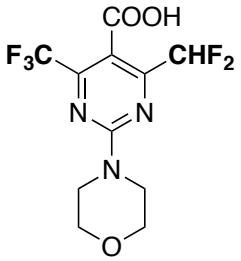
2-cyclohexyl-4-(difluoromethyl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.16)



Colourless solid (145mg, 98%). M.p.: 139.5 - 140.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.79 (br s, COO*H*), 6.78 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.8 Hz), 3.10 (tt, 1'-C*H*), 2.06 and 1.69 (d and qd, 4H, 2',6,-C*H*$_2$, ax/eq), 1.88 and 1.44 (dt and qt, 4H, 3',5'-C*H*$_2$, ax/eq), 1.77 and 1.33 (d and tt, 2H, 4'-C*H*$_2$, ax/eq) ppm.

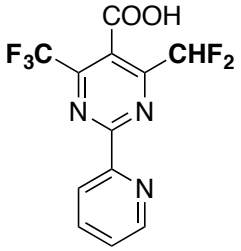
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -66.2 (s, CF_3), -117.9 (d, CHF_2, $^2J_{F-H}$ = 54 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.9 (N*C*N), 168.3 (CO), 159.1 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25.9 Hz), 154.0 (q, *C*CF$_3$, $^2J_{C-F}$ = 36.5 Hz), 120.1 (q, *C*F$_3$, $^1J_{C-F}$ = 277.4 Hz), 119.4 (*C*COOH), 112.3 (t, *C*HF$_2$, $^1J_{C-F}$ = 245.6 Hz), 47.2 (1'-*C*H), 31.6 (2',6,-*C*H$_2$), 26.0 (3',5'-*C*H$_2$), 25.8 (4'-*C*H$_2$) ppm.
Anal. calcd for $C_{13}H_{13}F_5N_2O_2$: C, 48.15; H, 4.04; F, 29.30; N, 8.64; O, 9.87. Found: C, 48.52; H, 4.16; N, 8.57.

4-(difluoromethyl)-2-morpholino-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.18)



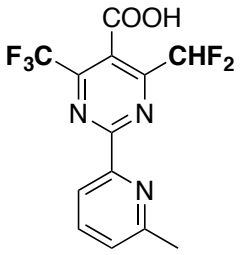
Colourless solid (263mg, 99%). M.p.: 242.2 - 243.1 °C.
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 14.0 (s.br, COO*H*), 7.04 (t, C*H*F$_2$, $^2J_{H-F}$ = 53.4 Hz), 3.81 (m, C*H*$_2$OC*H*$_2$), 3.69 (m, C*H*$_2$NC*H*$_2$) ppm.
^{19}F-NMR (376 MHz, DMSO-d$_6$): δ = -65.9 (s, C*F*$_3$), -120.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 53.8 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 164.9 (N*C*N), 160.2 (t, *C*CHF$_2$, $^2J_{C-F}$ = 24 Hz), 159.3 (*C*OOH), 153.6 (q, *C*CF$_3$, $^2J_{C-F}$ = 34.9 Hz), 120.0 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 111.7 (*C*COOH), 111.0 (t, *C*HF$_2$, $^1J_{C-F}$ = 242.4 Hz), 65.6 (*C*H$_2$O*C*H$_2$), 44.0 (*C*H$_2$N*C*H$_2$) ppm.
Anal. calcd for $C_{11}H_{10}F_5N_3O_3$: C, 40.38; H, 3.08; F, 29.03; N, 12.84; O, 14.67. Found: C, 40.53; H, 3.17; N, 12.75.

4-(difluoromethyl)-2-(pyridin-2-yl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.21)



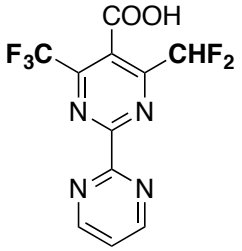
Colourless solid (460mg, 99%). M.p.: 202.4 - 203.6 °C.
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 14.1 (s.br, COO*H*), 8.85 (d, 6'-C*H*), 8.47 (d, 3'-C*H*), 8.09 (t, 4'-C*H*), 7.66 (dd, 5'-C*H*), 7.32 (t, C*H*F$_2$, $^2J_{H-F}$ = 52.8 Hz) ppm.
^{19}F-NMR (376 MHz, DMSO-d$_6$): δ = -65.3 (s, C*F*$_3$), -119.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 53 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 164.0 and 162.9 (*C*OOH and N*C*N), 159.2 (t, *C*CHF$_2$, $^2J_{C-F}$ = 25 Hz), 152.6 (q, *C*CF$_3$, $^2J_{C-F}$ = 35.7 Hz), 151.7 (2'-*C*), 150.2 (6'-*C*), 137.8 (4'-*C*), 126.6 (5'-*C*), 124.6 (3'-*C*), 123.0 (*C*COOH), 120.2 (q, *C*F$_3$, $^1J_{C-F}$ = 277 Hz), 111.8 (t, *C*HF$_2$, $^1J_{C-F}$ = 243 Hz) ppm.
Anal. calcd for $C_{12}H_6F_5N_3O_2$: C, 45.16; H, 1.89; F, 29.76; N, 13.16; O, 10.02. Found: C, 45.03; H, 1.99; N, 13.24.

4-(difluoromethyl)-2-(6-methylpyridin-2-yl)-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (III.23)



Colourless solid (265mg, 96%). M.p.: 202.3 - 202.8 °C.
^{1}H-NMR (400 MHz, MeOD-d_4): δ = 8.52 (d, 3'-C*H*), 8.10 (t, 4'-C*H*), 7.64 (d, 5'-C*H*), 7.08 (t, C*H*F_2, $^{2}J_{H-F}$ = 53.3 Hz), 2.76 (s, CH_3) ppm.
^{19}F-NMR (376 MHz, MeOD-d_4): δ = -67.6 (s, CF_3), -120.3 (d, CHF_2, $^{2}J_{F-H}$ = 53.4 Hz) ppm.
^{13}C-NMR (100 MHz, MeOD-d_4): δ = 165.9 (*C*OOH), 163.0 (N*C*N), 161.1 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 25.5 Hz), 160.3 (6'-*C*), 154.9 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 36.5 Hz), 151.5 (2'-*C*), 141.2 (4'-*C*), 128.6 (3'-*C*), 126.1 (*C*COOH), 123.9 (5'-*C*), 121.7 (q, *C*F$_3$, $^{1}J_{C-F}$ = 276 Hz), 113.2 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 244 Hz), 23.1 (*C*H$_3$) ppm.
HRMS (ESI) calcd for $C_{13}H_9F_5N_3O_3$ [M+H]$^+$: 334.0609. Found: 334.0580.

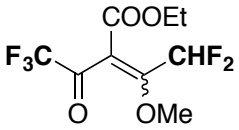
4-(difluoromethyl)-6-(trifluoromethyl)-[2,2'-bipyrimidine]-5-carboxylic acid (III.25)



Colourless solid (400mg, 99%). M.p.: 227.5 - 228.1 °C .
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.4 (s br, COO*H*), 9.12 (d, 4',6'-C*H*), 7.77 (t, 5'-C*H*), 7.33 (t, C*H*F_2, $^{2}J_{H-F}$ = 52.9 Hz) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -65.1 (s, CF_3), -119.0 (d, CHF_2, $^{2}J_{F-H}$ = 52.9 Hz) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 163.9, 162.0 and 160.0 (*C*OOH, N*C*N and N'*C*'N'), 159.4 (t, *C*CHF$_2$, J = 25.2 Hz), 158.3 (4',6'-*C*), 152.7 (q, *C*CF$_3$, $^{2}J_{C-F}$ = 35.9 Hz), 123.9 (*C*COOH), 122.8 (5'-*C*), 120.2 (q, *C*F$_3$, $^{1}J_{C-F}$ = 277 Hz), 111.8 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243 Hz) ppm.
Anal. calcd for $C_{11}H_5F_5N_4O_2$: C, 41.26; H, 1.57; F, 29.67; N, 17.50; O, 9.99. Found: C, 41.49; H, 1.89; F, N, 17.13.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow evaporation of a concentrated solution in Et_2O/DCM.

Side-products

ethyl 4,4-difluoro-3-methoxy-2-(2,2,2-trifluoroacetyl)but-2-enoate (III.34a)



A mixture of **III.2A.a** (1 equiv., 400 mg, 1.18 mmol), urea (1.01 equiv., 71 mg, 1.18 mmol), NaOMe (2.05 equiv., 130 mg, 2.41 mmol) and MS 4A (minor excess) in EtOH (2 mL) was heated at 50 °C for 30min in the μ-wave (High).

The mixture was filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in Et_2O 0 to 20%). Yield: 284mg of colourless solidifying oil (84%).

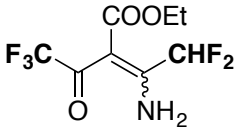
^{1}H-NMR (400 MHz, MeOD-d_4): δ = 6.54 (t, C*H*F_2, $^2J_{H-F}$ = 55.1 Hz), 4.13 (q, OC*H*$_2$CH$_3$), 3.35 (s, OC*H*$_3$), 1.26 (t, OCH$_2$C*H*$_3$) ppm.

^{19}F-NMR (376 MHz, MeOD-d_4): δ = -73.5 (s, C*F*$_3$), -127.8 (d, CH*F*$_2$, $^2J_{F-H}$ = 55 Hz) ppm.

^{13}C-NMR (100 MHz, MeOD-d_4): δ = 184.7 (t, *C*CHF$_2$, $^2J_{C-F}$ = 22.5 Hz), 177.5 (q, *C*OCF$_3$, $^2J_{C-F}$ = 32 Hz), 170.7 (*C*=O), 119.6 (q, *C*F$_3$, $^1J_{C-F}$ = 290 Hz), 110.0 (t, *C*HF$_2$, $^1J_{C-F}$ = 242 Hz), 103.1 (*C*COOEt), 61.3 (O*C*H$_2$CH$_3$), 49.8 (O*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_9H_{10}F_5O_4$ [M+H]: 277.0494. Found: 277.0477.

ethyl 3-amino-4,4-difluoro-2-(2,2,2-trifluoroacetyl)but-2-enoate (III.34b)



A mixture of **III.2A.a** (1 equiv., 500 mg, 1.64 mmol), chloroethanimidamide hydrochloride (2.12 equiv., 450 mg, 3.49 mmol) in HFIP (8 mL) was stirred at 70 °C for 15 min in the microwave. The mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%). Yield: 420mg of colourless solid (98%), ratio E/Z *ca*. 2:1. M.p.: 43.5 - 45.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.4 and 9.4 (2 x s br, N*H*H), 7.05 and 6.72 (2 x t, C*H*F_2, $^2J_{H-F}$ = 54.1 and 53.7 Hz), 6.70 and 6.46 (2 x s br, NH*H*), 4.27 (2 x q, OCH$_2$CH$_3$), 1.32 (2 x t, OCH$_2$C*H*$_3$) ppm.

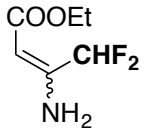
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -72.5 and -73.1 (2 x s, C*F*$_3$), -123.3 and -124.9 (dt and d, CH*F*$_2$, $^2J_{F-H}$ = 54.4 Hz, $^4J_{F-H}$ = 2.3 Hz and $^2J_{F-H}$ = 54.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 182.2 and 180.3 (2 x q, *C*CF$_3$, $^2J_{C-F}$ = 36.2 and 35.5 Hz), 167.3 and 165.1 (*C*=O), 161.0 and 160.2 (2 x t, *C*CHF$_2$, $^2J_{C-F}$ = 21.8 and 22.1 Hz), 116.7 and 116.3 (2 x q, *C*F$_3$, $^1J_{C-F}$ = 288 and 290 Hz), 108.3 and 108.2 (2 x t, *C*HF$_2$, $^1J_{C-F}$ = 245 and 246 Hz), 98.9 and 96.8 (2 x t, *C*COOEt, $^3J_{C-F}$ = 3 and 3 Hz), 62.1 and 61.5 (O*C*H$_2$CH$_3$), 13.7 and 13.6 (OCH$_2$*C*H$_3$) ppm.

Anal. calcd for $C_8H_8F_5NO_3$: C, 36.79; H, 3.09; F, 36.37; N, 5.36; O, 18.38. Found: C, 36.69; H, 3.18; N, 5.39.

Crystals of the compound suitable for X-ray crystallographic analysis were obtained after slow concentration in AcOEt/MeOH.

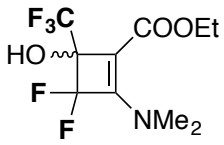
ethyl 3-amino-4,4-difluorobut-2-enoate (III.34c)



Isolated frequently during failed attempts to prepare pyrimidine products.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.17 (br s, NH_2), 5.96 (t, CHF_2, $^{2}J_{H-F}$ = 55 Hz), 4.84 (s, C*H*), 4.14 (q, O*C*H_2CH$_3$), 1.26 (t, OCH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -122.0 (d, CH*F*$_2$, $^{2}J_{F-H}$ = 54.4 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5 (*C*=O), 151.6 (t, *C*CHF$_2$, $^{2}J_{C-F}$ = 22 Hz), 112.0 (t, *C*HF$_2$, $^{1}J_{C-F}$ = 243 Hz), 86.5 (t, *C*H, $^{3}J_{C-F}$ = 7 Hz), 59.6 (O*C*H$_2$CH$_3$), 14.5 (OCH$_2$*C*H$_3$) ppm.

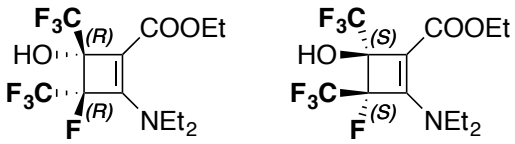
Cyclobutene rearrangement

ethyl 2-(dimethylamino)-3,3-difluoro-4-hydroxy-4-(trifluoromethyl)cyclobut-1-ene-1-carboxylate (III.3A.a)



A mixture of **III.2A.a** (1 equiv., 510 mg, 1.68 mmol), urea (1.86 equiv., 187 mg, 3.11 mmol) and Et$_3$N (2.79 equiv., 473 mg, 0.65 mL, 4.68 mmol) in MeCN (4 mL) was heated at 70 °C for 18 h. The mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 20%). Yield: 475 mg of colourless solid (98%). M.p.: 68.3 - 70.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.25 to 4.06 (2 x dq, O*C*H_2), 3.46 (s br, O*H*), 3.38 and 3.05 (2 x s, N(C*H*$_3$)$_2$), 1.25 (t, OCH$_2$C*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -75.1 (two adjacent d, C*F*$_3$, 2 x $^{4}J_{F-F}$ = 12-13 Hz), -111.5 to -116.8 (AB quartet, C*F*$_2$) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.0 (dd, *C*=O, $^{4}J_{C-F}$ = 5.6 Hz, $^{4}J_{C-F}$ = 4 Hz), 151.1 (t, *C*N(CH$_3$)$_2$, $^{2}J_{C-F}$ = 21.8 Hz), 123.1 (qd, *C*F$_3$, $^{1}J_{C-F}$ = 284 Hz, J = 2.5 Hz), 115.1 (dd, *C*F$_2$, $^{1}J_{C-F}$ = 285 Hz, $^{1}J_{C-F}$ = 295 Hz), 95.7 (dd, *C*C=O, $^{3}J_{C-F}$ = 14 Hz, $^{3}J_{C-F}$ = 13 Hz), 80.8 (qt, *C*CF$_3$, $^{2}J_{C-F}$ = 33.2 Hz, $^{2}J_{C-F}$ = 21 Hz), 60.5 (O*C*H$_2$CH$_3$), 41.1 and 40.0 (N(*C*H$_3$)$_2$), 14.2 (*C*H$_3$) ppm.
Anal. calcd for $C_{10}H_{12}F_5NO_3$: C, 41.53; H, 4.18; F, 32.85; N, 4.84; O, 16.60. Found: C, 41.60; H, 4.28; N, 4.91.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained after slow concentration in DCM/AcOEt.

ethyl 2-(dimethylamino)-3-fluoro-4-hydroxy-3,4-bis(trifluoromethyl)cyclobut-1-ene-1-carboxylate (III.3C.a)



Ishikawa reagent (1.2 equiv., 8.2 g, 10.1 mL, 40.7 mmol) was activated over 15min in dry MeCN (20 mL) into a Teflon flask under inert atmosphere by addition of BF_3•Et_2O (1.21 equiv., 5.82 g, 5.2 mL, 41.0 mmol) *via* syringe. A solution of ethyl 4,4,4-trifluoroacetoacetate (1 equiv., 6.25 g, 5 mL, 33.9 mmol) and dry pyridine (2.99 equiv., 8.02 g, 8.2 mL, 101 mmol) in dry MeCN (20 mL) was prepared under inert atmosphere into a Schlenk vessel and cooled to -30 °C, then was canulated onto the first solution. After 1 h at -30 °C, the mixture was stirred 18 h at room temperature. The mixture was evaporated *in vacuo*, then taken up in DCM and filtered. The filtrate was concentrated and taken up in toluene, then underwent an azeotropic distillation (55 °C/<50 mbar) after a second filtration through Celite. The resulting orange oil (12.73g) was left to crystallize over 2 weeks, to yield orange solid. M.p.: 45.7 - 47 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.19 (dq, OC*H*$_2$CH$_3$, $^2J_{H-H}$ = 28 and 50 Hz and $^3J_{H-H}$ = 7.2 and 7.2 Hz), 3.88 (s br, O*H*), 3.71 and 3.37 (s br, 2H + 2H, N(C*H*$_2$CH$_3$)$_2$), 1.28 (t, OCH$_2$C*H*$_3$, $^3J_{H-H}$ = 7.1 Hz), 1.20 (t, N(CH$_2$C*H*$_3$)$_2$, $^3J_{H-H}$ = 7.1 Hz) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -73.1 (d, C*F*$_3$, $^4J_{F-F}$ = 8.8 Hz), -76.4 (d, C*F*$_3$, $^4J_{F-F}$ = 15.1 Hz), -169.5 (m, C*F*) ppm.

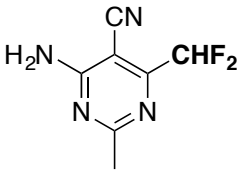
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.2 (s, *C*=O), 147.0 and 146.8 (s, *C*N(Et)$_2$), 123.5 (adjacent q, *C*CF$_3$OH, $^1J_{C-F}$ = 285.5 Hz), 121.0 (q, CF$_3$*C*F, $^1J_{C-F}$ = 284 Hz, $^2J_{C-F}$ = 32.5 Hz), 93.4 (qd, CF*C*F$_3$, $^1J_{C-F}$ = 249.6 Hz, $^2J_{C-F}$ = 32.2 Hz), 91.9 and 91.8 (s, *C*COOEt, 77.5 (qd, C*C*F$_3$OH, $^2J_{C-F}$ = 32.7 Hz, $^2J_{C-F}$ = 18.8 Hz), 60.5 (O*C*H$_2$CH$_3$), 45.4 and 45.2 (s br, N(*C*H$_2$CH$_3$)$_2$), 14.3 (OCH$_2$*C*H$_3$), 13.8 and 12.9 (s br, N(CH$_2$*C*H$_3$)) ppm.

Anal. calcd for $C_{13}H_{16}F_7NO_3$: C, 42.52; H, 4.39; F, 36.21; N, 3.81; O, 13.07. Found: C, 42.63; H, 4.43; N, 3.82.

Crystals of the compound suitable for X-ray crystallographic analysis were obtained and confirmed a *R,R* or *S,S* configuration.

Opening the route to mono-fluoroalkyl pyrimidines

4-amino-6-(difluoromethyl)-2-methylpyrimidine-5-carbonitrile (III.35)



A mixture of **III.48A** (1 equiv., 750 mg, 4.16 mmol) and acetamidine hydrochloride (1.35 equiv., 530 mg, 5.61 mmol) in dry EtOH (10 mL) was refluxed for 5 h. The mixture was evaporated *in vacuo* and purified by flash chromatography (AcOEt in cyclohexane 0 to 40%). Yield: 610mg of colourless solid (80%). M.p.: 220.0 - 223.0 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.70 to 7.70 (br d, NH_2), 6.85 (t, CHF$_2$, $^{2}J_{H-F}$ = 53 Hz), 2.44 (s, CH_3) ppm.

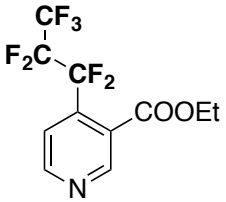
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -119.0 (d, CHF_2, $^{2}J_{F-H}$ = 53.7 Hz) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 170.0 (NCN), 163.7 (CNH$_2$), 161.9 (t, CCHF$_2$, $^{2}J_{C-F}$ = 24 Hz), 113.1 (CN), 112.4 (t, CHF$_2$, $^{1}J_{C-F}$ = 242 Hz), 82.9 (CCN), 25.7 (CH$_3$) ppm.

Anal. calcd for $C_7H_6F_2N_4$: C, 45.66; H, 3.28; F, 20.63; N, 30.43. Found: C, 45.66; H, 3.33; N, 30.43.

Synthesis of Perfluoroalkylated Pyridines

ethyl 4-(perfluoropropyl)nicotinate (III.12)



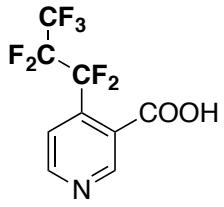
A mixture of perfluorobutyl iodide (2 equiv., 2010 mg, 1 mL, 5.81 mmol), Et$_3$N (2.01 equiv., 589 mg, 0.81 mL, 5.83 mmol) and tetrakis(triphenylphosphine)palladium (5.06 %, 170 mg, 0.147 mmol) in anhydrous hexane (10 mL) was vigorously stirred under argon at 60 °C for 30 min under inert atmosphere. The mixture was filtered under inert atmosphere. Dry MeCN (5 mL) was added, followed by BF$_3$•Et$_2$O (2.01 equiv., 828 mg, 0.74 mL, 5.84 mmol) under vigorous stirring. After 15 min at room temperature, a solution of ethyl 3-(dimethylamino)prop-2-enoate (1 equiv., 415 mg, 2.91 mmol) in dry MeCN (3 mL) was added *via* syringe onto the first solution. After 60 min, NH$_3$ 35% aq. (2.99 equiv., 422 mg, 0.48 mL, 8.68 mmol) was added *via* syringe, rapidly followed by conc. H$_2$SO$_4$ (1 equiv., 294 mg, 0.16 mL, 2.91 mmol). The mixture was stirred 30 min and concentrated *in vacuo*. The concentrate was diluted with DCM (30mL) and filtered, then evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 10%). Yield: 330mg of yellow residue (36%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 8.91 (s, 2-CH), 8.87 (d, 6-CH), 7.51 (d, 5-CH), 4.40 (q, OCH_2CH$_3$), 1.36 (t, OCH_2CH$_3$) ppm.

^{19}F-NMR (376 MHz, CDCl$_3$): δ = -80.2 (t, CF$_2$CF$_2$CF_3, $^{3}J_{F-F}$ = 10 Hz), -107.8 (m, CF$_2$CF_2CF$_3$), -123.8 (m, CF_2CF$_2$CF$_3$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.5 (*C*=O), 151.9 (6-*C*), 150.6 (2-*C*), 134.5 (dd, 4-*C*, $^{2}J_{C\text{-}F}$ = 24 Hz, $^{2}J_{C\text{-}F}$ = 25.7 Hz), 128.1 (t, 3-*C*, $^{2}J_{H\text{-}H}$ = 2.9 Hz), 121.8 (t, 5-*C*, $^{2}J_{H\text{-}H}$ = 6.8 Hz), 117.9 (qt, $CF_2CF_2CF_3$, $^{1}J_{C\text{-}F}$ = 288 Hz, $^{2}J_{C\text{-}F}$ = 34 Hz), 114.8 (tt, $CF_2CF_2CF_3$, $^{1}J_{C\text{-}F}$ = 258 Hz, $^{2}J_{C\text{-}F}$ = 33.6 Hz), 108.7 (tqt, $CF_2CF_2CF_3$, $^{1}J_{C\text{-}F}$ = 265 Hz, $^{2}J_{C\text{-}F}$ = 38 Hz, $^{2}J_{C\text{-}F}$ = 37 Hz), 62.8 (OCH_2CH_3), 13.9 (OCH_2CH_3) ppm.
HRMS (ESI) calcd for $C_{11}H_9F_7NO_2$ [M+H]: 320.0516. Found: 320.0536.

4-(perfluoropropyl)nicotinic acid (III.13)

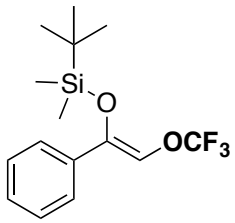


A solution of ethyl 4-(heptafluoropropyl)pyridine-3-carboxylate **III.12** (1 equiv., 300 mg, 0.94 mmol) in EtOH (2 mL) was stirred overnight at room temperature in presence of aq. NaOH solution (3 equiv., 2 M, 1.41 mL, 2.82 mmol). The mixture was acidified with HCl 1N until pH 1, then extracted with DCM. The combined organics were dried (Na_2SO_4), filtered and evaporated *in vacuo*, then triturated in pentane and dried in vacuo to quantitatively yield a yellow solid. M.p.: 112.7 - 114.6 °C.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 14.05 (br s, COO*H*), 9.00 (s, 2-C*H*), 8.97 (d, 6-C*H*), 7.79 (d, 5-C*H*) ppm.
^{19}F-NMR (376 MHz, DMSO-d_6): δ = -79.7 (t, $CF_2CF_2CF_3$, $^{3}J_{F\text{-}F}$ = 10 Hz), -107.1 (m, $CF_2CF_2CF_3$), -123.4 (m, $CF_2CF_2CF_3$) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6): δ = 166.5 (*C*=O), 152.0 (6-*C*H), 149.8 (2-*C*H), 131.9 (t, 4*C*-CF_2, $^{2}J_{C\text{-}F}$ = 24.5 Hz), 128.6 (3*C*-COOH), 121.7 (t, 5-CH, $^{2}J_{H\text{-}H}$ = 6 Hz), 117.5 (qt, *C*F_3, $^{1}J_{C\text{-}F}$ = 287 Hz, $^{2}J_{C\text{-}F}$ = 34 Hz), 114.6 (tt, *C*F_2, $^{1}J_{C\text{-}F}$ = 257 Hz, $^{2}J_{C\text{-}F}$ = 32 Hz), 108.1 (tq, CF_3CF_2, $^{1}J_{C\text{-}F}$ = 266 Hz, $^{2}J_{C\text{-}F}$ = 38 Hz) ppm.
Anal. calcd for $C_9H_4F_7NO_2$: C, 37.13; H, 1.38; F, 45.68; N, 4.81; O, 10.99. Found: C, 37.45; H, 1.55; N, 4.84.

Chapter IV

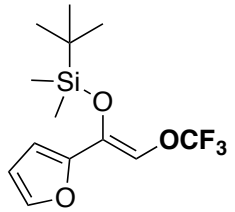
Preparation of key OCF_3-enaminoketone intermediates

tert-butyl((1-(furan-2-yl)-2-(trifluoromethoxy)vinyl)oxy)dimethylsilane (IV.3a)



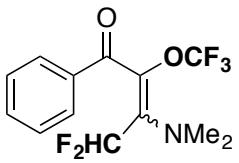
Prepared quantitatively according to the described procedure from: Synlett 2009, No. 7, 1131–1135. The crude resulting from the reaction was adsorbed onto silica, and the resulting cake was rinsed with cyclohexane, to yield the desired silyl enol ether.

tert-butyl((1-(furan-2-yl)-2-(trifluoromethoxy)vinyl)oxy)dimethylsilane (IV.4a)



Prepared using same conditions than **IV.3a** (Synlett 2009, No. 7, 1131–1135). The crude resulting from the reaction was adsorbed onto silica. The resulting cake was rinsed with cyclohexane
Yield: colourless oil (88-92%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 5'-C*H*), 6.65 (s, C*H*OCF_3), 6.44 and 6.39 (m and m, 1H + 1H, 3',4'-C*H*), 1.00 (s, 9H, C(CH_3)$_3$), 0.19 (s, Si(CH_3)$_2$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.6 (s, OCF_3) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.5 (C_{quat}CH), 142.2 (5'-*C*H), 134.3 (2'-*C*), 120.9 (q, O*C*F_3, J = 258 Hz), 119.0 (q, *C*HOCF_3, $^{3}J_{C-F}$ = 3.5 Hz), 111.2 and 108.1 (3',4'-$_C$H), 25.8 (*C*(CH_3)$_3$), 18.6 (C(*C*H_3)$_3$), -4.5 (Si(*C*H_3)$_2$) ppm.
HRMS (ESI) calcd for $C_{13}H_{20}F_3O_3Si$ [M+H]: 309.1128. Found: 309.1126.

3-(dimethylamino)-4,4-difluoro-1-phenyl-2-(trifluoromethoxy)but-2-en-1-one (IV.5a)



A solution of **IV.3a** (400 mg, 1.26 mmol) in dry MeCN (2 mL) was added to a solution of **2A** (1.23 equiv., 1.54 mmol) in dry MeCN (2 mL) under inert atmosphere. The mixture was stirred 45 min. Acetamidine hydrochloride (2.02 equiv., 240 mg, 2.54 mmol) was added under argon flux, and Et_3N (3.04 equiv., 385 mg, 0.53 mL, 3.81 mmol) was added very slowly *via* syringe. The resulting mixture was further stirred at room temperature for 2 h. The mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%). Yield: 274 mg of yellow oil (71 %). Yields between 43 and 99% were obtained. Ratio E/Z: *ca*. 60/40.

Isomer 1 (**60**/40):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, 2H, 2',6'-CH_{arom}), 7.50 (m, 3H, 3',4',5'-CH_{arom}), 6.78 (t, CHF$_2$, $^2J_{H-F}$ = 53 Hz), 2.80 (N(CH_3)$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -58.8 (s, CF_3), -118.6 (d, CHF_2, $^2J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 188.0 (*C*=O), 145.9 (t, *C*CHF$_2$, $^2J_{C-F}$ = 21.1 Hz), 138.2 (1'-C_{arom}), 132.5 (4'-C_{arom}), 128.8 and 128.5 (2',3',5',6'-C_{arom}), 125.6 (t, *C*OCF$_3$, $^3J_{C-F}$ = 6 Hz), 121.5 (q, O*C*F$_3$, $^1J_{C-F}$ = 259 Hz), 110.6 (t, *C*HF$_2$, $^1J_{C-F}$ = 242 Hz), 43.6 (N(*C*H$_3$)$_2$) ppm.

Isomer 2 (60/**40**):

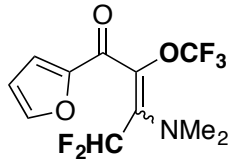
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 2H, 2',6'-CH_{arom}), 7.42 (m, 3H, 3',4',5'-CH_{arom}), 7.16 (t, CHF$_2$, $^2J_{H-F}$ = 52 Hz), 3.14 (N(CH_3)$_2$) ppm.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.0 (s, CF_3), -118.5 (d, CHF_2, $^2J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.8 (*C*=O), 146.7 (t, *C*CHF$_2$, $^2J_{C-F}$ = 21.1 Hz), 138.5 (1'-C_{arom}), 132.2 (4'-C_{arom}), 129.2 and 128.2 (2',3',5',6'-C_{arom}), 125.8 (t, *C*OCF$_3$, $^3J_{C-F}$ = 8.2 Hz), 121.0 (q, O*C*F$_3$, $^1J_{C-F}$ = 259 Hz), 111.3 (t, *C*HF$_2$, $^1J_{C-F}$ = 243 Hz), 43.0 (N(*C*H$_3$)$_2$) ppm.

HRMS (ESI) calcd for $C_{13}H_{13}F_5NO_2$ [M+H]: 310.0861. Found: 310.0884.

3-(dimethylamino)-4,4-difluoro-1-(furan-2-yl)-2-(trifluoromethoxy)but-2-en-1-one (IV.6a)



A solution of **III.4a** (4.32 g, 14 mmol) in dry MeCN (40 mL) was added to a solution of **2A** (1.1 equiv., 14 mmol) in dry MeCN (40 mL) at room temperature. The mixture was stirred 1 h. Acetamidine hydrochloride (2.0 equiv., 2.7 g, 28.6 mmol) was added under argon flux and Et_3N (2 equiv., 2.84 g, 3.9 mL, 28.1 mmol) was added very slowly *via* syringe. The mixture was further stirred at room temperature for 2 h. The mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 10%). Yield: 2.9 g (95wt.%) of yellow oil (69 %). E/Z *ca*. 65:35.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 and 7.59 (2 x m, 5'-CH), 7.47 and 6.75 (2 x t, CHF$_2$, $^2J_{H-F}$ = 52 Hz and $^2J_{H-F}$ = 53 Hz), 7.22 and 7.15 (2 x d, 3'-CH), 6.52 (m, 4'-CH), 3.13 and 3.04 (2 x s, N(CH_3)$_2$) ppm.

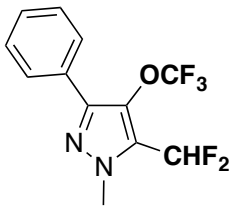
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.3 and -60.3 (OCF_3), -118.7 and -119.1 (2 x d, CHF_2, $^2J_{F-H}$ = 53 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.0 and 172.2 (*C*=O), 152.1 and 151.9 (2'-*C*), 148.0 and 147.4 (2 x t, *C*CHF$_2$, $^2J_{C-F}$ = 21 Hz), 146.6 and 146.0 (5'-*C*), 124.4 and 123.2 (2 x t, *C*-OCF$_3$, $^3J_{C-F}$ = 6 Hz and $^3J_{C-F}$ = 7 Hz),

121.7 and 121.2 (2 x q, O*C*F_3, $^1J_{C-F}$ = 257 Hz and $^1J_{C-F}$ = 258 Hz), 119.0 and 117.5 (3'-*C*), 112.1 and 112.0 (4'-*C*), 110.8 and 109.9 (2 x t, *C*HF_2, $^1J_{C-F}$ = 243 Hz), 44.4 and 43.2 (2 x m, N(*C*H_3)$_2$) ppm.
HRMS (ESI) calcd for $C_{11}H_{11}F_5NO_3$ [M+H]: 300.0649. Found: 300.0654.

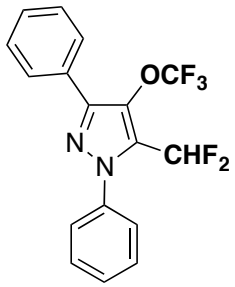
Synthesis of heterocycles bearing OCF_3 and CHF_2 motifs

5-(difluoromethyl)-1-methyl-3-phenyl-4-(trifluoromethoxy)-1*H*-pyrazole (IV.7a)



A solution of **IV.5a** (1 equiv., 386 mg, 1.04 mmol) in dry MeCN (3 mL) was treated with methyl hydrazine (1.8 equiv., 86 mg, 0.1 mL, 1.87 mmol) rapidly followed by conc. H_2SO_4 (0.53 equiv., 55.2 mg, 0.03 mL, 0.55 mmol). After 1 h, the mixture was diluted with DCM, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 188mg of colourless solid (62%).
M.p.: 49.4 - 50.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 2H), 7.44 (m, 2H), 7.38 (m, 1H), 6.75 (t, C*H*F_2, $^2J_{H-F}$ = 52.1 Hz), 4.06 (s, NC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.0 (s, OC*F*$_3$), -115.2 (d, CH*F*$_2$, $^2J_{F-H}$ = 52.1 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 142.5, 130.1, 129.7, 128.8, 128.6 (*C*CHF_2, $^2J_{C-F}$ = 24.5 Hz), 126.8, 120.6 (q, *C*F_3, $^1J_{C-F}$ = 260 Hz), 106.8 (t, *C*HF_2, $^1J_{C-F}$ = 235.4 Hz), 39.5 (N*C*H_3) ppm.
Anal. calcd for $C_{12}H_9F_5N_2O$: C, 49.32; H, 3.10; F, 32.51; N, 9.59; O, 5.48. Found: C, 49.57; H, 3.18; N, 9.52.

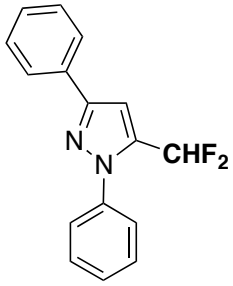
5-(difluoromethyl)-1,3-diphenyl-4-(trifluoromethoxy)-1*H*-pyrazole (IV.7c)



A solution of **IV.5a** (1 equiv., 500 mg, 1.29 mmol) in dry MeCN (3 mL) was treated with phenyl hydrazine (1.56 equiv., 218 mg, 0.2 mL, 2.02 mmol) rapidly followed by conc. H_2SO_4 (0.56 equiv., 73.6 mg, 0.04 mL, 0.728 mmol). After 24h at 80 °C, the mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 5%). Yield: 250mg of orange oil (55%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 to 7.33 (m, 6H), 7.26 to 7.23 (m, 4H), 6.83 (t, C*H*F_2, $^2J_{H-F}$ = 53.8 Hz) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.6 (t, OC*F*$_3$, $^6J_{F-F}$ = 4.8 Hz), -115.1 (dq, CH*F*$_2$, $^2J_{F-H}$ = 53.6 Hz, $^6J_{F-F}$ = 4.5 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.2, 139.0 (t, *C*CHF_2, $^2J_{C-F}$ = 27.8 Hz), 137.3, 129.7, 129.6, 129.2, 128.9, 128.8, 128.7, 126.5, 125.3, 120.6 (q, O*C*F_3, $^1J_{C-F}$ = 260 Hz), 110.2 (t, *C*HF_2, $^1J_{C-F}$ = 237 Hz),
Anal. calcd for $C_{17}H_{11}F_5N_2O$: C, 57.63; H, 3.13; F, 26.81; N, 7.91; O, 4.52. Found: C, 58.13; H, 3.24; N, 7.97.

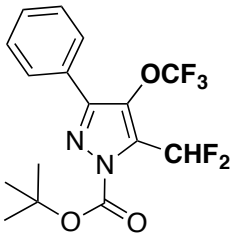
5-(difluoromethyl)-1,3-diphenyl-1*H*-pyrazole



Separated from **IV.7c** after flash chromatography.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 to 7.22 (m, 10H, arom.), 6.79 (t, C*H*F_2, $^2J_{H-F}$ = 55 Hz), 6.74 (s, 4-C*H*) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -111.7 (d, CH*F*$_2$, $^2J_{F-H}$ = 55 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.5 (t, 5-*C*CHF_2, $^2J_{C-F}$ = 30 Hz), 144.8 (3-*C*), 139.6 (N-*C*), 129.8, 129.2, 128.9, 128.8, 128.7, 128.3, 125.5 (arom.), 111.5 (t, *C*HF_2, J = 234 Hz), 104.9 (4-*C*H) ppm.

Ref.: Foster, R. S.; Adams, H.; Jakobi, H.; Harrity, J. P. A. *J. Org. Chem.* **2013,** *78*, 4049-4064.

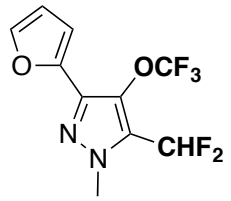
***tert*-butyl 5-(difluoromethyl)-3-phenyl-4-(trifluoromethoxy)-1*H*-pyrazole-1-carboxylate (IV.7d)**



A solution of **IV.5a** (1 equiv., 438 mg, 1.13 mmol) in dry MeCN (10 mL) was treated with *tert*-butyl carbazate (1.5 equiv., 224 mg, 1.7 mmol) rapidly followed by conc. H_2SO_4 (0.48 equiv., 55 mg, 0.03 mL, 0.55 mmol). The mixture was heated at 70 °C for 18 h. The mixture was diluted with DCM, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 25%). The intermediate mixture of pyrazoline diastereoisomers was taken up in toluene (5 mL) and cooled to 0 °C. Pyridine (5.46 equiv., 489 mg, 0.5 mL, 6.18 mmol) was added, followed by $SOCl_2$ (1.95 equiv., 262 mg, 0.16 mL, 2.21 mmol). The mixture was stirred 1 h at room temperature. After filtration, the mixture was partitioned between water and DCM. The organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*. A second flash chromatography (AcOEt in cyclohexane 0 to 2%) afforded 150mg of colourless oil (35%).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 3H, arom), 7.32 (m, 2H, arom), 6.79 (t, C*H*F_2, $^2J_{H-F}$ = 53.4 Hz), 1.30 (s, *t*Bu, 9H) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -59.2 (t, OC*F*$_3$, $^6J_{F-F}$ = 5 Hz), -116.4 (dq, CH*F*$_2$, $^2J_{F-H}$ = 53.4 Hz, $^6J_{F-F}$ = 5 Hz) ppm.

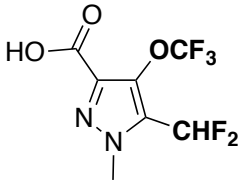
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.7 (*C*=O), 141.4 (t, *C*HF_2, $^2J_{C-F}$ = 29 Hz), 140.0 (3-*C*), 130.0 (m, *C*OCF_3), 129.9, 129.6, 128.4, 127.4 (arom), 120.3 (q, O*C*F_3, $^1J_{C-F}$ = 261 Hz), 110.0 (t, *C*HF_2, $^1J_{C-F}$ = 238 Hz), 87.2 (*C*$(CH_3)_3$), 27.4 (C(*C*$H_3)_3$) ppm.
Anal. calcd for $C_{16}H_{15}F_5N_2O_3$: C, 50.80; H, 4.00; F, 25.11; N, 7.41; O, 12.69. Found: C, 51.12; H, 4.30; N, 6.95.

5-(difluoromethyl)-3-(furan-2-yl)-1-methyl-4-(trifluoromethoxy)-1*H*-pyrazole (IV.10a)



A mixture of **IV.6a** (1 equiv., 100 mg, 0.304 mmol) and methyl hydrazine (1.84 equiv., 25.8 mg, 0.03 mL, 0.56 mmol) in MeCN (1 mL) was stirred 1 h at room temperature. The mixture was concentrated *in vacuo*. The crude was purified by flash chromatography (AcOEt in cyclohexane 0 to 1%), to give 75mg of colourless solid (87%). M.p.: 36.2 - 37.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, 5'-C*H*), 6.73 (d, 3'-C*H*), 6.72 (t, C*H*F_2, $^2J_{H-F}$ = 52 Hz), 6.49 (dd, 4'-C*H*), 4.05 (NC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -60.0 (s, OC*F*$_3$), -115.5 (d, CH*F*$_2$, $^2J_{F-H}$ = 52 Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.4 (2'-*C*), 142.9 (5'-*C*), 135.6 (3-*C*), 128.4 (t, *C*CHF_2, $^2J_{C-F}$ = 24.4 Hz), 128.2 (*C*OCF_3), 120.7 (q, O*C*F_3, $^1J_{C-F}$ = 260 Hz), 111.4 (4'-*C*), 108.9 (3'-*C*), 106.6 (t, *C*HF_2, $^1J_{C-F}$ = 235.7 Hz), 39.6 (N*C*H_3) ppm.
Anal. calcd for $C_{10}H_7F_5N_2O_2$: C, 42.57; H, 2.50; F, 33.66; N, 9.93; O, 11.34. Found: C, 43.15; H, 2.70; N, 9.65.

5-(difluoromethyl)-1-methyl-4-(trifluoromethoxy)-1*H*-pyrazole-3-carboxylic acid (IV.13a)



To a solution of 5-(difluoromethyl)-3-(furan-2-yl)-1-methyl-4-(trifluoromethoxy)-1H-pyrazole (1 equiv., 72 mg, 0.255 mmol) in a mixture of hexane (1.5 mL) / AcOEt (1.5 mL) / H2O (0.5 mL) was added $NaIO_4$ (10.1 equiv., 550 mg, 2.57 mmol), followed by $RuCl_3$ (5.67 %, 3 mg, 0.0145 mmol). The heterogeneous reaction mixture was vigorously stirred at room temperature overnight. The mixture was filtered through Celite and evaporated *in vacuo*. The resulting solid was triturated in Et_2O/pentane, to give 45mg of brown solid (68%).
M.p.: 145.0 - 147.5 °C (Denaturation >110 °C).
^{1}H-NMR (400 MHz, CD_3CN): δ = 6.96 (t, C*H*F_2, $^2J_{H-F}$ = 51.6 Hz), 4.01 (NC*H*$_3$) ppm.
^{19}F-NMR (376 MHz, CD_3CN): δ = -60.9 (t, OC*F*$_3$, $^6J_{F-F}$ = 2 Hz), -118.3 (d, CH*F*$_2$, $^2J_{F-H}$ = 52 Hz) ppm.
^{13}C-NMR (100 MHz, CD_3CN): δ = 160.6 (*C*=O), 134.9 (*C*COOH), 132.9 (*C*OCF_3), 130.2 (t, *C*CHF_2, $^2J_{C-F}$ = 26 Hz), 121.1 (q, O*C*F_3, $^1J_{C-F}$ = 258 Hz), 108.1 (t, *C*HF_2, $^1J_{C-F}$ = 236 Hz), 40.8 (N*C*H_3) ppm.
HRMS (ESI) calcd for $C_7H_5F_5N_2NaO_3$ [M+Na]: 283.0113. Found: 283.0125.
Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration in AcOEt/MeOH.

References – Chapter I

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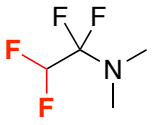

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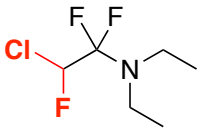

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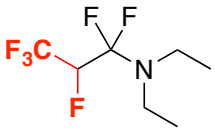

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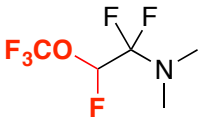

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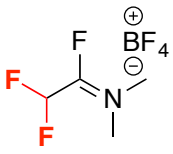

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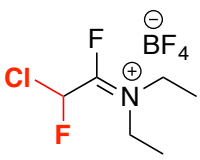

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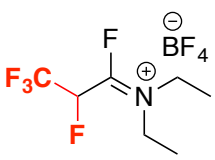

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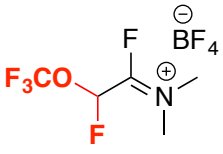

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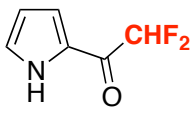

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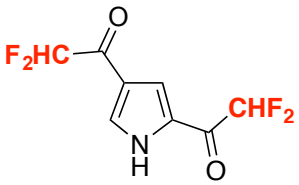

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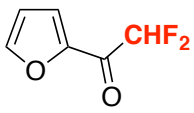

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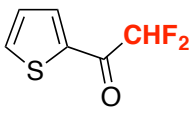

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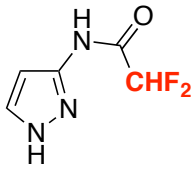

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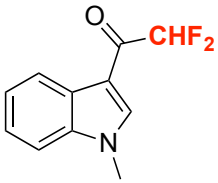

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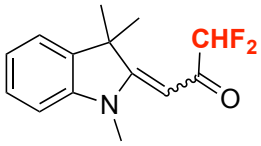

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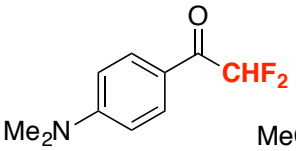

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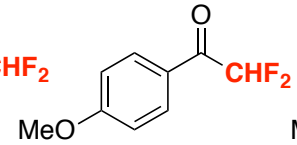

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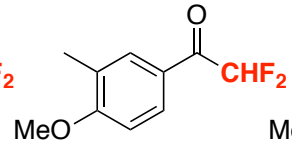

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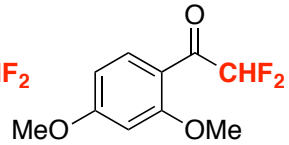

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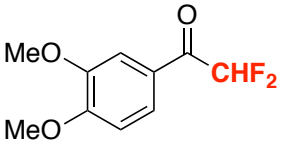

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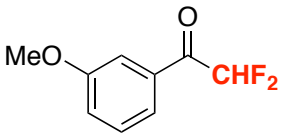

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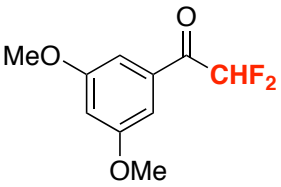

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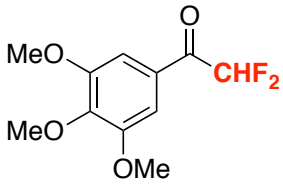

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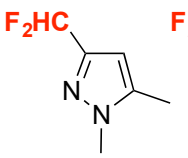

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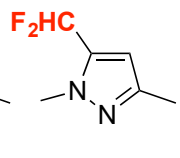

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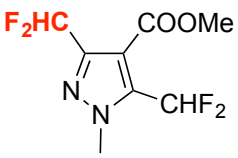

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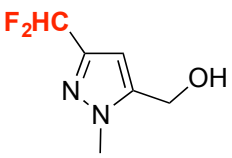

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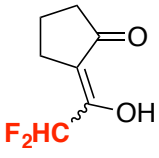

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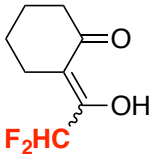

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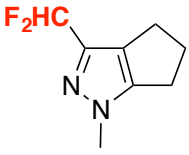

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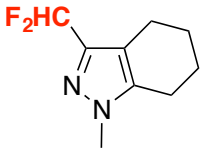

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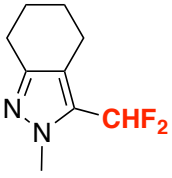

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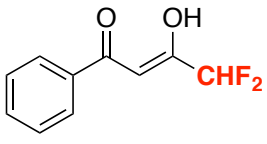

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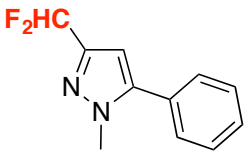

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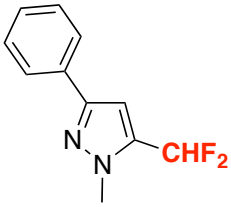

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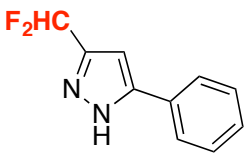

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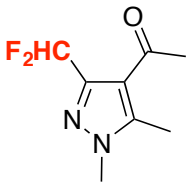

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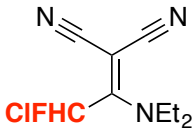

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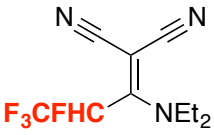

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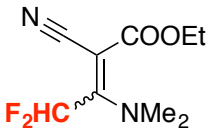

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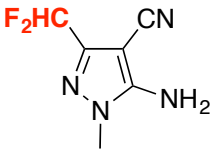

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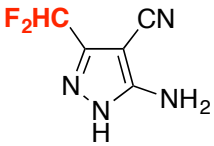

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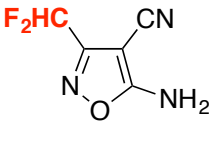

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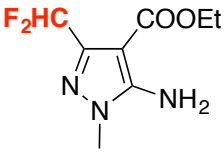

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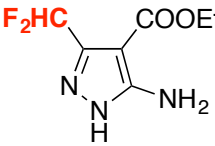

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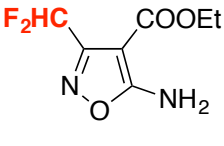

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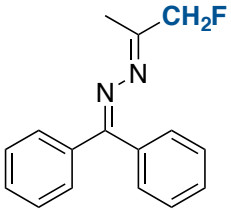

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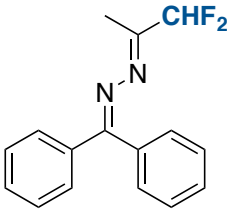
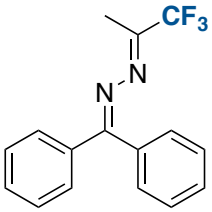
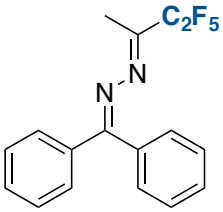


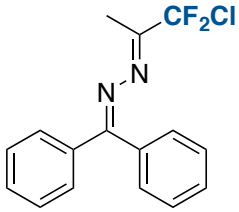
II.56b



II.56c



II.56d



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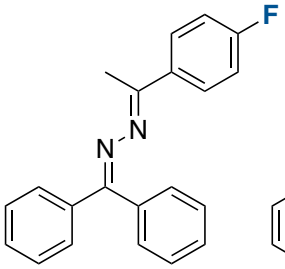

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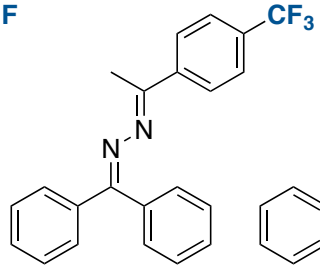
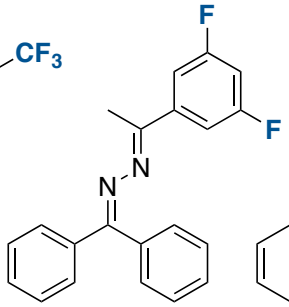
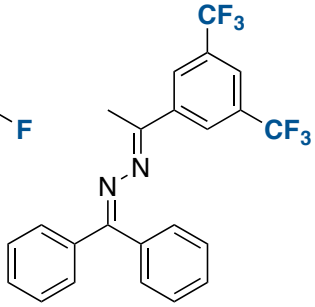


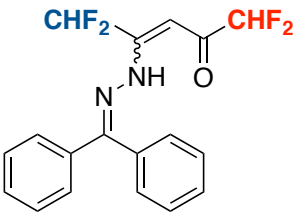
II.56g



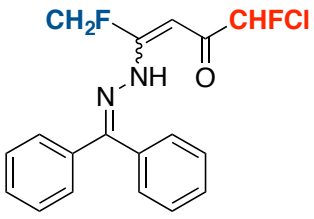
II.56h



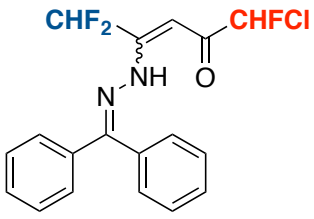
II.56i



II.57A.b



II.57B.a



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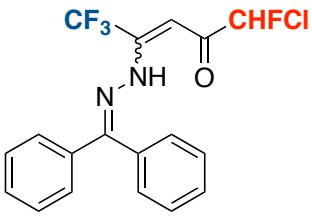
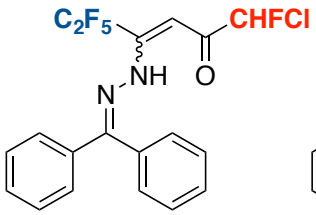


II.57B.c



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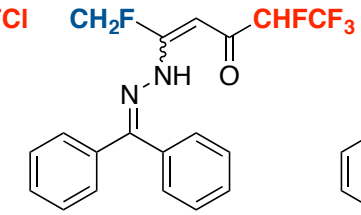
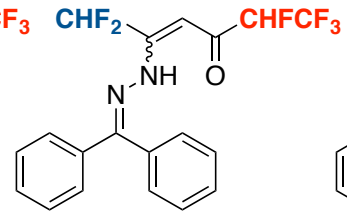
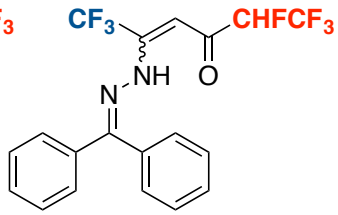


II.57C.a



II.57C.b



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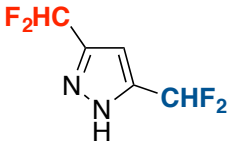
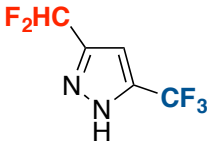
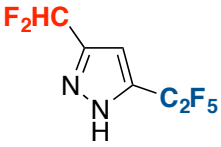


II.58A.b



II.58A.c



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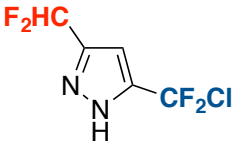
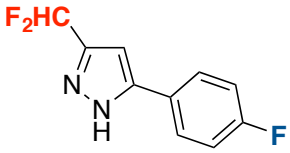
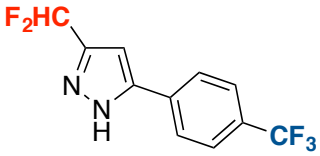


II.58A.e



II.58A.f



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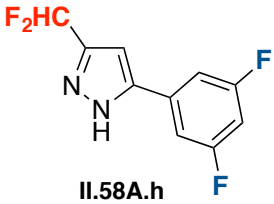
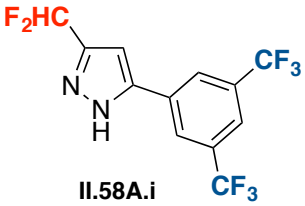


II.58A.h



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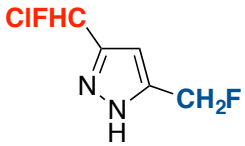

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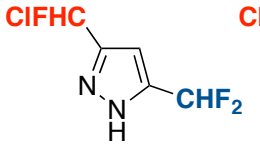
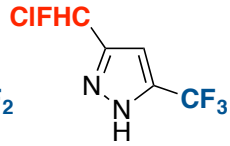
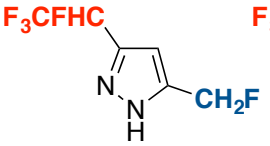


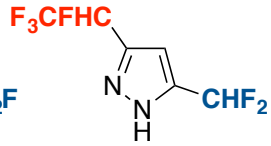
II.58B.b



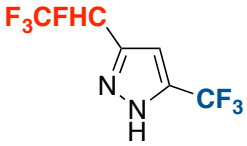
II.58B.c



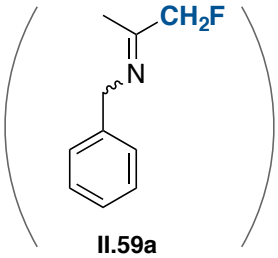
II.58C.a



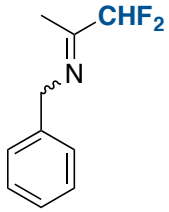
II.58C.b



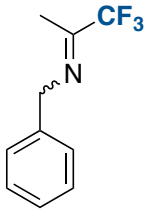
II.58C.c



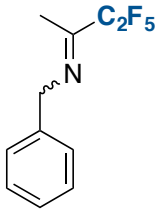
II.59a



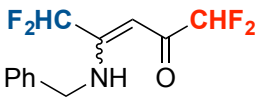
II.59b



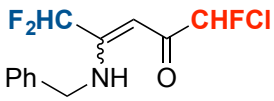
II.59c



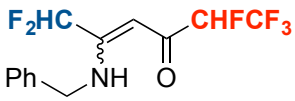
II.59d



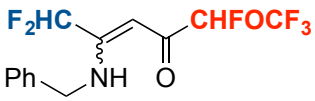
II.60A.b



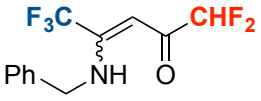
II.60B.b



II.60C.b



II.60A.c



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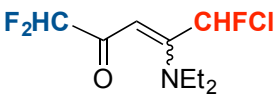
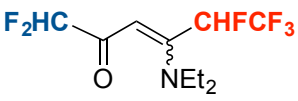
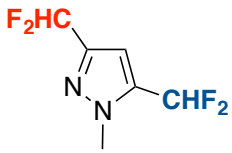


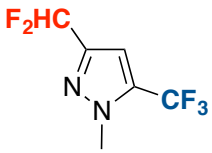
II.61B.b



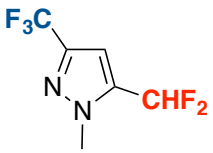
II.61C.b



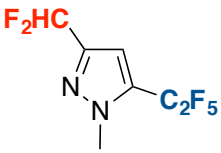
II.62A.b



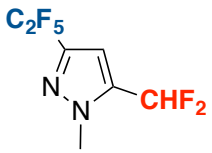
II.62A.c



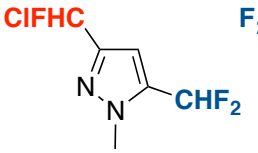
II.63A.c



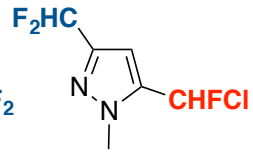
II.62A.d



II.63A.d



II.62B.b



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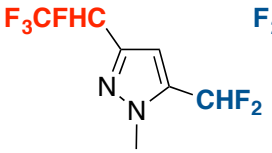
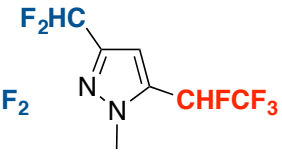
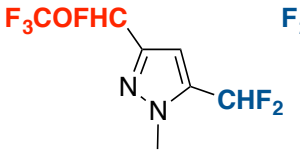


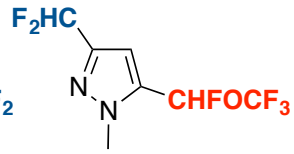
II.62C.b



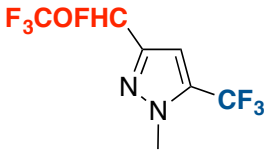
II.63C.b



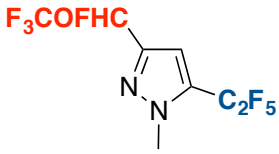
II.62D.b



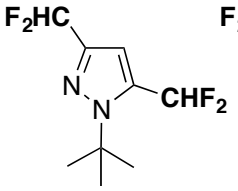
II.63D.b



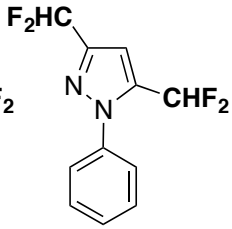
II.62D.c



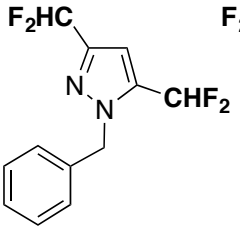
II.62D.d



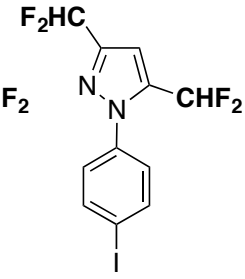
II.64a
(II.17)



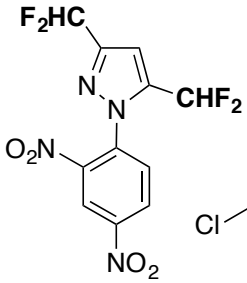
II.64b
(II.16)



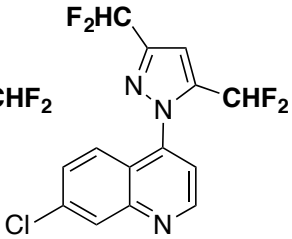
II.64c



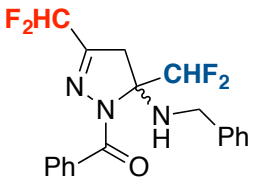
II.64d



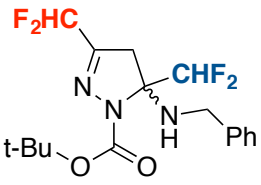
II.64e



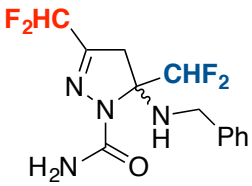
II.64f



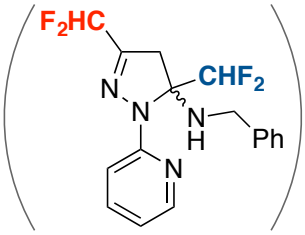
II.65A.b



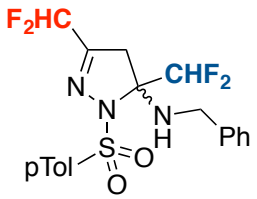
II.66A.b



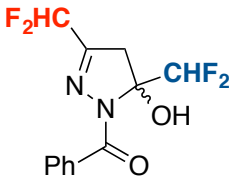
II.67A.b



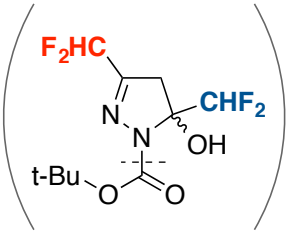
II.68A.b
unstable



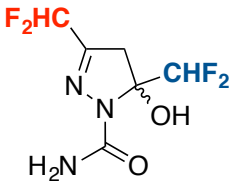
II.69A.b



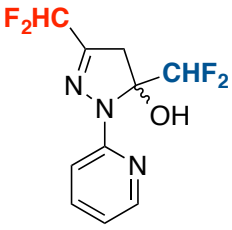
II.70A.b



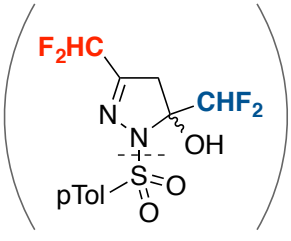
II.71A.b
unstable



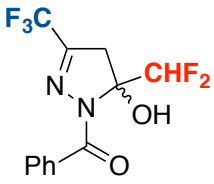
II.72A.b



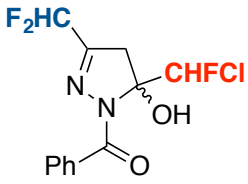
II.73A.b



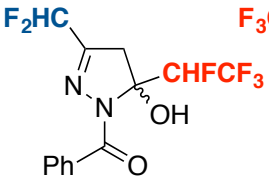
II.74A.b
unstable



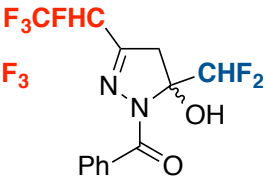
II.70A.c



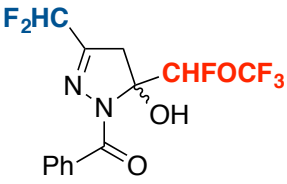
II.70B.b



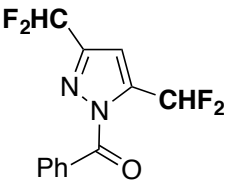
II.70C.b-P1



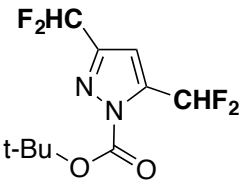
II.70C.b-P2



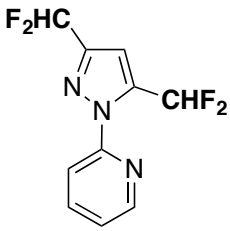
II.70D.b



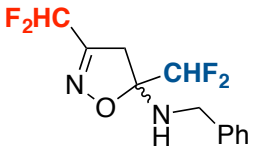
II.75



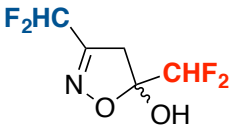
II.76



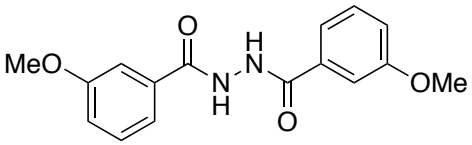
II.78



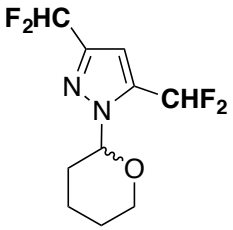
II.80A.b



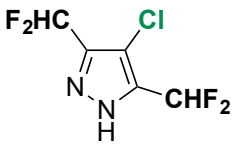
II.81A.b



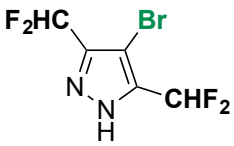
II.82



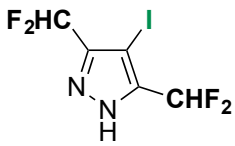
II.76



II.84a



II.84b



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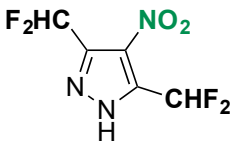

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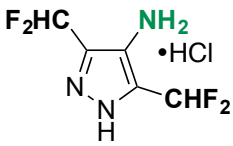
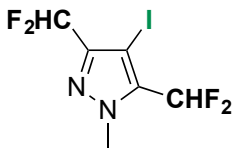
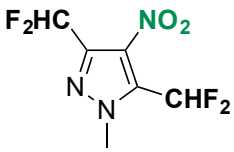


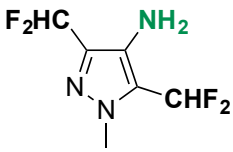
II.84e



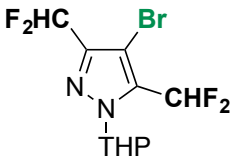
II.85c



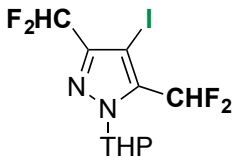
II.85d



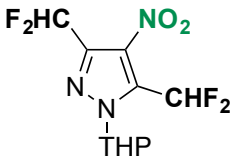
II.85e



II.86b



II.86c



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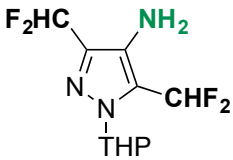
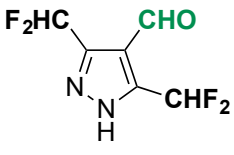
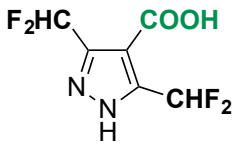


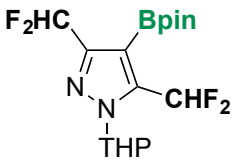
II.86e



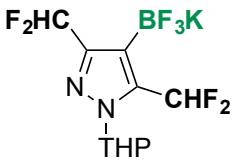
II.84f



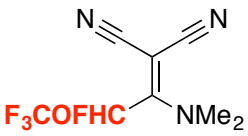
II.84g



II.86f



II.86g



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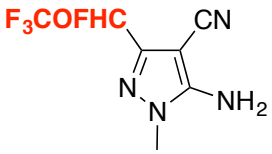

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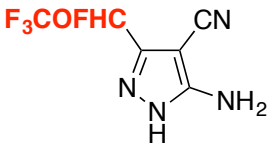

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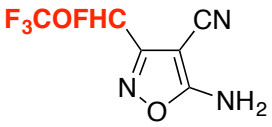

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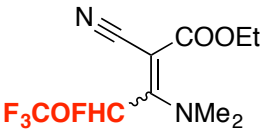

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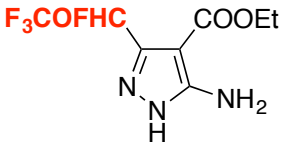

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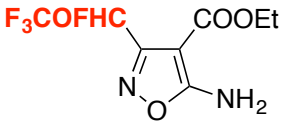

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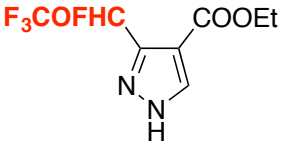

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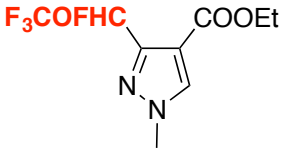
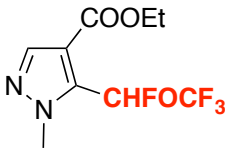


II.95b



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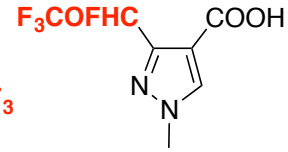

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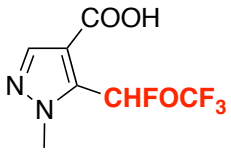

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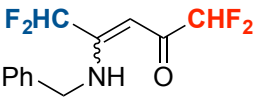

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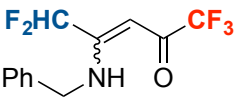

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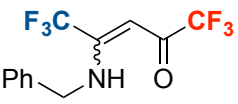

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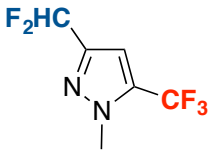

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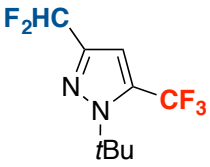

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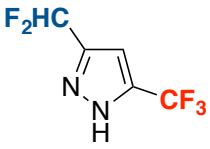

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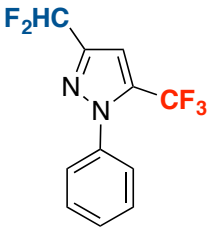

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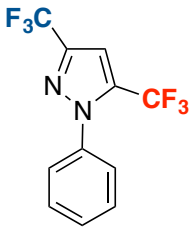

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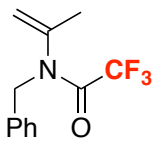

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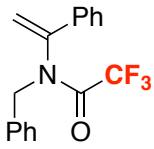

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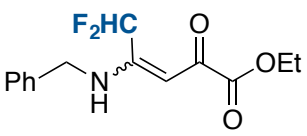

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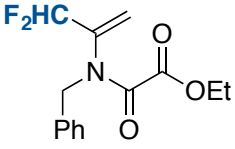

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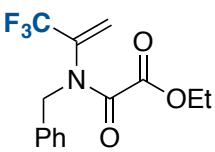

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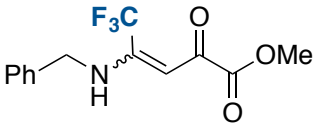

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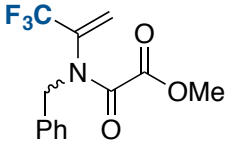

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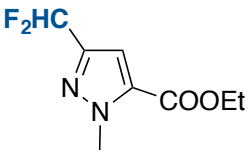

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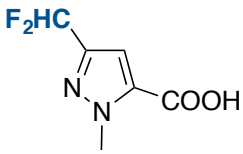

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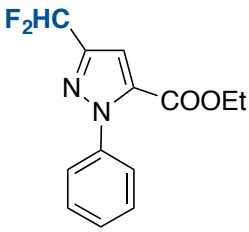

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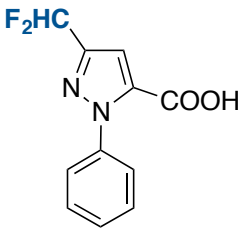

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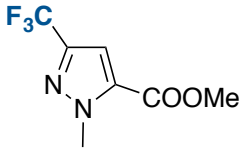

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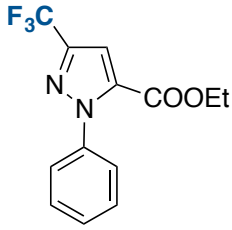

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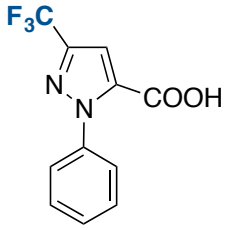

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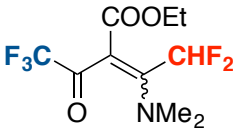
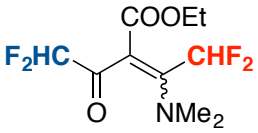
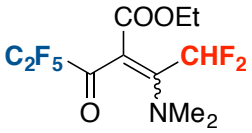


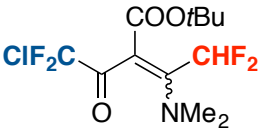
III.2A.a



III.2A.b



III.2A.c



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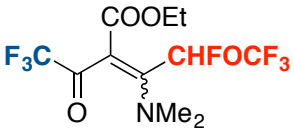
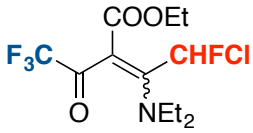


III.2D.a



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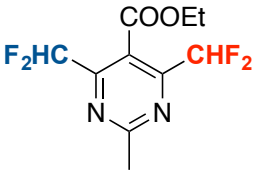
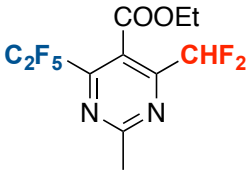
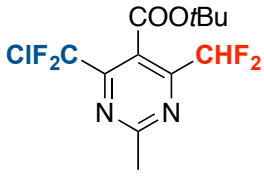


III.5A.b



III.5A.c



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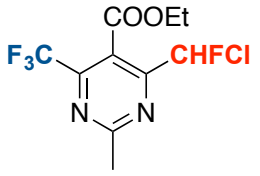
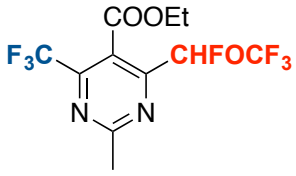


III.5B.a



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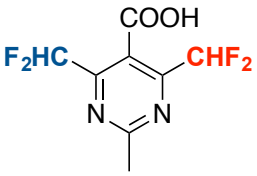
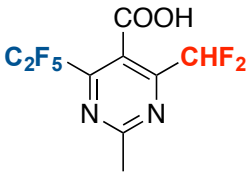
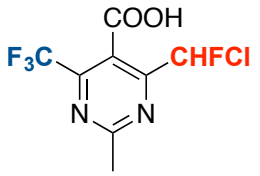


III.6A.b



III.6A.c



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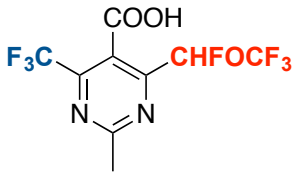
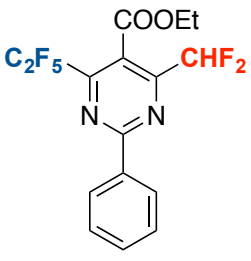
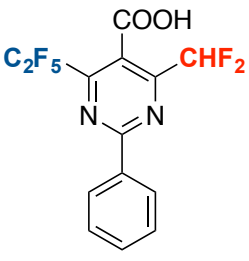


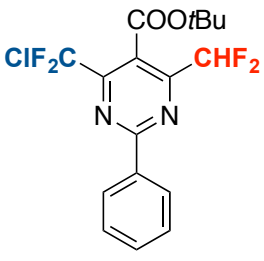
III.6D.a



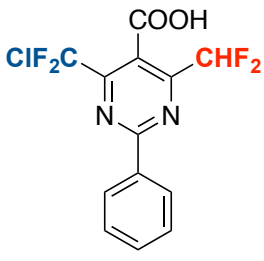
III.7A.c



III.8A.c



III.7A.d



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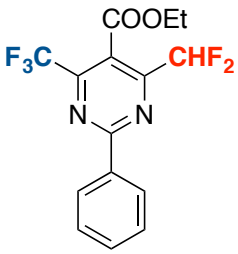

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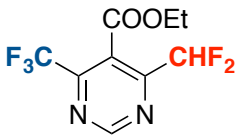

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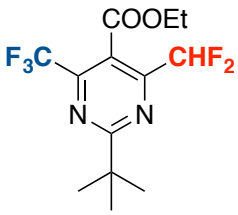

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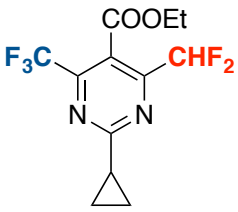

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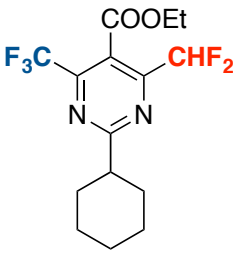

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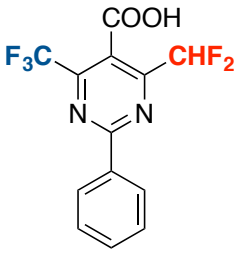

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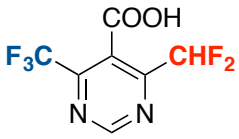

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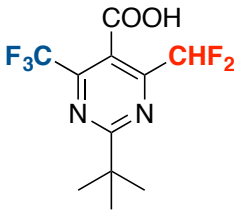

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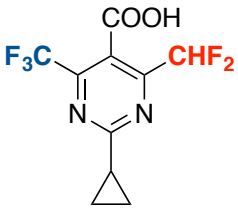

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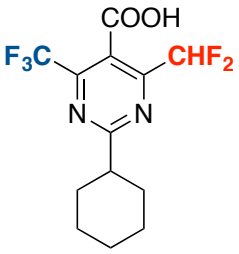

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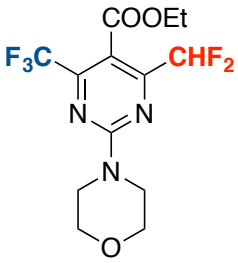

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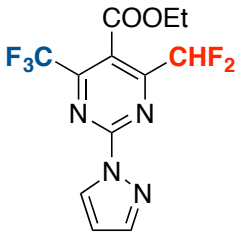

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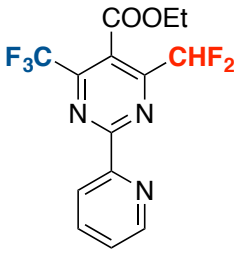

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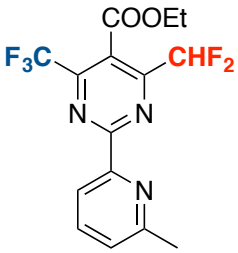

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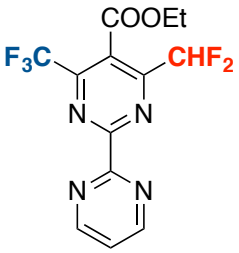

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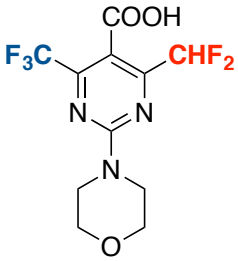

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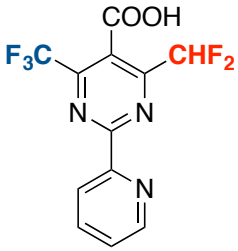

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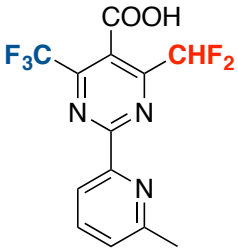

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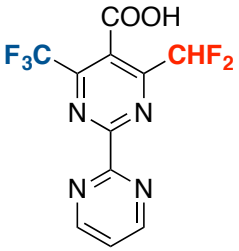

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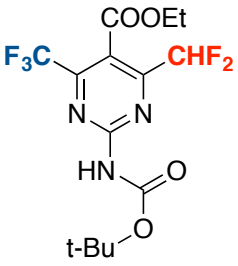

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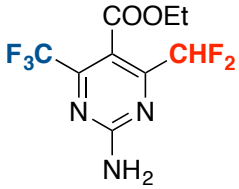

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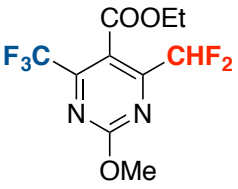

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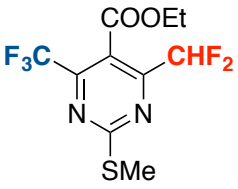

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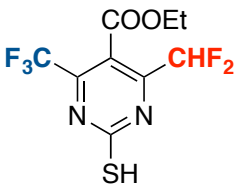

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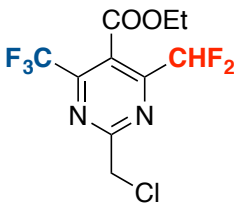

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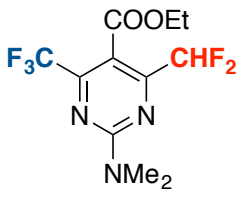

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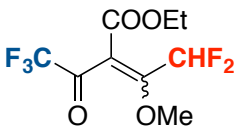
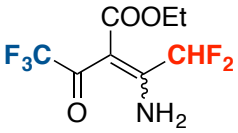
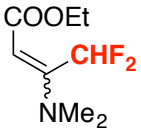


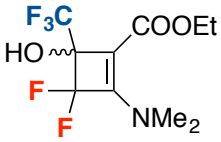
III.34a



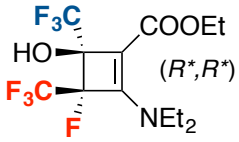
III.34b



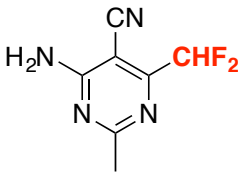
III.34c



III.3A.a



III.3C.a



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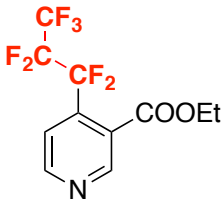

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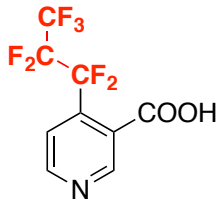

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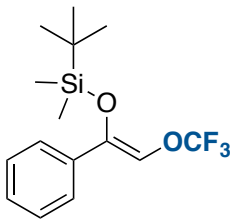
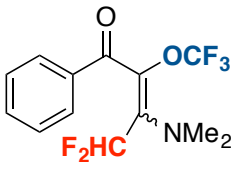
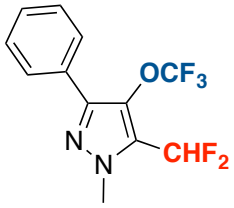


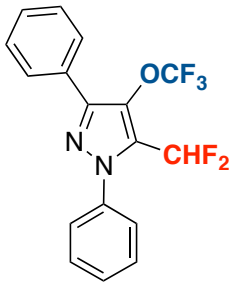
IV.3a



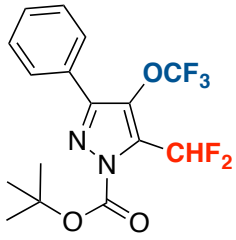
IV.5a



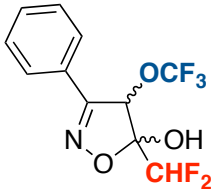
IV.7a



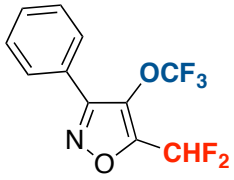
IV.7c



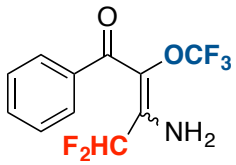
IV.7d



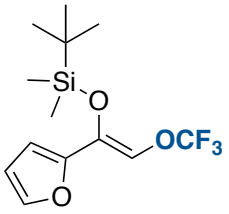
IV.8a



IV.8b



IV.9b



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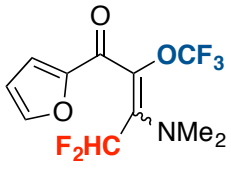
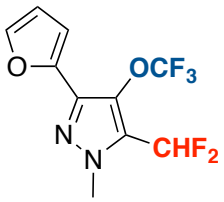
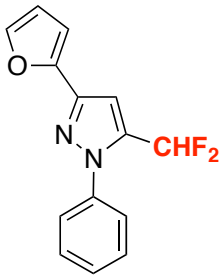


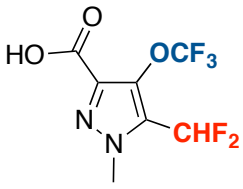
IV.6a



IV.10a



IV.11b



IV.13a

Etienne SCHMITT

Towards the synthesis of novel heterocyclic agrophores bearing emergent fluorinated substituents

Résumé en français

Durant ce doctorat en collaboration avec Bayer CropScience, une famille de réactifs de fluoration connue depuis plusieurs décennies (Réactifs de type Fluoroalkyl Amines, FARs) a été étudiée en détails (spécialement le TFEDMA) pour réaliser l'introduction de groupes fluorés émergents (EFSs). Après une activation à l'aide d'un acide de Lewis, les sels de fluoro-iminium obtenus ont été utilisés pour réaliser la difluoroacylation d'arenes et hétéroarènes riches en électrons, ou encore la synthèse efficace et régiosélective de pyrazoles et d'isoxazoles possédant un groupe -CHF_2 à partir de substrats variés (éthers vinyliques et apparentés, éthers d'énol silylés, composés CH-acides). Un nouveau FAR a été développé permettant l'introduction d'un nouvel EFS sur ces mêmes hétérocycles (fluoro-trifluoromethoxy-méthyl, -$CHFOCF_3$). La synthèse de nouveaux 3,5-bis(fluoroalkyl)-*N*H-pyrazoles a été réalisée à partir d'azines fluorées et de FARs. Une méthode régiosélective de synthèse de 3,5-bis(fluoroalkyl)-pyrazoles avec une très vaste diversité structurale accessible a ensuite été développée à l'aide de cétimines fluorées, d'hydrazines et de FARs. La synthèse de nouveaux carboxylates de bis(fluoroalkyl)pyrimidines a été développée à partir d'acétoacétates fluorés, d'amidines et de FARs. Trois produits de réarrangement de type cyclobutène hautement fonctionnalisé ont été isolés et caractérisés par cristallographie. La synthèse de pyrazoles et d'isoxazoles substitués par des groupes difluorométhyl et trifluoromethoxy a été réalisée à partir d'α-trifluoromethoxy-arylcétones, d'hydrazines et de FARs, et un exemple difficile d'acide pyrazole-3-carboxylique contenant ces deux substituants a été préparé. Le concept de FAR vinylogue a été illustré avec la préparation de l'acide 4-perfluoropropylnicotinique à partir d'iodure de perfluoropropyle.

Mots-clés: Réactifs de type Fluoroalkyl Amines (FARs), sels de fluoro-iminium, difluoromethylation, difluoroacylation, bis(fluoroalkyl), pyrazoles, isoxazoles, pyrimidines, cyclobutènes, nouveau FAR (-$CHFOCF_3$), trifluoromethoxy, FAR vinylogue, etc.

Résumé en anglais

During this 3-year PhD project in collaboration with Bayer CropScience, a family of fluorinating reagents (Fluoroalkyl Amino Reagents, FARs) was extensively studied (especially TFEDMA), and was used for various applications implying fluoro iminium salts after Lewis acid activation. The difluoroacylation of electron-rich arenes and heteroarenes was successfully developed. The introduction of Emergent Fluorinated Substituents (EFSs), such as difluoromethyl group (-CHF_2) was achieved into various substrates (vinyl ethers and analogues, silyl enol ethers, CH-acidic substrates) providing regioselectively difluoromethylated pyrazoles and isoxazoles. A new FAR was developed for the facile introduction of novel EFS (fluoro-trifluoromethoxy-methyl, -$CHFOCF_3$). A first method was developed allowing for the first access to 3,5-bis(fluoroalkyl)-*N*H-pyrazoles using fluorinated azines and FARs. The regioselective synthesis of 3,5-bis(fluoroalkyl)pyrazoles with tunable regioselectivity and broad substitution scope was developed using fluorinated ketimines, hydrazines and FARs. The synthesis of bis(fluoroalkyl)pyrimidine carboxylates was successfully achieved from fluorinated acetoacetates, amidines and FARs. Three highly functionalized cyclobutene products formed by rearrangement were isolated and characterised by crystallography. The syntheses of pyrazoles and isoxazoles bearing trifluoromethoxy and difluoromethyl motifs were developed from α-trifluoromethoxy-aryl-ketones, hydrazines and FARs, and a challenging pyrazole carboxylic acid bearing both substituents was synthesized. The concept of vinylogous FAR was exemplified with the synthesis of 4-perfluoropropylnicotinic acid from perfluoropropyl iodide.

Keywords: fluoroalkyl amino reagents (FARs), fluoro iminium salts, difluoromethylation, difluoroacylation, bis(fluoroalkyl), pyrazoles, isoxazoles, pyrimidines, cyclobutenes, new FAR, (-$CHFOCF_3$), trifluoromethoxy, vinylogous FAR, etc.