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Hexafluoroisopropanol-Assisted Friedel-Crafts Alkylation of Deactivated Alcohols

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Annual institute BBQ, June 2017

List of Abbreviations and Acronyms

Ac: acyl

AEA: arachidonyl ethanol-amine

AN: acceptor number obtained by analyzing the chemical shift of ^{31}P of triethylphosphine

Ar: aryl

ap: antiperiplanar 150° to 180°

Bu: butyl

COX: cyclooxygenase

DA: donor acceptor

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEAD: diethyl azodicarboxylate

DFT: density-functional theory

DMF: *N,N*-dimethylformamide

DMSO: dimethyl sulfoxide

dppf: 1,1'-dis(diphenylphosphino)ferrocene

ΔG: Gibbs free energy

ΔH: enthalpy

ΔS: entropie

Et: ethyl

Et(30): solvatochromic shift of 30th Reichardt's betaine

E^1 and E^2: first order and second order elimination reaction

FAAH: fatty acid amide hydrolase

GC: gas chromatography

GC-MS: gas chromatography coupled with mass

HBA: H-bond acceptance

HBD: H-bond donating ability

HOMO: highest occupied molecular orbital

HRMS: high resolution mass spectrometry

HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol

IC_{50}: half maximal inhibitory concentration

***i*Pr:** isopropyl

LUMO: lowest unoccupied molecular orbital

M: metal center

or $mol.L^{-1}$

Me: methyl

Mes: mesitylene

NAIDs: non-steroidal anti-inflammatory agents

NMP: *N*-methyl-2-pyrrolidone

NMR: nuclear magnetic resonance

N_{OTs}: nucleophilicity scale developed by Schleyer to describe the nucleophilic strength of a solvent

Nu: nucleophile

-*o*: ortho

-*p*: para

Ph: phenyl

Phen: phenanthroline

pK_a: negative base^{-10} logarithm of the acid dissociation constant (Ka) of a solution

RDS: rate determining step

sc: synclinal 30° to 90°

sp: synperiplanar 0° to 30°

S_N1 and S_N2: first order and second order nucleophilic substitution

TBAF: tetra-*n*-butylamonium fluoride

TBS: *tert*-butyldimethylsilyl

TEPO: triethylphosphine oxide

Tf: triflate

TFA: trifluoroacetic acid

TFE: trifluoroethanol

THF: tetrahydrofuran

TLC: thin layer chromatography

1,3,5 TMB: 1,3,5-trimethoxybenzene

TMEDA: tetramethylethylenediamine

TMS: trimethylsilyl

Ts: tosyl

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Résumé en Français

1) Introduction

Le 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) est un solvant aux propriétés atypiques que l'on ne retrouve pas avec des solvants plus classiques (Schéma 1).[1]

Par exemple :

(1) La présence de deux groupements trifluorométhyle confère au HFIP un fort effet inductif négatif, de sorte qu'il est k>10^7 fois plus acide (pKa = 9.3) que l'isopropanol (pKa = 17.1). Le HFIP a une plage d'acidité (les acidités accessibles dans un solvant donné) du même ordre de grandeur que l'eau. Cependant, en raison de sa basicité réduite, cette gamme est déplacée vers un régime beaucoup plus acide, comparable à celui de l'acide formique. Sa faible nucléophilie (N_{OTs} = 4.23) permet également d'éviter de rentrer en compétition avec d'autres nucléophiles, limitant ainsi les réactions secondaires indésirables. En fait, le paramètre de nucléophilie du solvant rapporté par le groupe de Mayr pour le mélange HFIP/eau [99:1] est la valeur la plus faible que l'on puisse trouver pour un solvant classique (N_1 = 1.93).

(2) Il possède une forte capacité à donner des liaisons hydrogène (HBD = 1.96) qui est renforcée par la formation d'un réseau de liaisons H entre les molécules de HFIP. Les calculs DFT confirment cette observation, car l'énergie de l'orbitale LUMO de HFIP diminue de moitié lors de sa dimérisation, ce qui en fait, en principe, un excellent solvant pour l'activation électrophile d'une base de Lewis.

(3) La haute polarité de HFIP (ε=15.7) associée à sa faible nucléophilie en font également un solvant de choix pour la génération et l'étude d'espèces cationiques. La question reste cependant de savoir si HFIP stabilise les cations (phénomène thermodynamique) ou s'il les laisse simplement persister suffisamment longtemps pour réagir (phénomène cinétique), ce qui fait actuellement l'objet de nombreuses discussions.

(4) Bien que cela ne soit pas important pour nos études, le HFIP est stable en conditions redox, ce qui en fait un solvant idéal pour les processus électrochimiques, la photocatalyse ainsi que pour les transformations nécessitant des conditions très oxydantes.

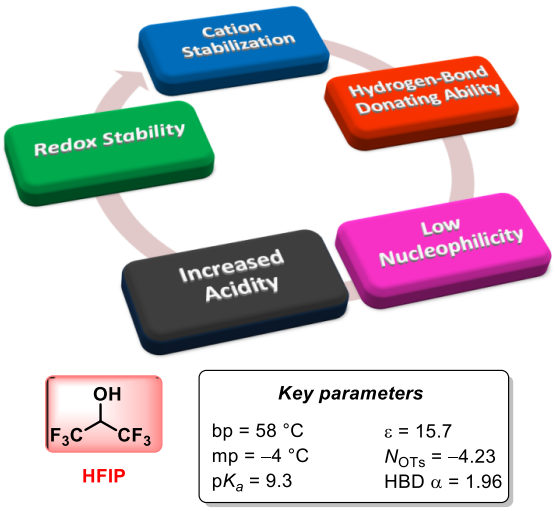

Figure 1. Propriétés de HFIP

Ce solvant a ainsi récemment attiré l'attention des chimistes de synthèse pour le développement de nouveaux outils synthétiques, tout particulièrement lorsqu'il est combiné avec des acides de Lewis ou des acides de Brønsted comme catalyseurs. Pendant longtemps, l'efficacité catalytique de HFIP a été essentiellement attribuée à sa faculté de stabiliser des intermédiaires cationiques grâce à son fort pouvoir ionisant et sa faible nucléophilie.[1] Cependant, des études mécanistiques plus poussées ont récemment mis en évidence un fonctionnement beaucoup plus complexe qui impliquerait un effet coopératif entre le catalyseur et HFIP.[2]

Ainsi, au cours des dernières années, plusieurs systèmes catalytiques utilisant un acide de Lewis ou de Brønsted en combinaison avec HFIP ont prouvé leur versatilité dans de nombreuses réactions,[3] comme par exemple des réactions de Friedel-Crafts, d'hydroarylation, d'hydrofunctionalisation et de cyclisation. Un des champs de recherche qui a particulièrement bénéficié de ce type d'associations est la substitution nucléophile directe d'alcools que l'on considère désactivés (typiquement des alcools possédant des groupements fortement électro-attracteurs en position α) en utilisant seulement une quantité catalytique d'activateur. En revanche, l'activation d'alcools aliphatiques primaires ne possédant pas de groupements fonctionnels comme des aryles, vinyles ou propargyles susceptibles de stabiliser un carbocation intermédiaire est extrêmement rare en raison de la faible propension de la fonction hydroxyle à agir comme un groupe partant.[4] Ces réactions restent pourtant hautement attractives car elles génèrent uniquement de l'eau comme sous-produit. De plus, les alcools sont des substrats très répandus et généralement peu coûteux. Le développement de méthodes de substitution directe d'alcools a par ailleurs été signalé comme étant un thème de recherche prioritaire par l'*ACS Green Chemistry Institute Pharmaceutical Roundtable*.[5] Pour ces raisons, le développement de méthodes d'activation directe d'alcools qui utilisent un système acide de Lewis ou acide de Brønsted/HFIP constitue pour nous un domaine de recherche majeur.

Cette thèse visait à étendre le champ d'application de la catalyse acide dans HFIP, notamment dans des réactions d'alkylation d'alcools désactivés de type Friedel-Crafts. Ce projet était constitué de deux axes de recherche, l'un sur l'activation d'alcools propargyliques substitués par des groupements trifluorométhyles, et le second sur l'activation de substrats très faiblement réactifs, à savoir des alcools aliphatiques primaires.

2) Résultats et discussions

a) Synthèse d'allènes, d'indènes, de chromènes et d'alcènes à partir d'alcools propargyliques substitués par un groupement trifluorométhyle dans l'HFIP.

Inspirés par les précédents travaux effectués par notre groupe sur l'activation d'alcools benzyliques hautement désactivés (Schéma 2),[6] nous avons cherché à étendre ce type de réactivité à des alcools propargyliques portant un groupement CF_3 pour accéder dans un premier temps à des allènes trifluorométhylés en utilisant un système acide de Lewis (ou de Brønsted)/HFIP.

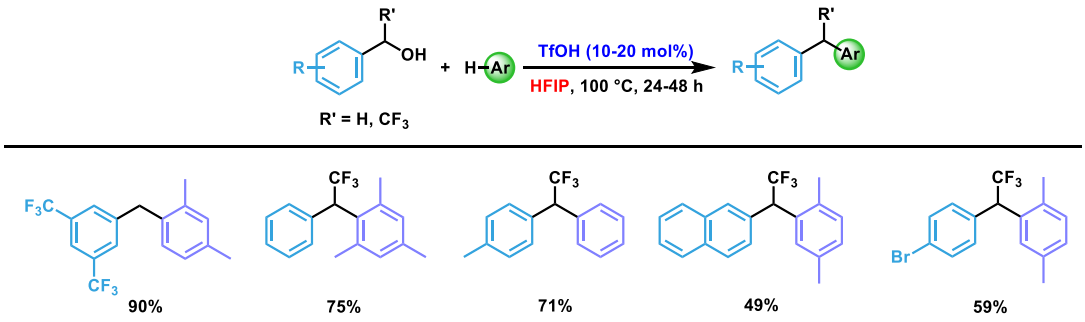

Schéma 1. Alkylation de Friedel-Crafts d'alcools benzyliques désactivés

Les alcools propargyliques constituent des briques moléculaires particulièrement attractives en synthèse grâce aux nombreuses transformations qu'ils peuvent engendrer. Par exemple, la substitution directe d'un alcool propargylique par un nucléophile peut conduire à deux types de produit, soit un alcyne α-substitué soit un allène, suivant les substituants présents sur le précurseur de départ (Schéma 3).

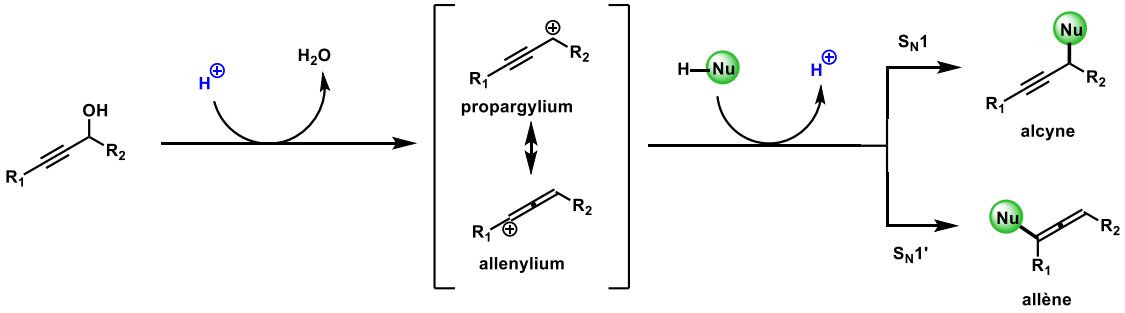

Schéma 2. Réactivité des alcools propargyliques dans des réactions de substitution nucléophile

Notre étude s'est concentrée sur les substrats portant un groupement CF_3 car celui-ci est connu pour être un bioisostère des substituants méthyles ou chlorures, pour augmenter la lipophilie et jouer sur la stabilité métabolique. Ce type de fonctionnalité est très populaire en chimie médicinale (Prozac, Celebrex, sustiva, etc.).

La première étape de ce projet était de tester différents acides en combinaison avec HFIP pour la synthèse d'allènes à partir d'alcools tertiaires. Les meilleurs résultats ont été obtenu avec $FeCl_3$ et une large variété d'allènes a pu être préparée avec jusqu'à 96% de rendement (Schéma 4). Des expériences de contrôle ont permis de mettre en évidence que $FeCl_3$ active en réalité HFIP qui est donc la véritable espèce active pour la réaction, celui-ci agissant comme un acide de Brønsted.

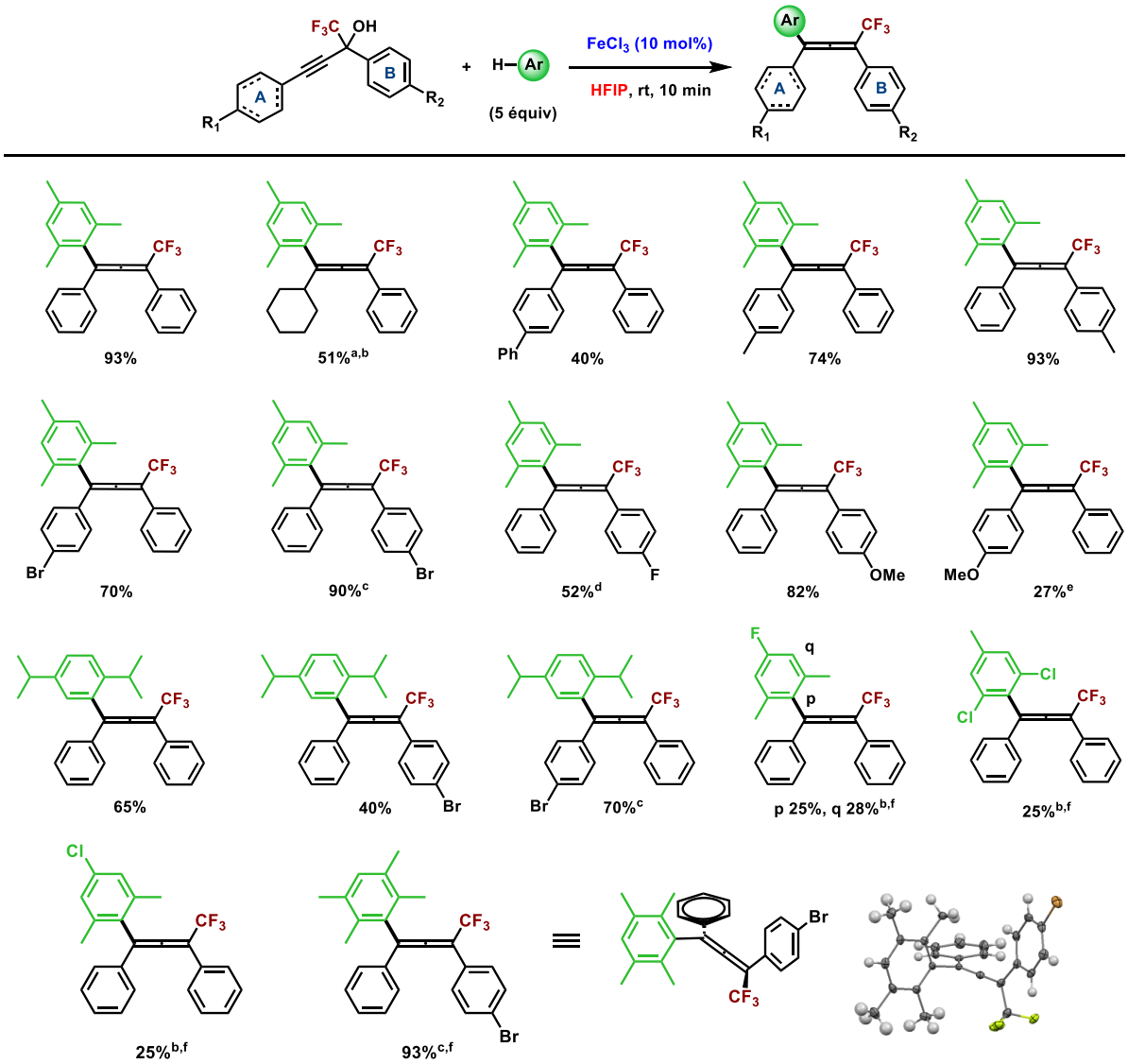

Schéma 3. Champ d'application pour la formation d'allènes. [a] réaction à 50 °C. [b] temps de réaction de 24 h. [c] temps de réaction de 3 h. [d] temps de réaction de 5 min. [f] réaction à 80 °C.

De façon intéressante, en prolongeant le temps de réaction et en augmentant la température, un autre produit a été obtenu, à savoir un indène (Schéma 5). Ce composé est obtenu par une réaction de Friedel-Crafts intramoléculaire à partir de l'allène, ce que nous avons confirmé en conduisant la réaction à partir de l'allène pur dans des conditions réactionnelles identiques.

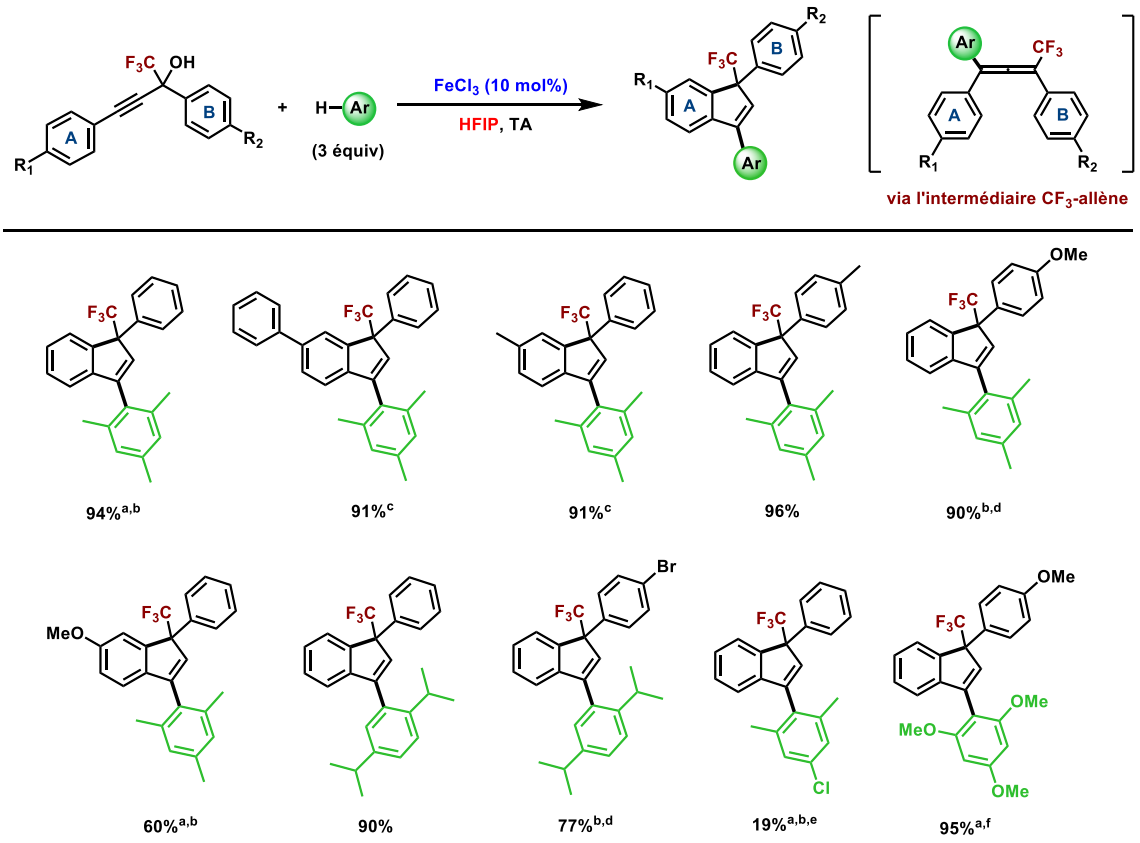

Schéma 4. Champ d'application pour la formation d'allènes. [a] temps de réaction de 24 h. [b] réaction à 80 °C. [c] réaction à 50 °C. [d] temps de réaction de 1 h. [e] Isolé sous forme d'une mixture de régioisomères. [f] réaction à 120 °C

Dans un second temps, nous avons décidé d'introduire un groupement hydroxyle en position *ortho* du cycle A, dans le but de générer des composés de type chromène *via* un mécanisme de piégeage intramoléculaire (Schéma 6). Nous avons pu noter que lorsque les substrats de départ étaient protégés par un groupement TBS, la réaction conduisait aux mêmes produits.

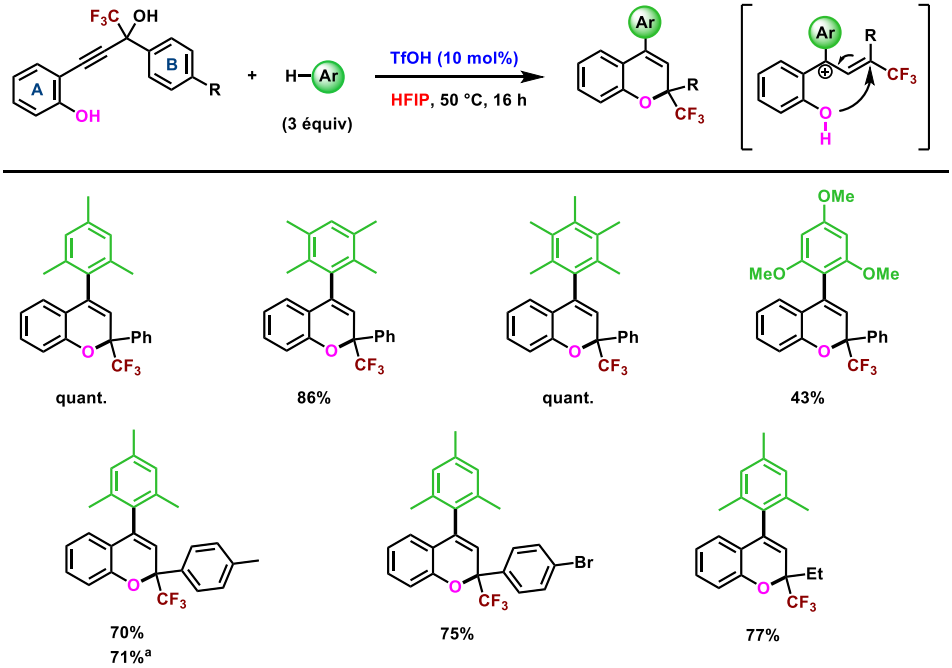

Schéma 5. Champ d'application pour la formation de chromènes. [a] temps de réaction de 24 h

En revanche, les alcools propargyliques secondaires ont présenté une réactivité différente de celle des alcools propargyliques tertiaires. A cause de leur encombrement stérique plus limité, le nucléophile présent dans le milieu peut s'additionner deux fois, ce qui a conduit à la formation de divers alcènes (Schéma 7). Il a pu être observé par RMN et par cristallographie aux rayons X qu'il y avait un phénomène de π-stacking entre les deux cycles aromatiques.

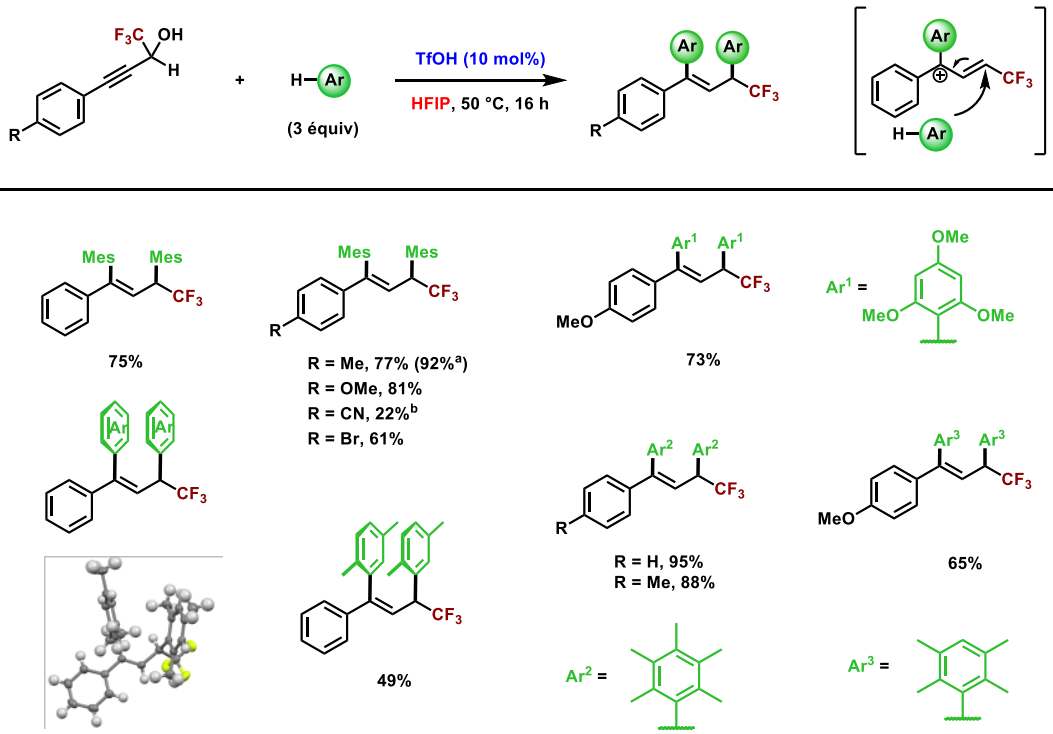

Schéma 6. Champ d'application pour la formation d'alcènes. [a] réaction à l'échelle du 1 mmol. [b] réaction à 100 °C pendant 88 h. Mes = 1,3,5-triméthylbenzène.

b) Alkylations de Friedel-Crafts d'alcools aliphatiques primaires dans l'HFIP

Après l'activation d'alcools benzyliques et propargyliques hautement désactivés, les recherches de notre laboratoire se sont orientées vers une transformation plus complexe, la substitution nucléophile directe d'alcools aliphatiques primaires. En raison de la difficulté inhérente à leur activation et l'instabilité liée à la potentielle formation d'un carbocation primaire, seules deux méthodes substitution directe utilisant la catalyse hétérogène (montmorillonite, zéolite) ont été rapportées dans la litérature.[7] Cependant, ces méthodes conduisent à un mélange de produits linéaires (addition du nucleophile en position terminale) et de produits branchés (addition du nucléophile à une autre position de la chaine aliphatique).

Dans ce contexte, nous pensions que l'utilisation de HFIP combinée avec un acide de Brønsted fort, comme l'acide triflique, pourrait permettre l'activation de ce type d'alcools. Même si les rendements ne sont pas toujours excellents à cause de formation d'oligomères en produits secondaires, cette approche est tout de même très sélective pour la formation de produits linéaires (Schéma 8). Comme attendu, les produits branchés ont été observés lorsque la réaction était conduite à des concentrations plus élevées (1 M contre 0.25 M). Des calculs DFT effectués par le Dr. Chris Rowley supportent un mécanisme de type S_N2 pour l'activation de ces alcools primaires.

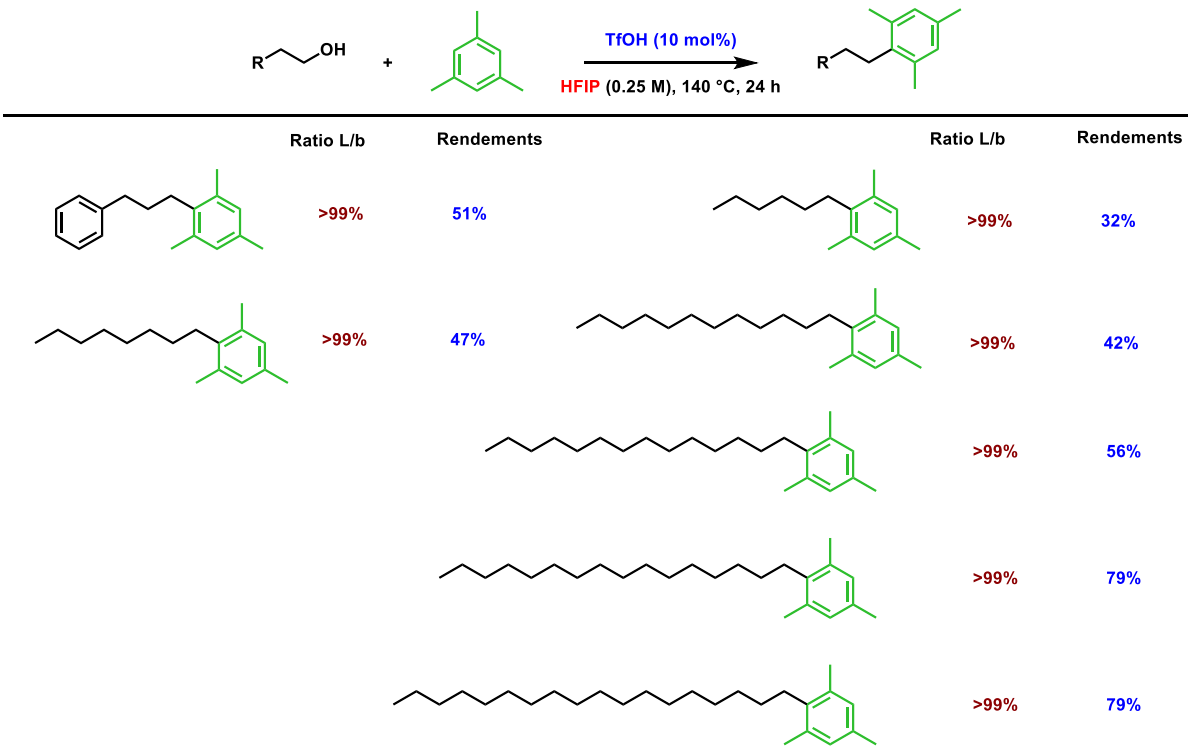

Schéma 7. Champ d'application pour l'activation d'alcools primaires

La combinaison TfOH/HFIP s'est révélée être également hautement efficace pour l'activation de dérivés 2-phényléthanols (Schéma 9). Cette différence de réactivité peut être attribuée à la formation d'un intermédiaire réactionel stable de type arénium qui a souvent été décrit dans la litérature.[8]

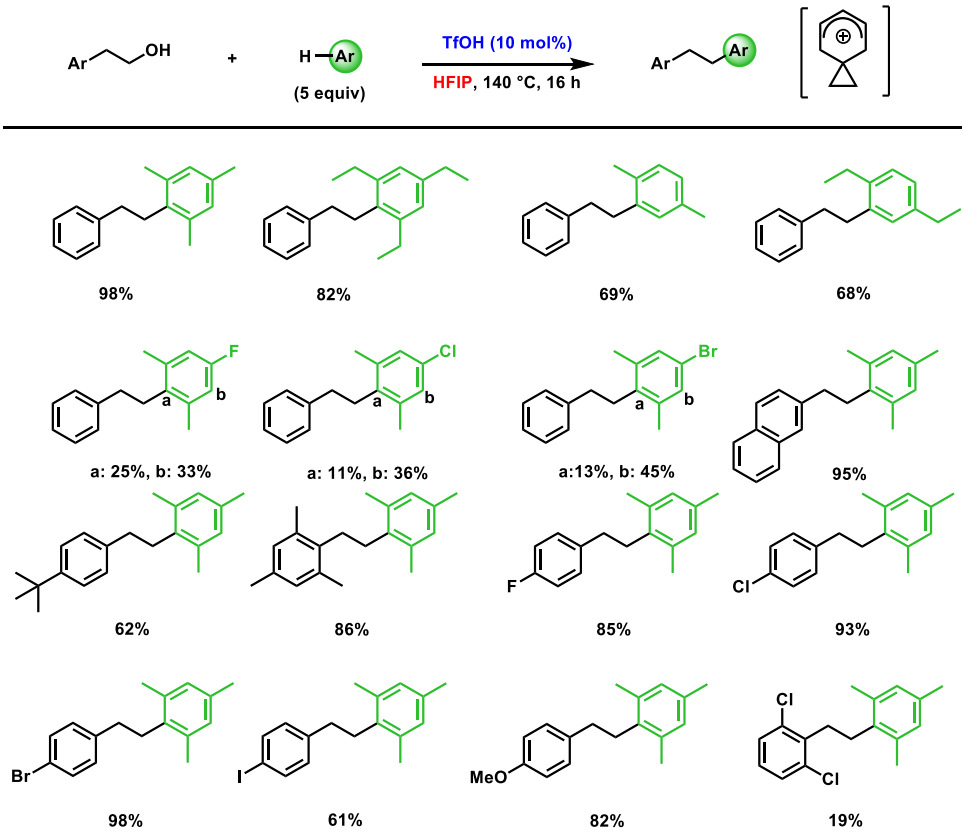

Schéma 8. Champ d'application pour l'activation de 2-phényléthanols

3) Conclusion générale

Ainsi, nous avons pu démontrer la versatilité de la combinaison de HFIP avec un acide de Brønsted ou de Lewis dans plusieurs réactions inédites, laissant entrevoir le potentiel de cette méthode pour son exploitation dans de nouvelles transformations. Dans le cas d'alcools peu réactifs (alcools aliphatiques primaires ou alcools substitués en position α par un groupement électro-attracteur), l'utilisation de la combinaison TfOH/HFIP s'est généralement avérée être la solution la plus efficace pour résoudre les problèmes de réactivités.

En résumé, une méthode efficace pour la synthèse d'allènes, d'indènes, de chromènes et d'alcènes portant un groupement CF_3 à partir d'alcools propargyliques a pu être développée. En utilisant un système similaire, l'activation d'alcool primaire a également été rendue possible mais reste encore à optimiser. Cette méthode s'est montrée particulièrement sélective pour la formation du produit linéaire, ce qui n'avait jamais été rapporté auparavant dans la littérature.

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Introduction

1.1. HFIP: a solvent with atypical properties

Hexafluoroisopropanol or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is a versatile solvent with a wide range of applications in organic chemistry, material science and biology, without forgetting to mention its fundamental theoretical interest.[1] The aim of this section is to present the key physical and chemical properties of HFIP and explain why this solvent stands apart from other fluorinated and non-fluorinated solvents.[2]

1.1.1. Generalities about HFIP

HFIP is an alcohol solvent that is miscible with water and most of the common organic solvents.[1] Due to its low boiling point (59 °C), HFIP can be easily recovered by distillation once the reaction is complete. As an example, some industrial processes began to emerge, relying on its co-distillation with heptanes.[3] HFIP is also thermally stable, which allows its use in reactions at high temperatures.

However, what makes HFIP a unique solvent is the combination of a variety of properties that cannot be found all at once in other traditional solvents. Among them, we can cite:

(1) the presence of the two trifluoromethyl groups that generate a strong negative inductive effect, which in turn makes HFIP 10^7 times more acidic than isopropanol (pK_a of 9.3 and 17.1, respectively). Besides its low pK_a, HFIP has a range of acidity achievable in a given solvent that is comparable to that of water, though it is closer to formic acid in terms of absolute values (Figure 1).

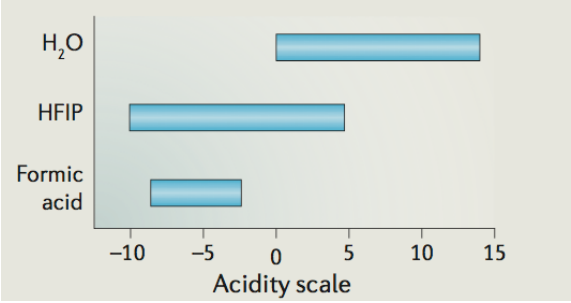


Figure 1: Acidity scale (the acidities achievable in a given solvent). Reproduced from ref 1e.

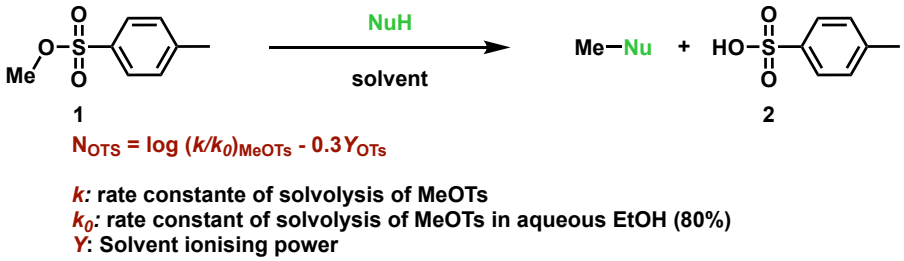
(2) Another important feature of HFIP is its low nucleophilicity, which is critical to prevent side reactions that could occur in transformations involving other nucleophilic species. To continue the comparison with *i*PrOH, the value of the nucleophilic parameter of

[1] (a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18; (b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925; (c) T. Sugiishi, M. Matsugi, H. Hamamoto, H. Amii, *RSC Adv.* **2015**, *5*, 17269; (d) J. Wencel-Delord, F. Colobert, *Org. Chem. Front.* **2016**, *3*, 394; (e) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088; (f) S. K. Sinha, T. Bhattacharya, D. Maiti, *React. Chem. Engl.* **2019**, *4*, 244; (g) V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun.* **2020**, *56*, 11548.

[2] A. J. Phillips, *e-EROS Encycl. Reagents Org. Synth.* http://dx.doi. org/10.1002/047084289X.rn01164 (2010).

[3] S. J. Brenek, S. Caron, E. Chisowa, M. P. Delude, M. T. Drexler, M. D. Ewing, R. E. Handfield, N. D. Ide, D. V. Nadkarni, J. D. Nelson, M. Olivier, H. H. Perfect, J. E. Phillips, J. J. Teixeira, R. M. Weekly, J. P. Zelina, *Org. Process Res. Dev.* **2012**, *16*, 1348.

HFIP is N_{OTs} = −4.23, while N_{OTs} = 0.2 for *i*PrOH (Scheme 1). N_{OTs} is a nucleophilicity scale developed by Schleyer to describe the nucleophilic strength of a solvent.[4] In the equation below, 0.3 is a nucleophile-specific parameter linked to methyl tosylate. Thus, the higher the N_{OTs} parameter, the higher the nucleophilicity of a given solvent.



Scheme 1: Nucleophilicity parameter N_{OTs}

(3) Due to its high dielectric constant (ε= 15.7) and low nucleophilicity, HFIP is an excellent solvent to form and study cationic species.[1,5]
(4) Due to its redox stability, its use in electrochemical processes and transformations involving highly oxidizing reaction conditions is extremely widespread.[6]

Nevertheless, the most important property of HFIP remains probably its strong H-bond donating ability, which will be a recurrent thread in this manuscript. However, before examining it in more detail, let us first compare HFIP to other alcohol solvents.

1.1.2 H-bond donating ability, polarity and acidity of HFIP *vs* fluorinated and non-fluorinated solvents

The H-bond donating ability (HBD), polarity and acidity of a molecule are intimately linked to each other. Nevertheless, differences can be observed between related classes of molecules. For instance, the acidity and polarity of compounds do not always correlate, and the same is true for H-bond donating ability. The work of Bonnet-Delpon and co-workers emphasized that those variations are important in the case of fluorinated and non-fluorinated alcohols.[7]

With respect to trifluoromethylated solvents, the pK_a will be dependent on the number of CF_3 groups present at the α-position of the alcohol (Table 1). While the pK_a will be around 12 in the case of one CF_3, a pK_a will be around 9 with two CF_3.

[4] F. L. Schadt, T. W. Bentley, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1976**, *98*, 7667.
[5] G. Hallett-Tapley, F. L. Cozens, N. P. Schepp, *J. Phys. Org. Chem.* **2009**, *22*, 343.
[6] S. Ayata, A. Stefanova, S. Ernst, H. Baltruschat, *J. Electro. Chem.* **2013**, *701*, 1.
[7] D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. Bonnet-Delpon, *J. Org. Chem.* **2011**, *76*, 1126.

Solvent	pK_a (H_2O)	pK_a (MeOH/H_2O)
TFE	12.4	11.8
$PhCF_3CHOH$	11.9	11.7
HFIP	9.3	9.5
$Ph(CF_3)_2COH$	8.8	9.3

Table 1: pK_a of fluorinated alcohols

Bonnet-Delpon and co-workers compared the properties of several fluorinated and non-fluorinated alcohols using three different methods (Figure 2):

Regarding the H-bond acceptance (HBA), they used the Kamlet-Taft scale (β parameter). This parameter is obtained by measuring the solvatochromic shift of 4-nitrophenol **3** compared to that of 4-nitroanisole **4** in the presence of a given alcohol. The closer that parameter is to 0, the lower the HBA of the molecule.

Two other methods were used to compare the H-bond donating ability. The first one is the use of $E_T(30)$, which is the solvatochromic shift of Reichardt's "betaine 30" **5**. This parameter is employed to measure the polarity of a solvent and is sensitive to the bulkiness of the solvent. The second one is the acceptor number (AN) parameter, which is obtained by analyzing the ^{31}P chemical shift of triethylphosphine oxide **6** (TEPO), known as the Gutmann-Becket method. As TEPO is a smaller molecule than Reichardt's betaine 30, the AN parameter is less sensitive to steric hindrance. In both cases, the higher the value of AN, the more polar the solvent.

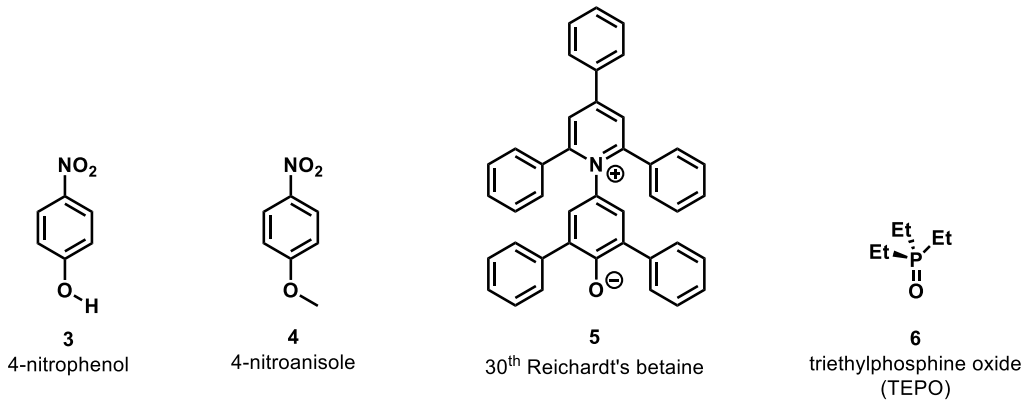


Figure 2: Molecules used to determine HBA and HBD

β parameters of different fluorinated and non-fluorinated solvents are gathered in (Table 2). Remarkably, the values of β for alcohols bearing two trifluoromethyl groups are close to 0, thereby not acting as hydrogen-bond acceptance. On the other hand, trifluoromethylated alcohols such as TFE and $PhCF_3CHOH$ displayed measurable β values, which means that they can slightly accept hydrogen bonds.

Solvent	β (Kamlet-Taft HBA scale)
EtOH	0.81
TFE	0.22
$PhCF_3CHOH$	0.28
HFIP	~0
$Ph(CF_3)_2COH$	~0
$All(CF_3)_2COH$	0.03
$Pr(CF_3)_2COH$	~0

Table 2: β parameter of several alcohols

Using a plot of $E_T(30)$ *versus* AN (Figure 3), a correlation could be observed between all the non-fluorinated alcohols, with the exception of ^{t}BuOH. Most of the studied trifluoromethylated alcohols ($PhCF_3CHOH$, $Ph(CF_3)_2COH$, $All(CF_3)_2COH$ and $Pr(CF_3)_2COH$) have a better AN than $E_T(30)$. In other words, they are less efficient at stabilizing bulky molecules. Yet, TFE and HFIP do not suffer from this downside.

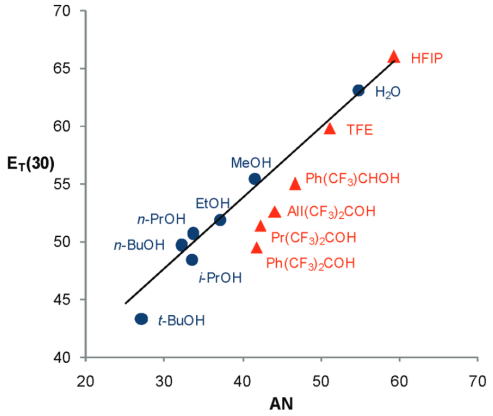


Figure 3: Plot of $E_T(30)$ VS AN ($E_T(30)$ = 0.614 x AN + 29.28)

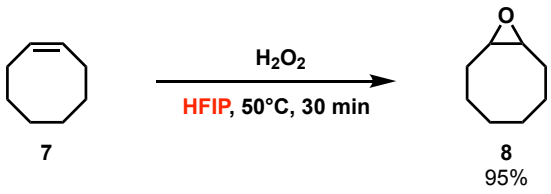
In summary, HFIP is a highly polar solvent able to stabilize cations regardless of their bulkiness. Most of the stabilizing effects of HFIP are due to its HBD because of its very low β parameter. The pK_a of a trifluoromethylated alcohol depends on how many CF_3 groups it has. However, the ability of HFIP to form aggregates plays a major role in its H-bond donating ability.

1.1.3. `Boosting' effect of HFIP aggregates

Olefin epoxidation by hydrogen peroxide is an appealing reaction, since water is the only byproduct of this reaction and the process is rather user-friendly.[8,9,10,11] This reaction is one of the best examples of the boosting effect of HFIP on chemical reactivity, as, in HFIP, this reaction is 10^5 time faster when compared to other polar solvent such 1,4-dioxane (Scheme 2). Several computational studies have been carried out on this reaction. In their initial studies,

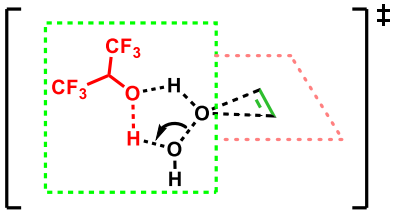
[8] A. Berkessel, J. A. Adrio, *Adv. Synth. Catal.* **2004**, *346*, 275.
[9] A. Berkessel, J. A. Adrio, D. Hüttenhain, J. Neudörfl, *J. Am. Chem. Soc.* **2006**, *128*, 8421.
[10] A. Berkessel, J. A. Adrio, *J. Am. Chem. Soc.* **2006**, *128*, 13412.
[11] O. Hollóczki, A. Berkessel, J. Mars, M. Mezger, A. Wiebe, S. R. Waldvogel, B. Kirchner, *ACS Catal.* **2017**, *7*, 1846.

Shaik and co-workers considered that the mode of action of HFIP was monomolecular.[12] However, recent studies leaned towards the involvement of higher aggregates.[8]



Scheme 2: HFIP-assisted epoxidation of cyclooctene with H_2O_2

Indeed, kinetic studies on the epoxidation of cyclooctene by Berkessel and Adrio indicated a first order kinetic dependence in cyclooctene and a kinetic dependence on HFIP between 2 and 3, depending on the co-solvent used.[10] Furthermore, the ΔS calculated for the rate-determining step using an Eyring plot is higher than the one for traditional epoxidation by peracids (ΔS = -39 cal.mol^{-1}.K^{-1} and ΔS = -18 to -30 cal.mol^{-1}.K^{-1}, respectively).[13] From prior investigations, the authors deduced that 2 to 3 molecules of HFIP were involved in the rate determining step, but only 1 molecule of olefin and 1 molecule of peroxide. The highly negative entropy, obtained by using an Eyring plot, compared with more traditional epoxidation is consistent with the involvement of higher-order HFIP aggregates in the transition state of the RDS. A concerted mechanism involving a spiro-bicyclic intermediate has also been proposed as a transition state for the oxygen transfer from H_2O_2 to the olefin (Scheme 3). Complementary in-silico studies by Kirchner and co-workers confirmed the involvement of such aggregates, with hydrogen peroxide interacting with 3 molecules of HFIP and ethylene (Figure 4).[11]



Scheme 3: Spiro-bicyclic intermediate in HFIP-assisted olefin epoxidation

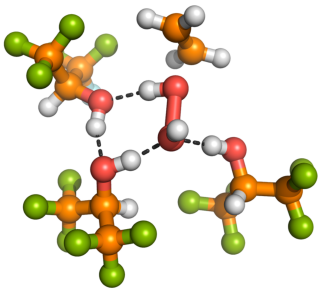


Figure 4: HFIP-promoted epoxidation of ethylene

Considerable efforts have been dedicated to the analyses of those aggregate. Berkessel, and co-workers combined DFT, NMR, kinetic and X-ray data with this aim.[9] Titration experiments

[12] S. P. de Visser, J. Kaneti, R. Neumann, S. Shaik, *J. Org. Chem.* **2003**, *68*, 2903.
[13] V. G. Dryuk, *Tetrahedron* **1976**, *32*, 2855.

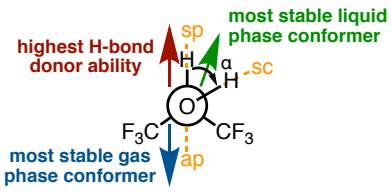
monitored by ^{1}H NMR between HFIP and an electron acceptor, 1,4-dioxane, showed only one signal for the OH proton with a significant downfield shift. Consequently, those two observations led the authors to the conclusion that HFIP aggregates are dynamic. In other words, HFIP aggregates are not fixed in solution. They are involved in a dynamic hydrogen bonding interaction with 1,4 dioxane but are disrupted so rapidly that they could not be observed by NMR.

As a monomer, in gas phase, the hydroxyl group of HFIP adopts an antiperiplanar (ap) conformation as the synclinal (sc) conformation is around 1 $kcal.mol^{-1}$ higher in energy than the (ap) one (Scheme 4). In agreement with quantum-chemical investigations and X-ray studies (Figure 5), the HFIP hydroxyl group adopts a (sc) to synperiplanar (sp) conformation in the liquid phase. This phenomenon reaches its maximum intensity for dimers or trimers of HFIP.

All the torsion angles are given between the CH bound and the OH bound of HFIP along the CO bound:
sp: synperiplanar 0° to 30°
sc: synclinal 30° to 90°
ap: antiperiplanar 150° to 180°

Overall, the authors emphasized that the conformation along the hydroxyl bond in HFIP is critical for the H-bond donating ability. At the electronic level, the closer the conformation is to (sp), the lower is the σ*OH and the higher the dielectric constant.

In summary, the HBD of HFIP is directly related to its ability to generate aggregates in the liquid phase. Those aggregates induce a specific conformation along the CO bond, a synclinal conformation, which is different from that of the monomer in the gas phase. HFIP dimers and trimers have been identified as responsible for the reactivity of HFIP.



Scheme 4: HFIP conformers

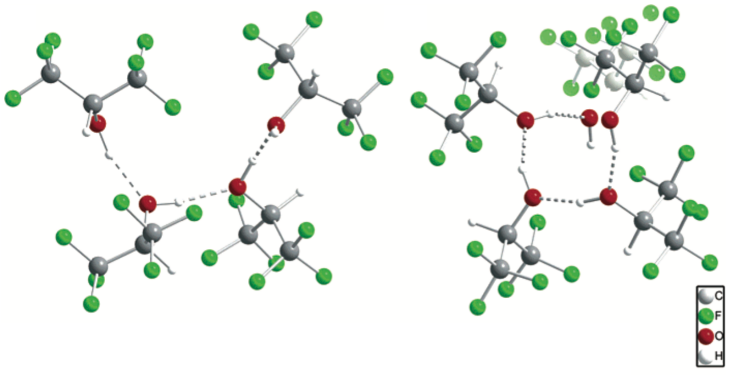


Figure 5: HFIP X-Ray structures[11]

Moreover, molecular orbital studies on HFIP by Lebœuf and co-workers demonstrated that the energy of the LUMO of HFIP decreased by half upon dimerization. Therefore, HFIP might not only be considered as an efficient H-bond donating solvent, but also as a Lewis base acceptor.[14]

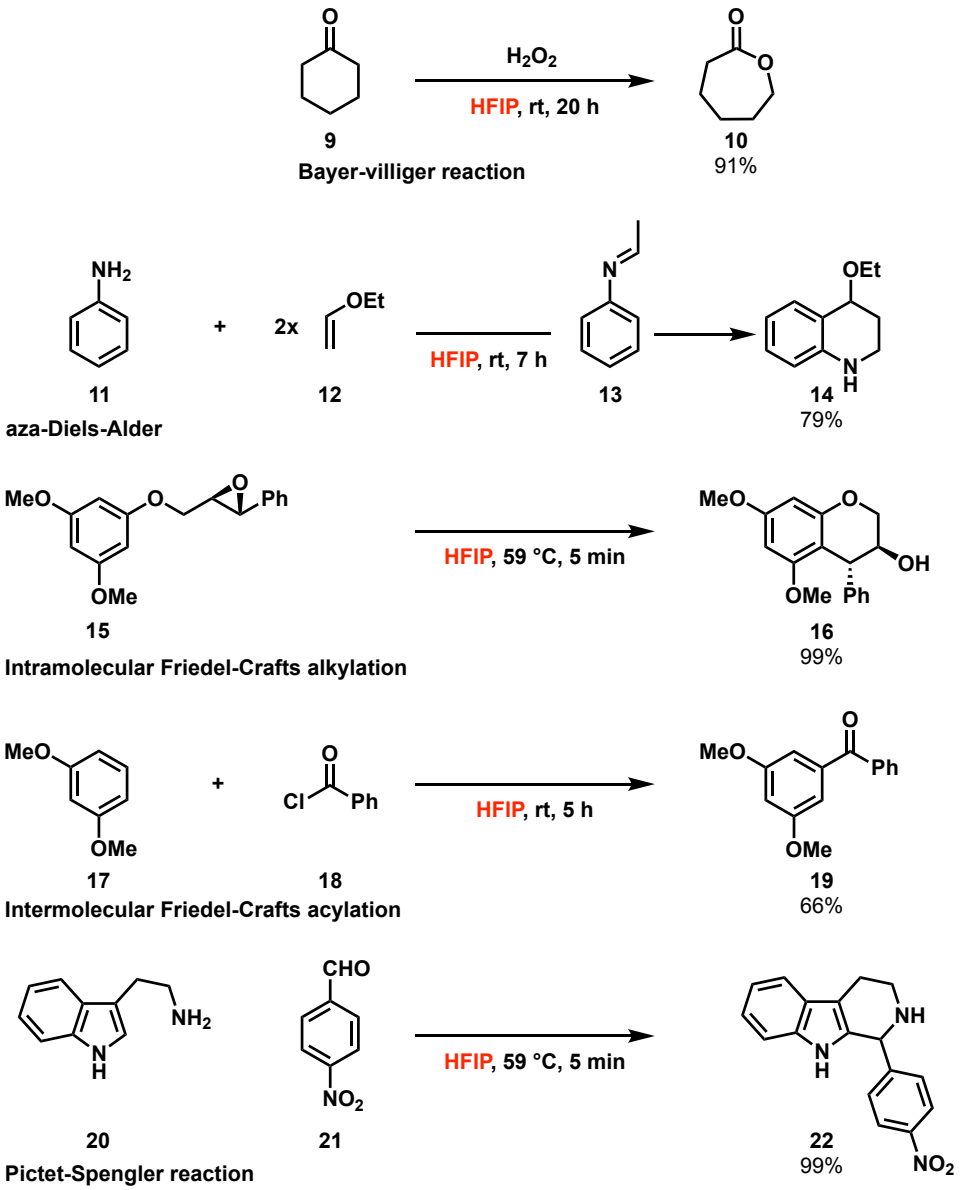
1.2. Use of HFIP as a solvent in organic synthesis

The objective of this section is to provide an overview of reactions that can be performed in HFIP. This part will focus on reactions that could not be achieved without HFIP or that required stoichiometric amounts of activating agent in the absence of HFIP. To stay consistent with the previous chapter, a first sub-part will be dedicated to transformations involving HFIP as sole promoter. A second sub-part will be devoted to the combination of Brønsted or Lewis acid catalysts with HFIP. To facilitate the reading and give a general view toward the progress in the area, the reactions will be described in chronological order.

1.2.1. HFIP as Sole Promoter

From the past 20 years, many reports have been published on the remarkable reactivity of HFIP (as well as TFE) as sole promoter (Scheme 5). Interestingly, the scope of reactions promoted by HFIP as a solvent is not limited to epoxidation; in 2000, the group of Neumann reported the Baeyer-Villiger oxidation of ketones with hydrogen peroxide.[15] Later on, the group of Berkessel demonstrated that this version of the Baeyer-Villiger oxidation was going through a completely different mechanism from the classic peracid-induced reaction.[16] In 2003, the group of Bonnet-Delpon developed a method for the aza-Diels-Alder reaction between *N*-arylimines, starting from arylimine **13** and enol ether **12** (Povarov reaction).[17] In 2010, the group of Qu accomplished the intramolecular Friedel-Crafts cycloalkylation of arene epoxide **15**.[18] This reaction could be conducted in both HFIP and TFE, although HFIP proved to be much more efficient. More recently, Aubé and co-workers described an intermolecular Friedel-Crafts acylation under similar reaction conditions.[19] In 2014, the group of Qu reported that tetrahydro-β-carbolines could be synthesized via a Pictet-Spengler reaction between tryptamine **20** and aldehydes such as **21**.[20]

[14] D. Lebœuf, L. Marin, B. Michelet, A. Perez-Luna, R. Guillot, E. Schulz, V. Gandon, *Chem. Eur. J.* **2016**, *22*, 16165.
[15] K. Neimann, R. Neumann, *Org. Lett.* **2000**, *18*, 2861.
[16] A. Berkessel, M. R. M. Andreae, H. Schmickler, J. Lex, *Angew. Chem. Int. Ed.* **2002**, *41*, 4481.
[17] A. Di Salvo, M. V. Spanedda, M. Ourévitch, B. Crousse, D. Bonnet-Delpon, *Synthesis*, **2003**, 2231.
[18] G.-X. Li, J. Qu, *Chem. Commun.* **2010**, *46*, 2653.
[19] R. H. Vekariya, J. Aubé, *Org. Lett.* **2016**, *18*, 3534.
[20] L.-N. Wang, S.-L. Shen, J. Qu, *RSC Adv.* **2014**, *4*, 30733.



Scheme 5: Examples of reactions with HFIP as sole promoter

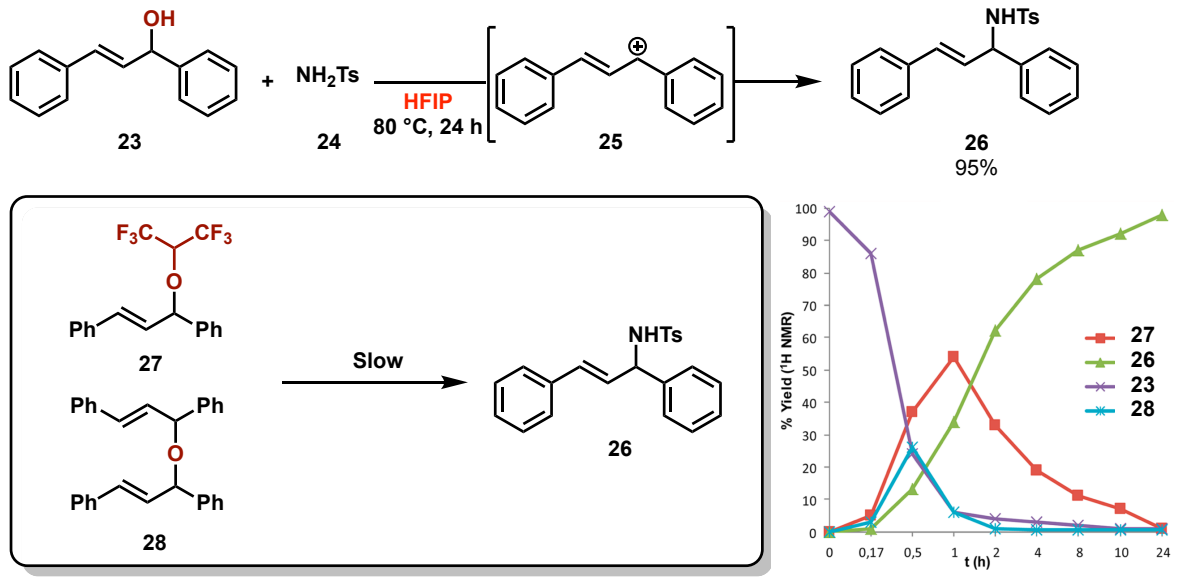
Aside from those examples, manifold examples have been depicted in the literature regarding reactions using HFIP as sole promoter. The next set of reactions will be more detailed, as they are representative of what could be accomplished in HFIP without any additional catalyst.

In 2012, the group of Nájera discovered that substitution of allylic alcohols could be directly achieved in HFIP (Scheme 6).[21] A large range of nucleophiles was tolerated, including amines, silyl enol ethers and arenes. Surprisingly, even more basic aliphatic amines worked with this method. This reaction proved to be particularly efficient for aromatic allylic alcohols as substrates. The key challenge of the process is to avoid the dimerization of the starting material or the trapping of the intermediate by the solvent.

Regarding the mechanism, three pathways have been identified: one involves a direct substitution and two involve indirect substitution. In the case of the direct substitution

[21] P. Trillo, A. Baeza, C. Nájera, *J. Org. Chem.* **2012**, *77*, 7344.

pathway, the aromatic allylic alcohol **23** reacts directly with tosylamide to form the allylic adduct **25** via a postulated carbocationic intermediate. The indirect pathways go through the formation of two carbocation reservoirs, the HFIP product **27** and the ether **28** formed by dimerization of the starting material. Owing to its Lewis acidic character and its strong H-bond donating ability, the formation of those byproducts is reversible. For every substrate studied, HFIP proved to be more active than its analog TFE.



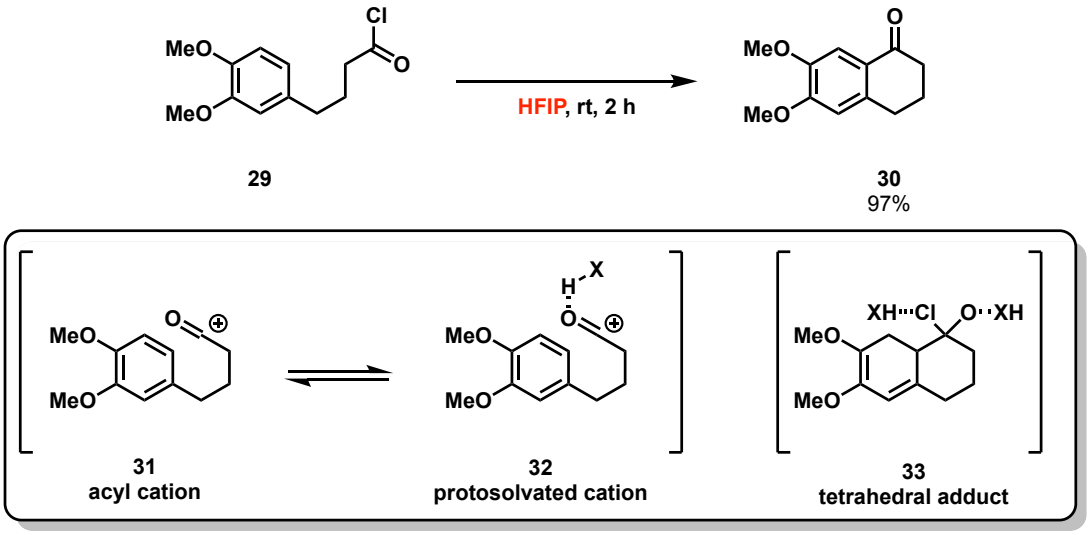
Scheme 6: Substitution of allylic alcohols with HFIP as a sole promoter

The group of Aubé[22] investigated a catalyst-free version of the intramolecular Friedel-Crafts acylation using HFIP as sole promoter (Scheme 7). Original versions of this reaction required the use of stoichiometric amounts of acid catalyst because of the coordination of the ketone product to the acid catalyst. Surprisingly, the reaction worked well with other polar HBA-free solvent such as DCM in the presence of a catalytic amount of HFIP. On the other hand, the use of a solvent with a strong H-bond acceptance such as 1,4-dioxane in combination with HFIP shut down the reaction, which highlights the importance of the HBD ability of HFIP in this reaction.

Regarding the mechanism, the possibility that the transformation of the acyl chloride **29** into the ketone **30** goes through an HFIP ester was ruled out, as the adduct of **28** and HFIP proved to be inefficient to furnish the product **30** in HFIP. The authors suggested that the reactivity might be explained by the intrinsic acidity of HFIP acidity. As anticipated, the addition of a base precluded the reaction. However, the reaction of **29** in DCM in the presence of 1 equivalent of HFIP was far more efficient than the one in DCM in the presence 1 equivalent of HCl, which is produced during the reaction. Yet, as pK_a(HCl) < pK_a(HFIP), the HBD of HFIP might play a major role in this reaction aside from its acidity. Based on those data, the authors proposed two plausible intermediates. First, an *in-situ* ionization of **29** could occur to form an acyl cation **31** that could be in equilibrium with a protosolvated cation **32**. Their second idea was the possibility that the aryl ring directly attacked the acyl chloride to generate a

[22] H. F. Motiwala, R. H. Vekariya, J. Aubé, *Org. Lett.* **2015**, *17*, 5484.

tetrahedral adduct **33**. Such activated species could exist owing to the strong HBD of HFIP and its Lewis acids character.



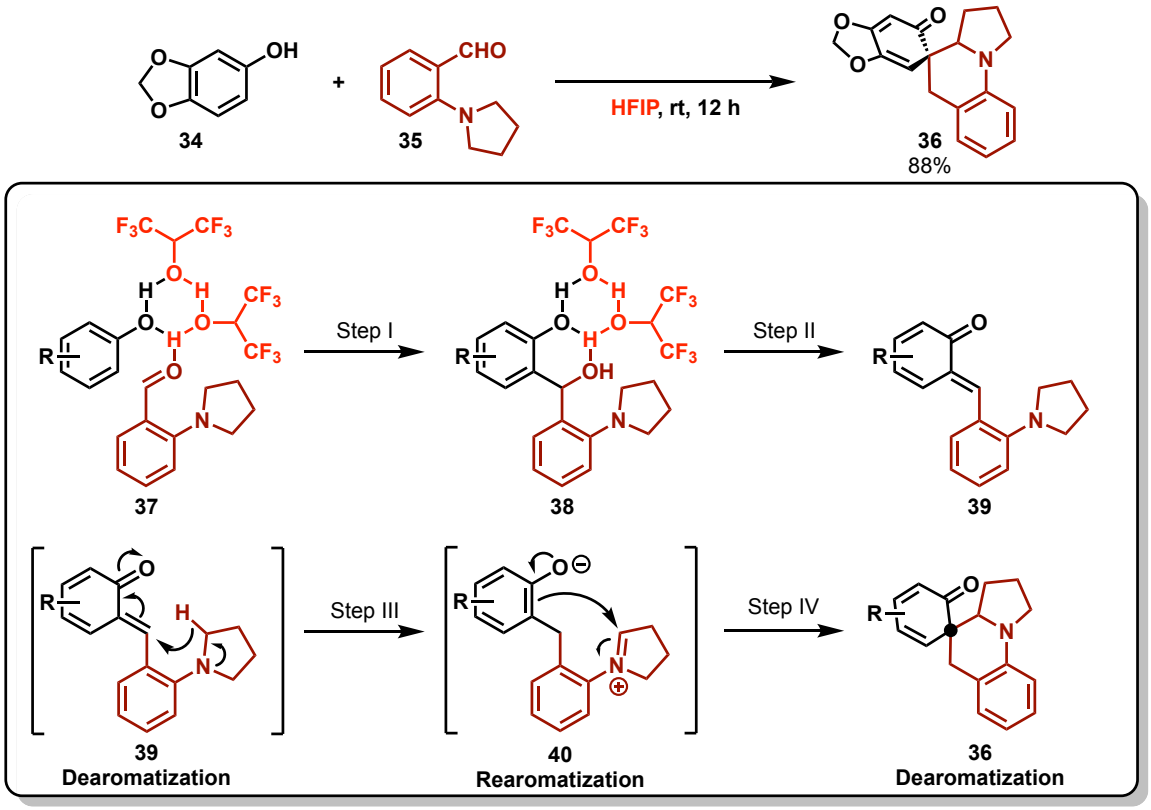
Scheme 7: Intramolecular Friedel-Crafts acylation with HFIP as a sole promoter

Challenging reactions could thus be achieved with simple reaction conditions. Xiao and co-workers reported an elegant one-pot reaction using HFIP. In this reaction, a cascade dearomative cyclization occured between phenol **34** and *o*-aminobenzaldehyde **35** to form nitrogen-containing compound **36** (Scheme 8).[23]

Such densely functionalized cyclic amines are of high interest for the pharmaceutical industry. Although this reaction involves several chemical events, the use of mild conditions featuring HFIP as a solvent prevented the formation of any side product.

Regarding the mechanism, KIE experiment indicated that the [1,5]-hydride shift was not the rate determining step. Thus, the authors deduced that the driving force for this reaction was the ability of the *ortho*-quinone methide **39** formed *in-situ* to trigger the [1,5]-hydride shift by a rearomatization process (step 3). The authors suggested that HFIP assisted the formation of the *ortho*-quinone methide due to its HBD ability through the aggregates **37** and **38**.

[23] S.-S. Li, X. Lv, D. Ren, C.-L. Shao, Q. Liu, J. Xiao, *Chem. Sci.* **2018**, *9*, 8253.



Scheme 8: Synthesis of nitrogen-containing polycyclic compound using HFIP as a sole promoter

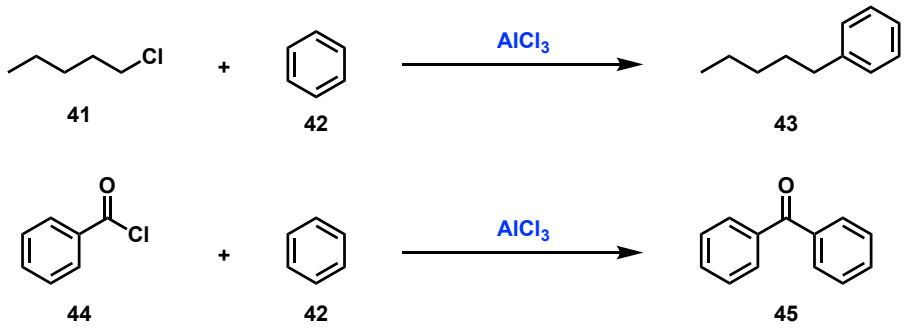
1.3. HFIP in combination with Brønsted and Lewis acids

This part aims to present a global view on the state of the art in the field of Brønsted and Lewis acid catalysis in HFIP, focusing on the different types of reactions.

1.3.1. Friedel-Crafts reaction

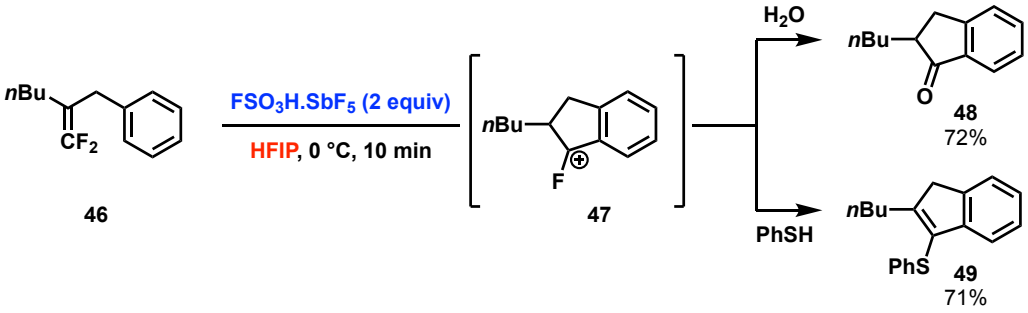
The Friedel-Crafts reaction was first reported in 1887 by Charles Friedel and James Manson Crafts.[24,25] They started their investigations by mixing alkyl chlorides and $AlCl_3$. A large acid chloride release was observed. From this observation, they concluded that `the organic chlorides are attacked by aluminum chlorides' and assumed that it would be of interest in organic synthesis. Indeed, based on this discovery, they developed two famous reactions (Scheme 9): the Friedel-Crafts alkylation, which is the reaction between an alkyl halide and an aromatic nucleophile, and the Friedel-Crafts acylation, which is the addition/elimination of an acyl halide with an aromatic nucleophile.

[24] C. Friedel, J.-M. Crafts, *Compt. Rend. Acad. Sci. Paris*, **1877**, *84*, 1392.
[25] C. Friedel, J.-M. Crafts, *Compt. Rend. Acad. Sci. Paris*, **1877**, *84*, 1450.



Scheme 9: Original Friedel-Crafts reactions

One of the first reports of Friedel-Crafts reaction using HFIP as solvent was published in 2004 by the group of Ichikawa.[26] This study described the defluorinative Friedel-Crafts cyclization of 1,1-difluoroalkene (Scheme 10). Original Friedel-Crafts reactions required the use of chloride, bromide or iodide as a leaving group. Fluoride was usually let aside as the strength of the C-F bond is much higher than that of other carbon-halogen bonds. Surprisingly, the authors found that the reaction was quicker and furnished better yields with fluorinated substrates than with chlorinated or brominated substrates, although 2 carbon-halide bonds had to be broken during the reaction. This difference of reactivity was attributed to the ability of fluorine to stabilize carbocations in the α-position by injecting electron density on the π-vacant orbital (hyperconjugation effect) and its ability to be stable in its anionic form owing to its electronegativity. Once again, HFIP proved to be superior to other fluorinated and non-fluorinated solvents for this reaction due to its high ionizing power and low nucleophilicity.



Scheme 10: Friedel-Crafts defluorinative cyclization of 1,1-difluoroalkenes

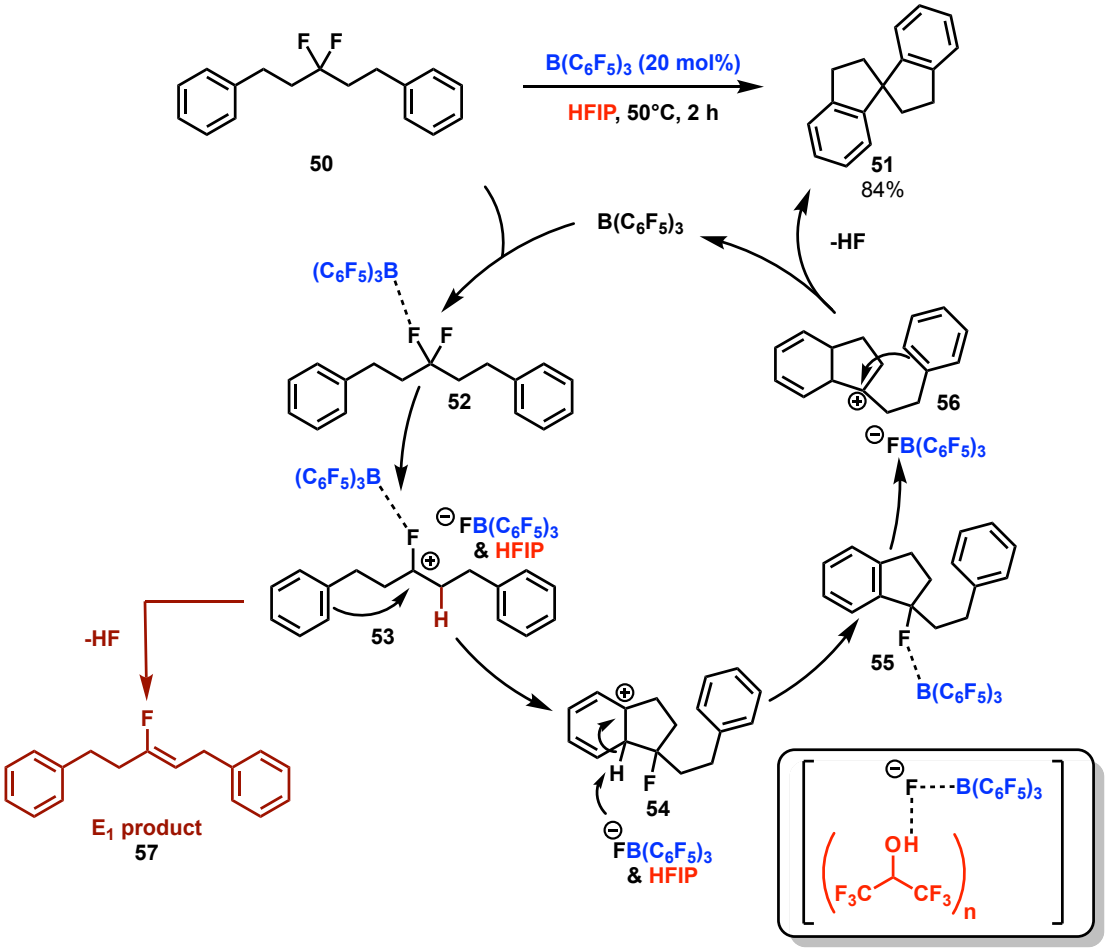
Then, in 2008 and 2015, the group of Ichikawa extended the scope of the Friedel-Crafts defluorinative cyclization of 1,1-difluoroalkene to the synthesis of *ortho*-condensed polycyclic helicenes.[27] These compounds exhibit interesting optical activity and great potential in molecular recognition, asymmetric synthesis, dyes and material science. In 2015, they described that, under similar reaction conditions, dibenzo[*g,p*]chrysenes that are π-twisted polycyclic unsaturated molecules could be prepared.[28] Such molecules have application as semiconductors for thin-film transistors or organic light-emitting diodes.

In the same vein, in 2019, the group of Shibata developed a cascade Friedel-Crafts cyclization of fluorinated arylalkanes catalyzed by $B(C_6F_5)_3$ for the synthesis of spirobiindanes (Scheme

[26] J. Ichikawa, H. Jyono, T. Kudo, M. Fujiwara, M. Yokota, *Synthesis* **2005**, 39.
[27] J. Ichikawa, M. Yokota, T, Kudo, S. Umezaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 4870.
[28] N. Suzuki, T. Fujita, J. Ichikawa, *Org. Lett.* **2015**, *17*, 4984.

11).[29] This method overcame two major challenges, namely the activation of inert Csp^3-F bond and avoiding the formation of competing elimination E[1] product. Indeed, the use of another solvent such 1,4-difluorobenzene led to the elimination product. This product was also observed when more basic leaving groups such as bromide were used.

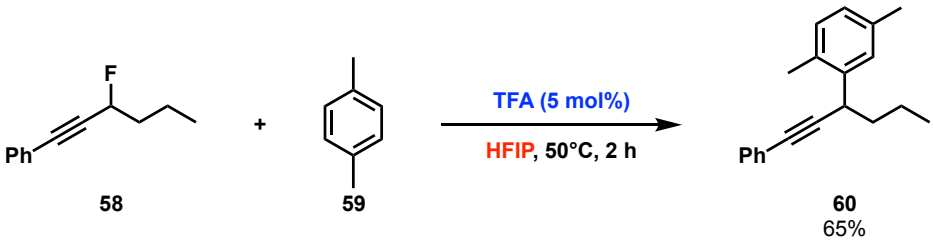
Herein, HFIP served a dual purpose. It reduced the Brønsted basicity of the fluoride anion, therefore suppressing the elimination process, and it stabilize the numerous carbocationic intermediates involved in this reaction. Similar effects on the basicity of fluorides have been observed for CsF[30] and TBAF[31] regarding tertiary alcohols.



Scheme 11: Defluorinative Friedel-Crafts cyclization of fluorinated arylalkanes into spirobiindanes

To conclude the discussion on defluorinative Friedel-Crafts reactions in HFIP, this reactivity is not limited to intramolecular cyclizations. The group of Paquin reported the Friedel-Crafts aromatic propargylation of secondary propargylic fluorides in 2017 (Scheme 12).[32] As for all defluorinative Friedel-Crafts, up to one equivalent of HF is produced during the process. As HF pK_a(HF) is lower than pK_a(TFA), the authors suggested that the generation of HF becomes the true active species during the reaction.

[29] J. Wang, Y. Ogawa, N. Shibata, *iScience*, **2019**, *17*, 132.
[30] D. W. Kim, H.-J. Jeong, S. T. Lim, M.-H. Sohn, J. A. Katzenellenbogen, D. Y. Chi, *J. Org. Chem.* **2008**, *73*, 957.
[31] D. W. Kim, H.-J Jeong, S. T. Lim, M.-H. Sohn, *Angew. Chem. Int. Ed.* **2008**, *47*, 8404.
[32] J.-D. Hamel, M. Beaudoin, M. Cloutier, J.-F. Paquin, *Synlett* **2017**, 2823.

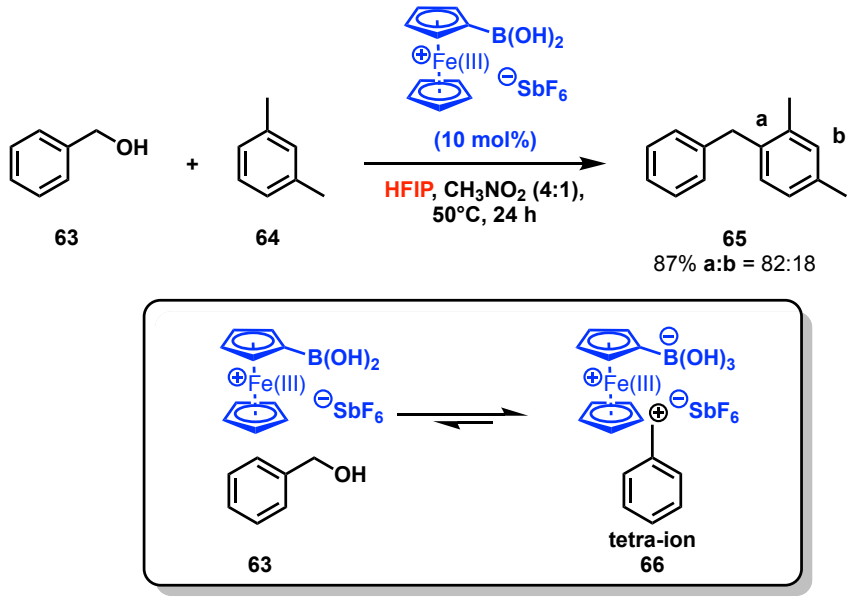


Scheme 12: Friedel-Crafts alkylation of secondary fluoropropargylic alcohols

The group of Paquin group also reported that even fluorobenzylic substrates could undergo the Friedel-Crafts reaction with arene nucleophiles in a mixture of solvents HFIP/DCM (Scheme 13).[33] In that case, no acid catalyst was required. However, employing TFA as a catalyst drastically improved the rate conversion.

Scheme 13: Friedel-Craft alkylation of fluorobenzylic substrate

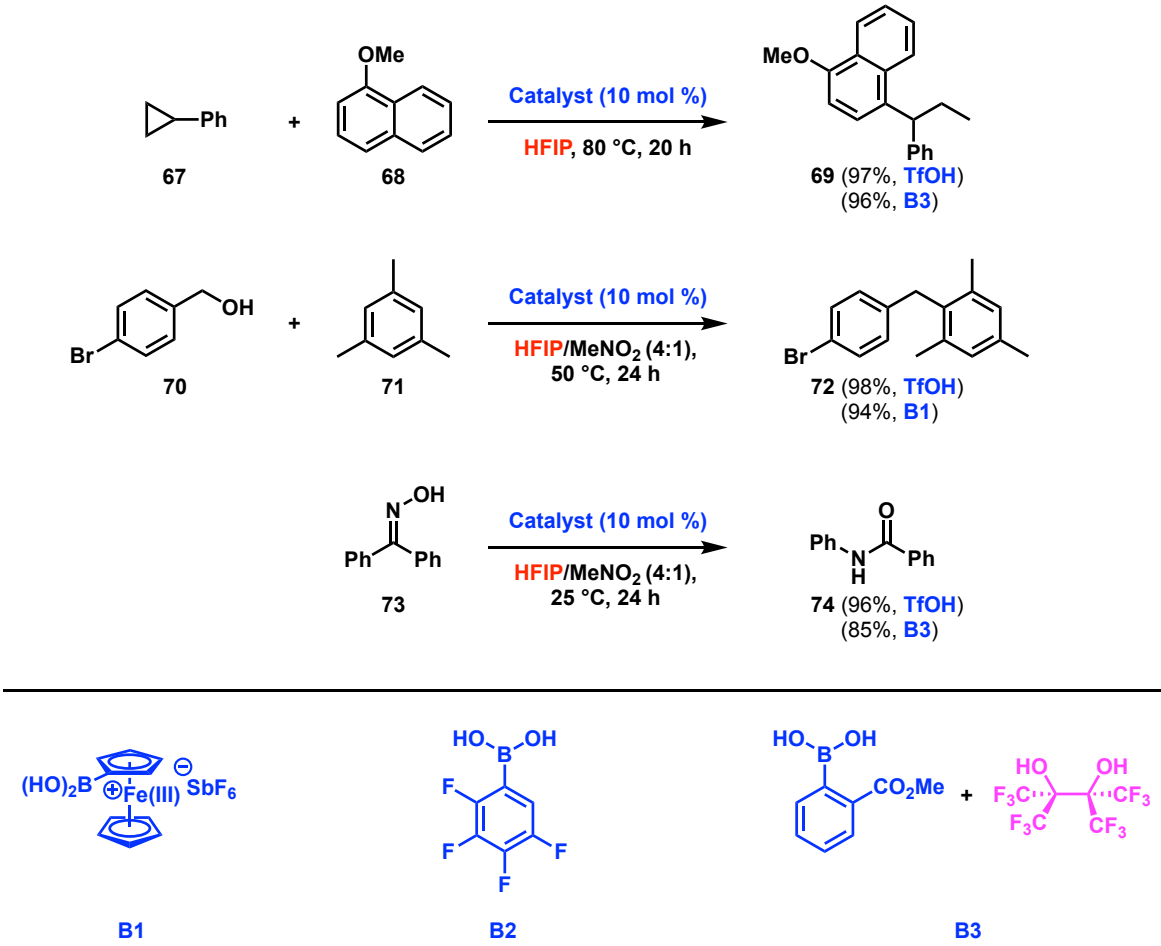
In 2015, the Hall group was the first to report a catalytic version of the Friedel-Crafts reaction with benzylic alcohols in HFIP, using ferroceniumboronic acid hexafluoroantimonate as a catalyst (Scheme 14).[34] Regarding the mechanism, the authors suggested that the catalyst was involved in the stabilization of the benzylic carbocation. In their proposal, the benzylic alcohol reacted with the boron moiety, while the ferrocenium ion and the hexafluoroantimonate counterion stabilized the formation of the benzylic cation by forming a tetra-ion.



Scheme 14: Friedel-Crafts reaction of benzylic alcohols catalyzed by ferroceniumboronic acid hexafluoroantimonate

[33] P. A. Champagne, Y. Benhassine, J. Desroches, J.-F. Paquin, *Angew. C hem. Int. Ed.* **2014**, *53*, 13835.
[34] X. Mo, J. Yakiwchuk, J. Dansereau, J. A. McCubbin, D. G. Hall, *J. Am. Chem. Soc.* **2015**, *137*, 9694.

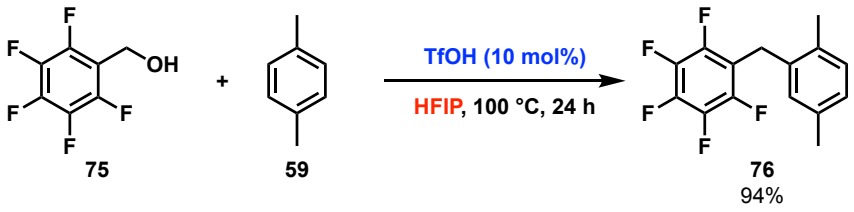
Nevertheless, this interpretation was recently questioned by our group as the involvement of HFIP would make this process more complex.[35] We reported a series of control experiments with boronic and Brønsted acids and analyzed their reactivity, kinetics, and their acidity by the Gutmann-Beckett method. In several examples, strong Brønsted acids or simple H-bond donors showed a similar reactivity to boronic acids (Scheme 15). In most cases, it was concluded that the true mode of catalysis might involve either dual H- bond catalysis or Brønsted acid catalysis, in which HFIP would be the active species.



Scheme 15:Comparison of boronic and Brønsted acids as catalysts in the presence of HFIP

One additional catalytic effect in the Friedel-Crafts reaction with benzylic alcohol could be the *in-situ* formation of hexafluoroantimonic acid, a strong Brønsted acid. With this possibility in mind, our lab wondered whether this reaction could be achieved with simple Brønsted acid in HFIP (Scheme 16). [36] Interestingly, the utilization of triflic acid as a catalyst not only allowed the Friedel-Crafts reaction but was also compatible with highly deactivated substrates that could not be employed under the reaction conditions developed by the group of Hall.

[35] S. Zhang, D. Lebœuf, J. Moran, *Chem. Eur. J.* **2020**, *26*, 9883.
[36] V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085



Scheme 16: Friedel-Crafts reaction of highly deactivated benzylic alcohols

To probe the role of HFIP, the reaction was monitored by ^{1}H NMR titration using benzylic alcohol **75** and HFIP with increasing amount of triflic acid (Figure 6). It was noteworthy that the H_m proton of **75** did not shift with increasing amount of TfOH while the HFIP signals H_y and H_z shifted downfield. Thus, the TfOH acidic proton preferentially interacts with HFIP over the benzylic alcohol **75**. In other words, TfOH is likely not the true catalyst of this reaction, which would be instead an HFIP/TfOH aggregate. This is consistent with the results of kinetic experiments. Indeed, a first order dependence in concentration of TfOH and benzylic alcohol was observed, while a fifth order dependence in HFIP concentration was found, highlighting the involvement of HFIP aggregates. Finally, a S_N1-type mechanism was proposed based on a racemization experiment (Scheme 17).

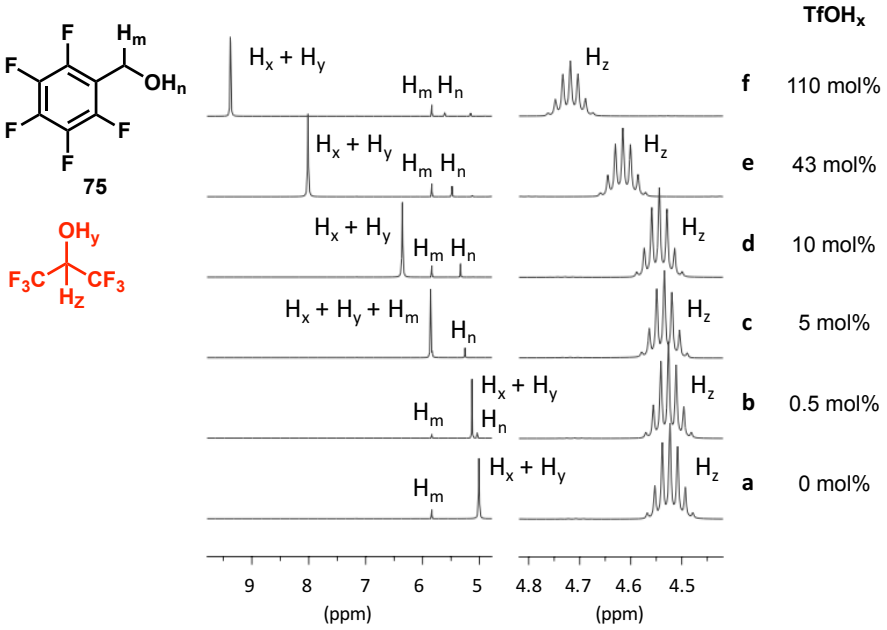
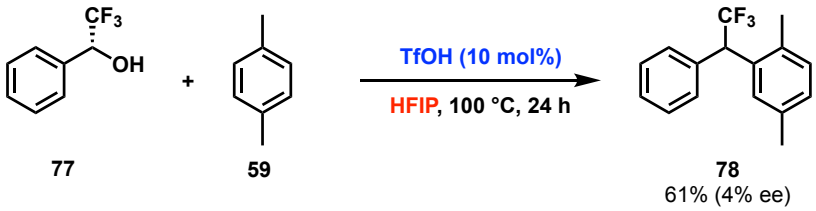
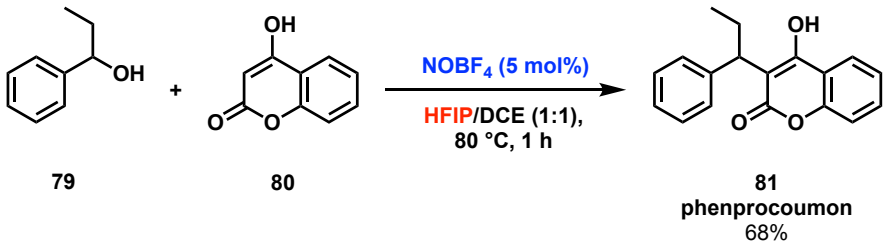


*Figure 6: ^{1}H titration of a mixture of HFIP (1 equiv) and **75** (0.05 equiv) with TfOH*



*Scheme 17: Friedel-Crafts alkylation of benzylic alcohol **77** in TfOH/HFIP system, racemization experiment*

In 2018, the group of Antonchick reported a similar reaction using $NOBF_4$ as a catalyst in a HFIP/DCE mixture.[37] In addition to be the first report of Friedel-Crafts reaction using an inexpensive nitrosonium salt, this reaction could be achieved with benzyl ether instead of benzyl alcohols. In that case, the reaction occurred in an intramolecular fashion. It is noteworthy that they achieved the synthesis of phenprocoumon, an oral anticoagulant drug using $NOBF_4$ in HFIP/DCE (Scheme 18). Regarding the mechanism, a S_N1 process was also proposed as enantiopure starting materials led to racemic products and the use of radical scavengers did not affect the reactivity. However, Lewis acid catalysis seemed to be involved in this reaction as neither HCl nor nitromethane promoted the reaction, ruling out the hypothesis of hidden Brønsted catalysis.

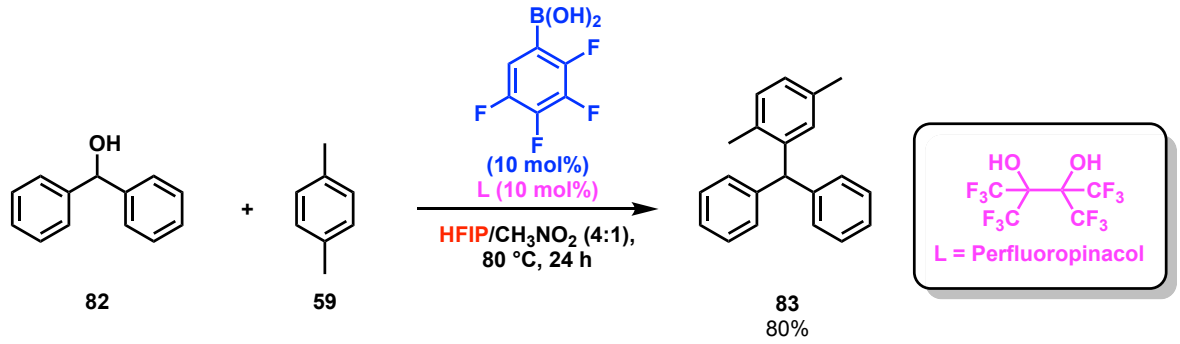


Scheme 18: Synthesis of phenprocoumon by Friedel-Crafts reaction using nitrosonium salt in HFIP/DCE

While investigating a boronic acid-catalyzed Beckmann rearrangement,[38] the group of Hall discovered that the use of perfluoropinacol as an additive could improve the reactivity by forming an electrophilic boronic ester. Based on this result, they transposed this idea to the Friedel-Crafts process (Scheme 19). Indeed, a significant improvement of the reactivity of highly deactivated benzylic alcohol was observed.[39]

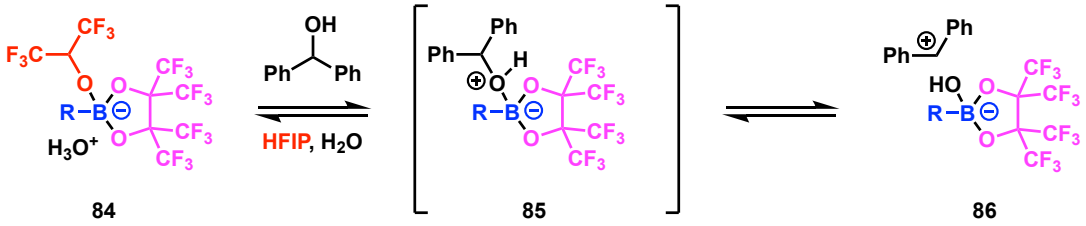
Regarding the mechanism, the authors suggested the involvement of a tetracoordinate boron species as a critical intermediate for the reaction. Indeed, when water was added, products **86** and **88** were experimentally observed by ^{11}B NMR and by mass spectrometry. Addition of water or HFIP on the boron catalyst did not occur in the absence of perfluoropinacol. Moreover, no target product was obtained without the presence of perfluoropinacol. The authors identified the hydronium boronate **86** formed as a key player in the reactivity as no product was obtained in strictly anhydrous conditions. In addition, the use of a proton scavenger, the sterically hindered amine 2,6-di-*tert*-butylpyridine, completely inhibited the formation of the desired product. Yet, the authors emphasized that it does not mean that a strictly Brønsted acid system is at work as they experimentally observed by ^{11}B NMR that boronate **86** formed a complex with 2,6-di-*tert*-butylpyridine that is not an efficient catalyst for this reaction. Therefore, they proposed three different pathways for the alcohol activation: (1) a strictly Lewis acid catalysis where the benzylic alcohol is directly coordinated to the Lewis acidic tetracoordinate boron ester, (2) a Brønsted acid catalysis where the acidic water of the hydronium borate salt **84** protonates the benzylic alcohol, and (3) a Lewis acid-assisted Brønsted acid catalysis where the acidity of HFIP is enhanced upon coordination to the borate species in order to transfer its proton to the benzylic alcohol.

[37] L. Bering, K. Jeyakumar, A. P. Antonchick, *Org. Lett.* **2018**, *20*, 3911.
[38] X. Mo, T. D. R. Morgan, H. T. Ang, D. G. Hall, *J. Am. Chem. Soc.* **2018**, *140*, 5264.
[39] H. T. Ang, J. P. Ryugus, D. G. Hall, *Org. Biomol. Chem.* **2019**,*17*, 6007.

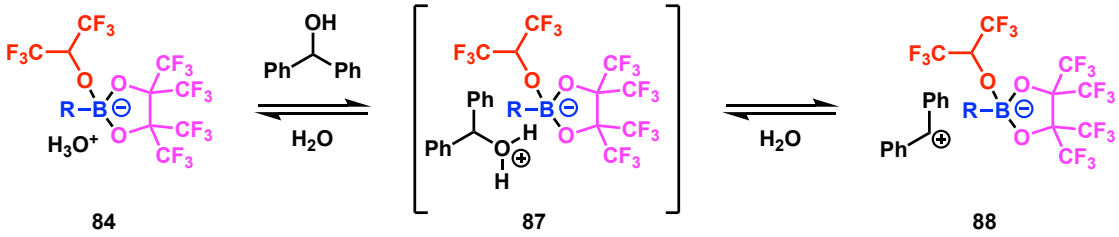


Plausible Modes of Alcohol Activation

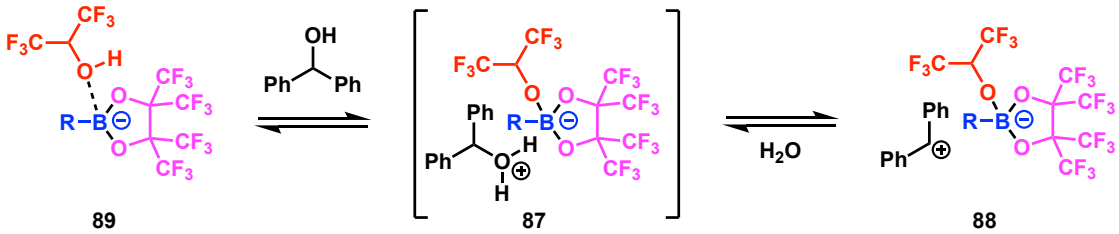
1) Lewis Acid Catalysis (B-O bond formation)



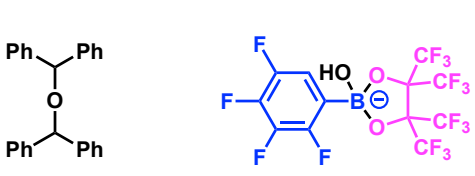
2) Brønsted Acid Catalysis (water-mediated protonation)



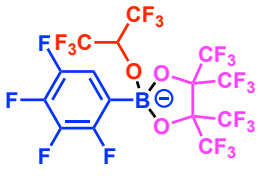
3) Lewis Acid-Assisted Brønsted Acid Catalysis (protonation)



Experimentally Observed Products



^{11}B: 9.3 ppm
m/z: 658.98 calculated
659.0 observed

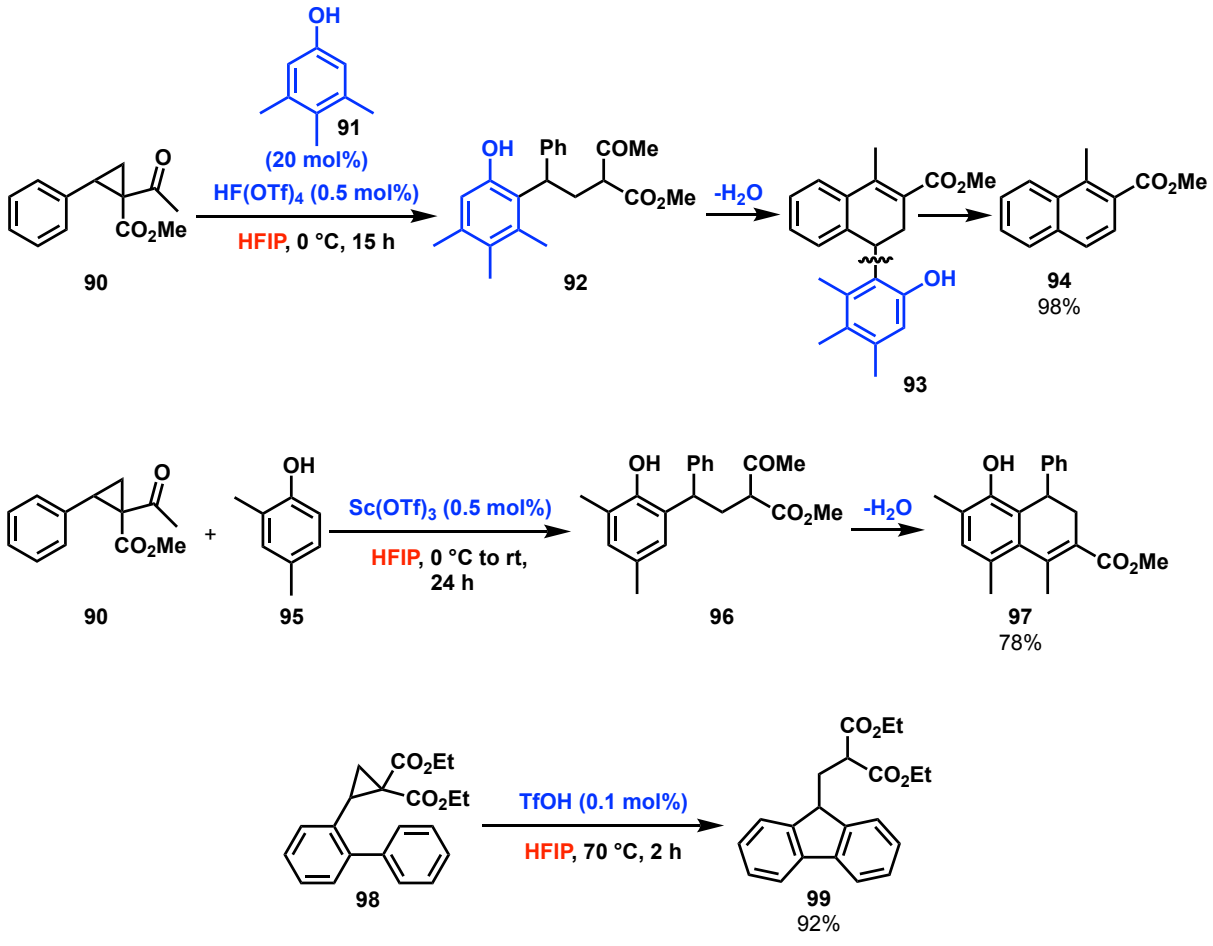


^{11}B: 8.5 ppm
m/z: 508.98 calculated
509.0 observed

Scheme 19: Boronic acid/perfluoropinacol combination for the Friedel-Crafts alkylations of benzylic alcohols in HFIP

1.3.2. Hydroarylation

Donor-acceptor cyclopropanes are useful building blocks for the synthesis of acyclic, alicyclic and heterocyclic compounds.[40] Due to its unique properties, HFIP proved to be a solvent of choice for the acidic catalytic activation of donor-acceptor cyclopropanes (Scheme 20). In 2017, the group of Xu developed an intramolecular cascade ring-opening of donor-acceptor cyclopropanes by using $Hf(OTf)_4$ and 3,4,5-trimethylphenol as catalysts (Scheme 20, eq. 1).[41] This elegant cascade reaction is one of the rare examples with the use of a phenol derivative as an organocatalyst. On the other hand, addition of a hindered Brønsted base such as 2,6-di-*tert*-butylpyridine completely prevented the reactions. The authors concluded that formation of TfOH during the reaction might be critical for the reactivity. Unfortunately, no control experiments with TfOH were carried out to support this claim. In the same vein, the group of Xu developed a [4+2] annulation between electron-rich phenols and donor-acceptor cyclopropanes by using $Sc(OTf)_3$ as a catalyst (Scheme 20, eq. 2).[42] More recently, the group of Li developed a method for the synthesis of 9*H*-fluorenes through an intramolecular arylative ring-opening of donor-acceptor cyclopropanes (Scheme 20, eq. 3).[43] This reaction

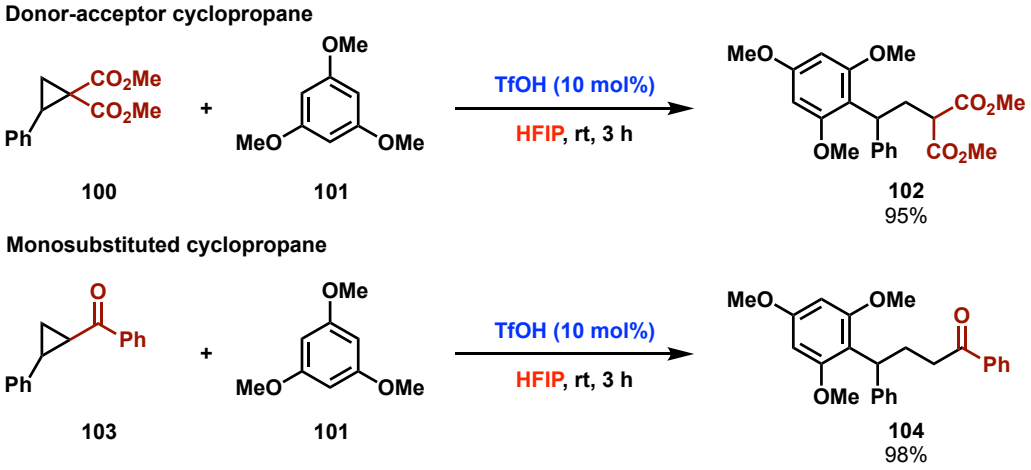


Scheme 20: Hydroarylation of donor acceptor cyclopropanes in HFIP

[40] (a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; (b) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504; (c) D. B Werz, A. T. Biju, Angew. *Chem. Int. Ed.* **2020**, *59*, 3385.
[41] H. Ma, X.-Q. Hu, Y.-C. Luo, P.-F. Xu, *Org. Lett.* **2017**, *19*, 6666.
[42] Y.-C. Luo, H. Ma, X.-Q. Hu, P-F. Xu, *J. Org. Chem.* **2017**, *82*, 1013.
[43] D. Wang, J. Zhao, J. Chen, Q. Xu, H. Li, *Asian J. Org. Chem.* **2019**, *8*, 2032.

could be also conducted in DCM with good yields. On the other hand, in that case, the reaction required 6 equiv. of TfOH compared to only 0.1 equiv. in HFIP.

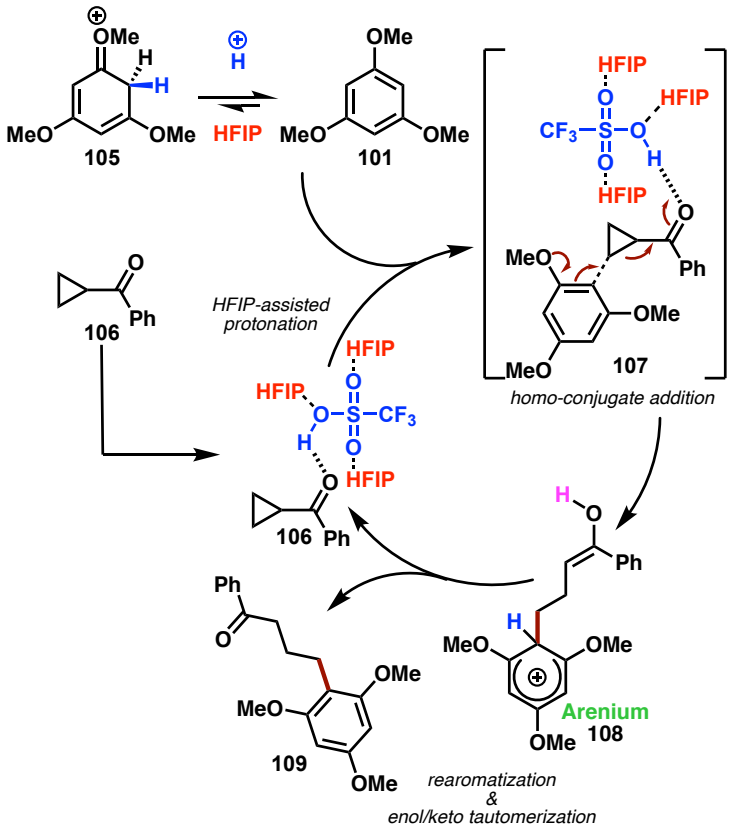
Prior to Li's report, our group made several breakthroughs in the arylative ring-opening of cyclopropanes.[44,45] Our initial goal was to determine whether a combination of a Brønsted acid with HFIP could efficiently promote the hydroarylation of donor-acceptor cyclopropanes (Scheme 21, eq. 1). In a similar fashion to the Friedel-Crafts alkylation, TfOH provided the best results as a catalyst. Furthermore, those conditions allowed even the activation of weakly-polarized cyclopropanes bearing a single electron-withdrawing group and those bearing electron-deficient aryl groups. Regarding the nucleophiles, the reaction tolerates a wide range of nucleophile including arenes, azides, diketones and alcohols (Scheme 21, eq. 2). Nevertheless, heteroaromatic substrates such as indole required a milder acid, $B(C_6F_5)_3 \cdot H_2O$.



Scheme 21: Hydroarylation of DA cyclopropanes and monosubstituted cyclopropanes

To account for the reactivity, mechanistic studies relying on kinetic experiments (Hammet plot) and DFT calculations were performed (Scheme 22). The formation of the arenium ion **108** was identified as the RDS for this reaction. The racemization of the product from an enantiopure donor-acceptor cyclopropane combined with ^{1}H NMR monitored kinetic experiments supported a homo-conjugate addition pathway (S_N2-like mechanism). Indeed, by plotting the reaction rates of several para-substituted cyclopropanes vs Hammett substituent parameter the authors observed (1) that a positive charge was generated in the RDS as a negative slope with a strong relationship was observed with most data (2) that the magnitude of this slope is consistent with a S_N2-like mechanism.

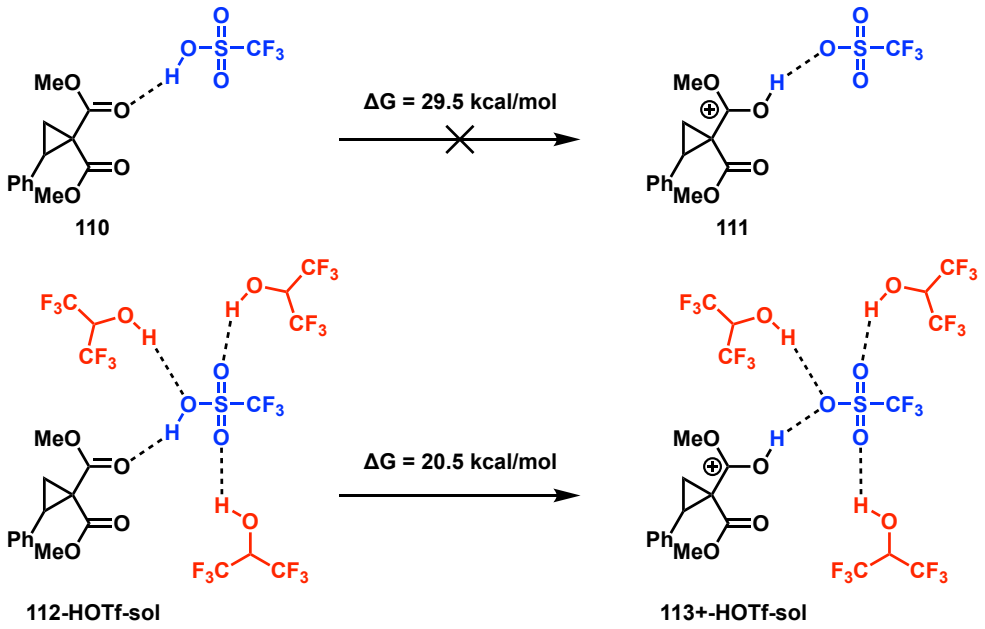
[44] E. Richmond, V. D. Vuković, J. Moran, *Org. Lett.* **2018**, *20*, 574.
[45] E. Richmond, J. Yi, V. D. Vuković, F. Sajadi, C. N. Rowley, J. Moran, *Chem. Sci.* **2018**, *9*, 6411.



Scheme 22: Mechanistic proposal for hydroarylation of cyclopropyl ketone in HFIP/TFOH conditions

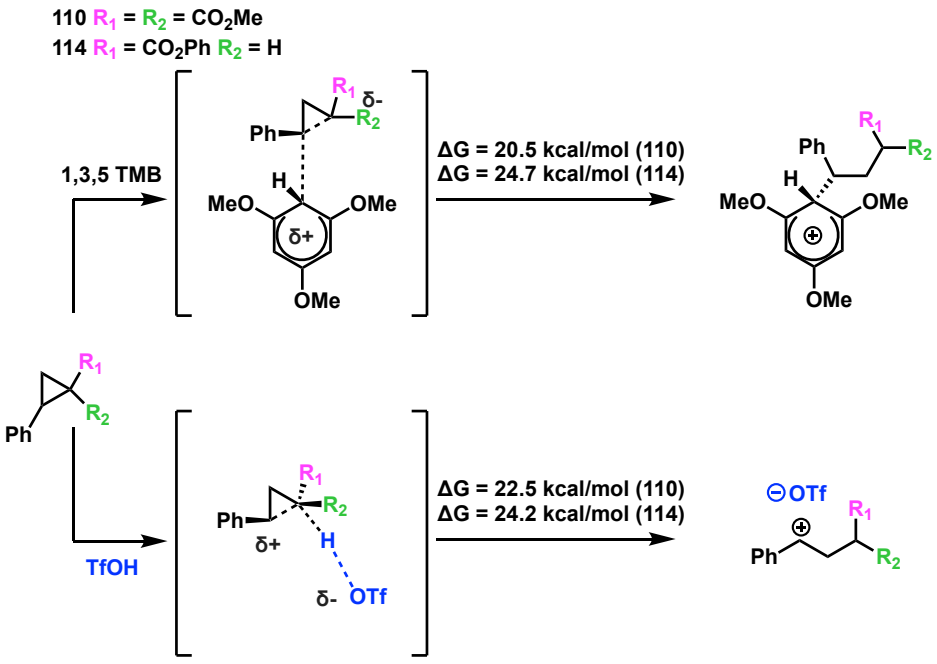
To probe the role of HFIP in the hydroarylative ring-opening of donor-acceptor and monosubstituted cyclopropanes under HFIP/TfOH reaction conditions, a series of computational studies were carried out by Zhang and Feng.[46] In their report, the authors emphasized the importance of considering the explicit solvation effect while conducting DFT calculations. Regarding the rate determining step, two models were studied (Scheme 23). One without explicit solvation effect (Scheme 23, eq.1) and one involving the solvation with three HFIP molecules (Scheme 23, eq.2). An energy barrier of 29.5 kcal/mol was calculated for the solvent-excluded model, which would require roughly 100 °C for the reaction to take place. On the other hand, regarding the model including explicit solvation effect, an energy barrier of 20.5 kcal/mol was calculated, enabling reactivity at room temperature, which is consistent with our experimental results (Scheme 21). Those results showed the importance of HFIP toward the lowering of the energetic barrier.

[46] Y. Zhou, R.-C. Xue, Y. Feng, L. Zhang, *Asian J. Org. Chem.* **2020**, *9*, 311.



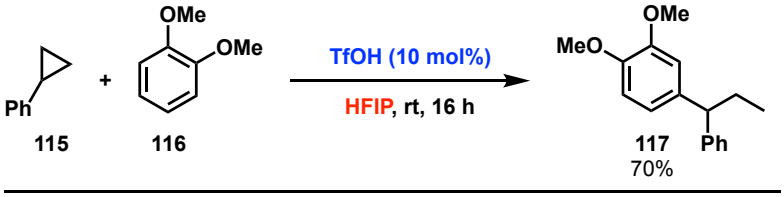
Scheme 23: Donor-acceptor cyclopropanes ring opening models from DFT calculations

^{1}H NMR titration of TfOH into a solution of cyclopropyl ketone, HFIP and 1,3,5-trimethoxybenzene conducted by our group revealed a preferential protonation of the nucleophile 1,3,5-trimethoxybenzene. Taking this information into account, the groups of Zhang and Feng proposed two alternative modes of activation for the ring-opening of donor-acceptor cyclopropanes and cyclopropyl ketone (Scheme 24), in which either the nucleophile or TfOH induced the activation. In summary, the activation pathway will likely change between those two depending on the pair nucleophile/cyclopropane. In the case of DA cyclopropanes and cyclopropyl ketones, the rate determining step is the formation of the arenium ion that occurs through a homo-conjugate (S_N2-like) addition pathway.



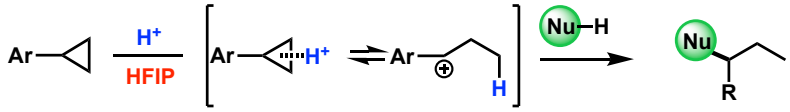
Scheme 24: General modes of activation for the ring-opening reaction of donor-acceptor cyclopropanes and cyclopropyl ketones

Interestingly, aryl-substituted cyclopropanes exhibited a different reactivity, leading to branched products (Scheme 25). A S_N1-type mechanism was proposed by our group as, in the absence of nucleophile, aryl cyclopropanes decomposed under HFIP/TfOH reaction conditions, which is consistent with the formation of carbocationic species.



Mechanistic proposal for hydroarylation of aryl cyclopropanes

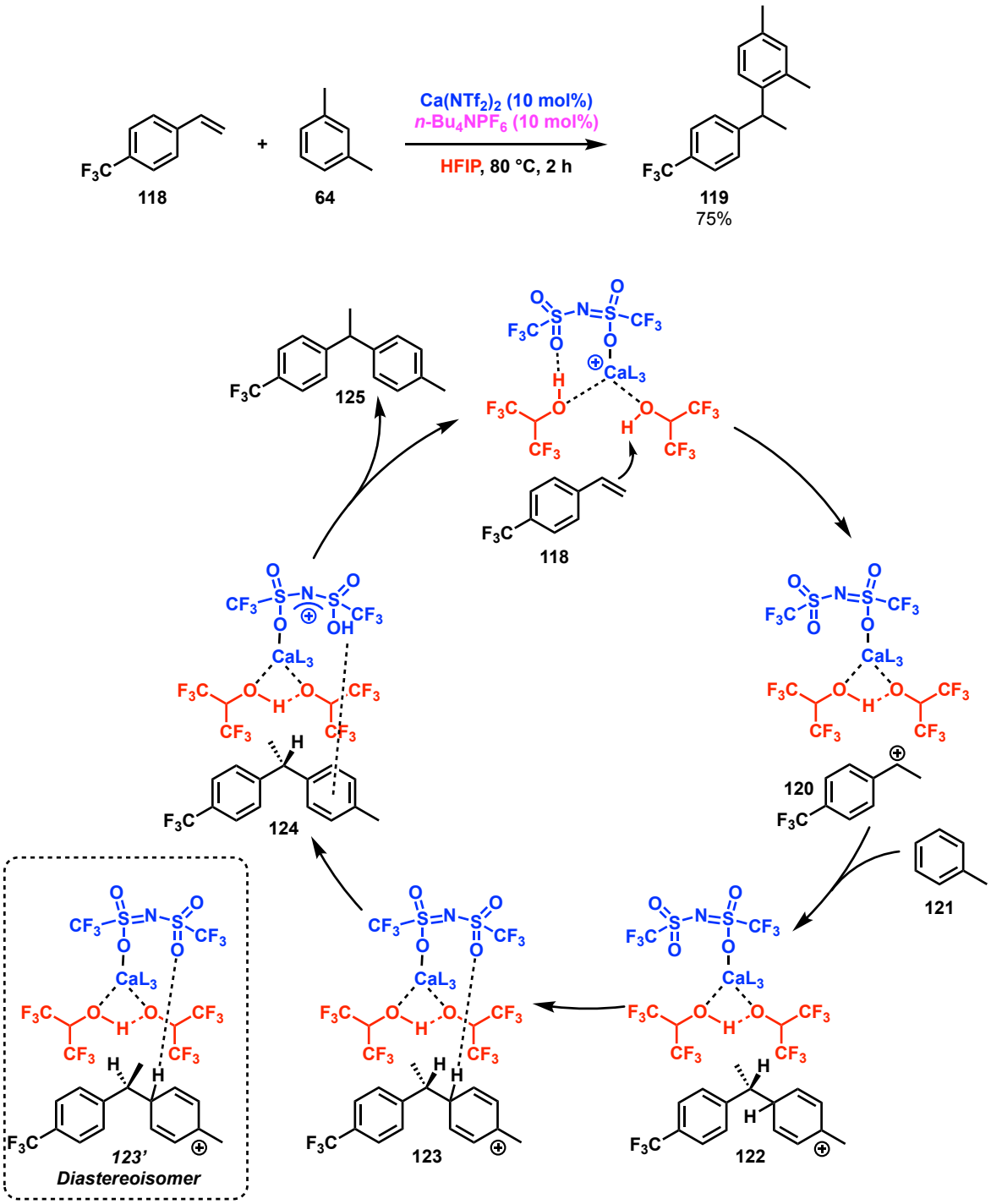
S_N1-type cyclopropane ring-opening.
Decomposition in the absence of nucleophile.



Scheme 25: Ring-opening of aryl cyclopropanes

In another vein, Lebœuf and co-workers succeeded to report the first hydroarylation of highly deactivated styrene by using a Ca(II)/HFIP system (Scheme 26).[47] DFT calculation supported a mechanism in which an efficient cooperative effect occurred between HFIP and calcium(II) triflimide. Not surprisingly, the protonation of the styrene derivative was identified as the RDS followed by the addition of the aryl nucleophile to the benzylic cation to form an arenium ion. The resulting Wheland-type intermediate should then rotate so that the NTf_2 is spatially close enough to capture the proton. Since the addition of the arene creates a new stereogenic center, and the calcium complex is chiral, both directions of rotation do not have the same energetic requirements. One of the diastereoisomers is however significantly more stable than the other one (ΔG (**123**) = 16.5 kcal/mol < ΔG (**123'**) = 23.9 kcal/mol). Then, the arenium ion undergoes a rearomatization that leads to the product **125**.

[47] C. Qi, V. Gandon, D. Lebœuf, *Angew. Chem. Int. Ed.* **2018**, *57*, 14245.

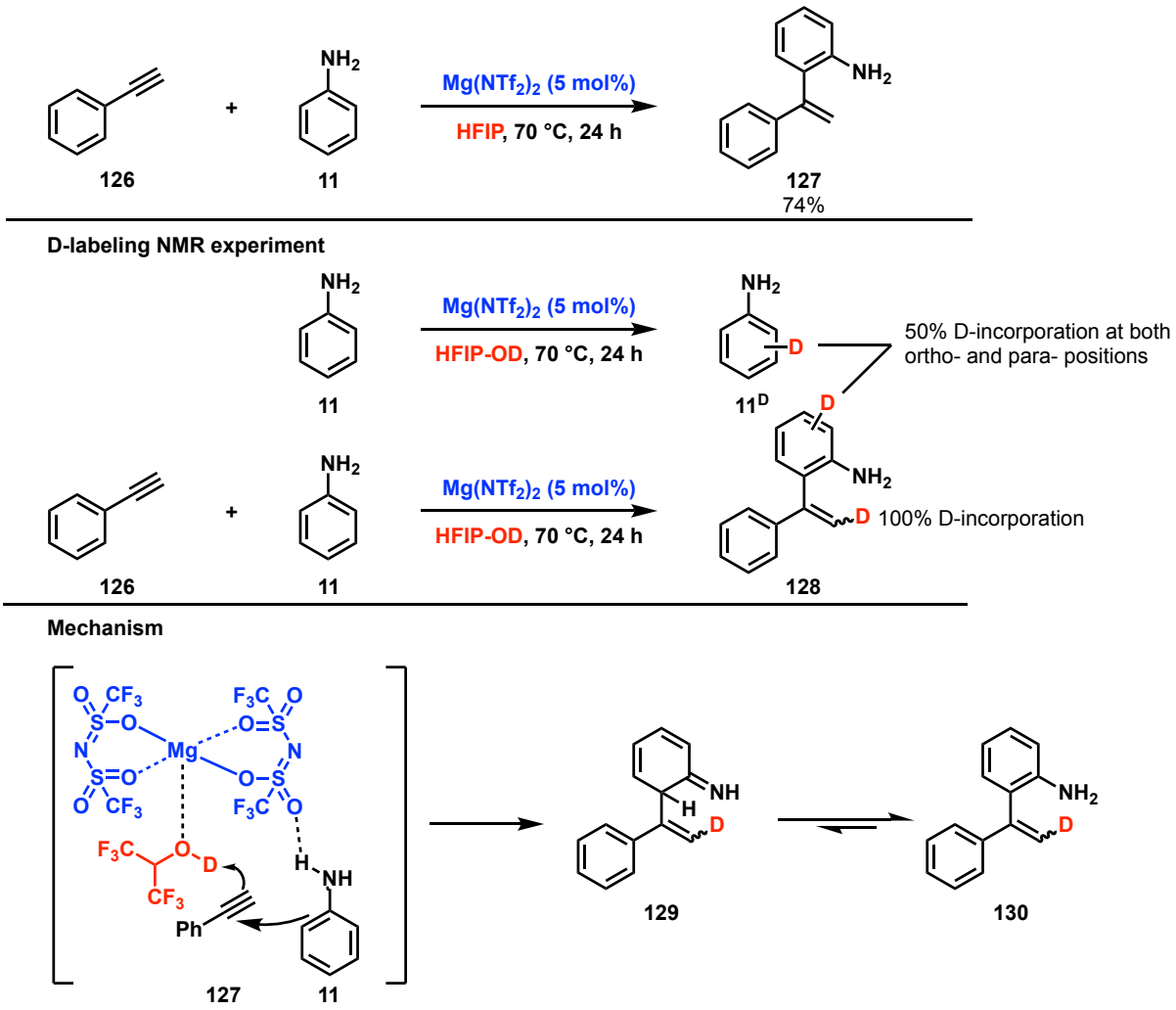


Scheme 26: Mechanistic proposal for hydroarylation of highly deactivated styrene

In 2019, Magre and Rueping found out that magnesium (II) triflimide salt was also efficient for the selective *ortho*-C alkylation of anilines with alkynes (Scheme 27).[48] Mechanistic investigations using deuterium labeling and NMR experiments suggested a similar mechanism to the system with $Ca(NTf_2)_2$, involving first protonation of the π system with HFIP. Indeed, when deuterated hexafluoroisopropanol HFIP-OD was used, complete incorporation of deuterium was observed at the alkene moiety. Unlike prior discussed reactions with boronic

[48] A. Chatupheeraphat, M. Rueping, M. Magre, *Org Lett* **2019**, *21*, 9153.

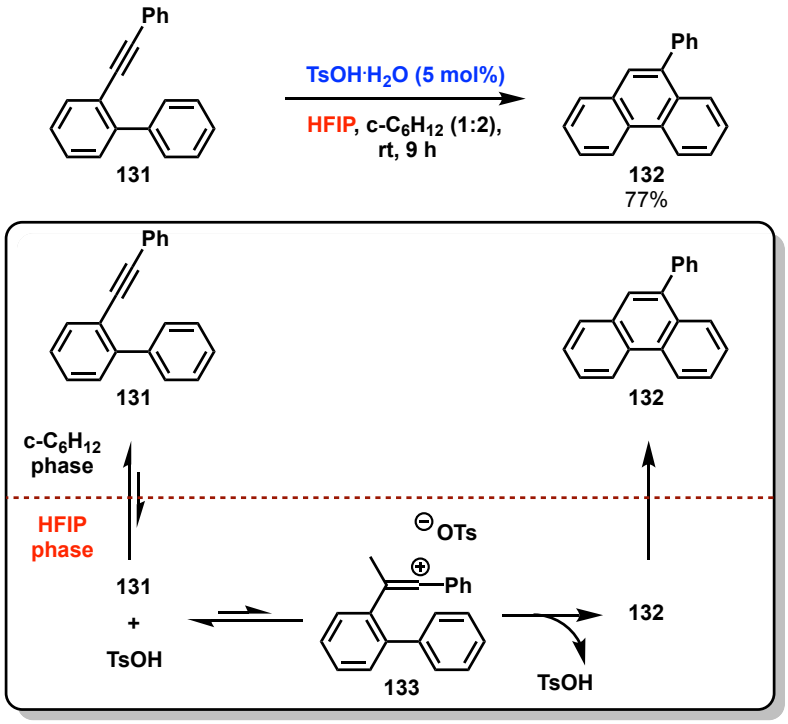
acids, the addition of the proton scavenger 2,6-*tert*-butylpyridine did not affect the reactivity, which is consistent with the Lewis acid mechanism proposed.



Scheme 27: HFIP-assisted magnesium(II)-catalyzed hydroarylation of alkynes with anilines

Regarding alkyne activation, the group of Ichikawa recently depicted a biphasic system, using HFIP/cyclohexane and $TsOH \cdot H_2O$ as a catalyst for the Brønsted acid-catalyzed hydroarylation of unactivated alkynes to synthesize phenanthrene frameworks (Scheme 28). [49] In this reaction, the apolar alkyne is essentially located in the cyclohexane phase, while the toluenesulfonic acid monohydrate resides in the HFIP phase. At the interface, the alkyne can be protonated by the $TsOH \cdot H_2O$ to form a vinyl cation that will migrate in the HFIP phase due to the stabilizing properties of the latter. The separation of the vinyl cation species from the starting material via this biphasic system precludes the formation of side-products and proved to be critical for the success of the reaction when compared to the sole use of HFIP as a solvent. Moreover, the author emphasized that the phase containing the catalyst as well as HFIP could be reused several times.

[49] Takahashi, T. Fujita, N. Shoji, J. Ichikawa, *Chem. Commun*. **2019**, *55*, 9267.

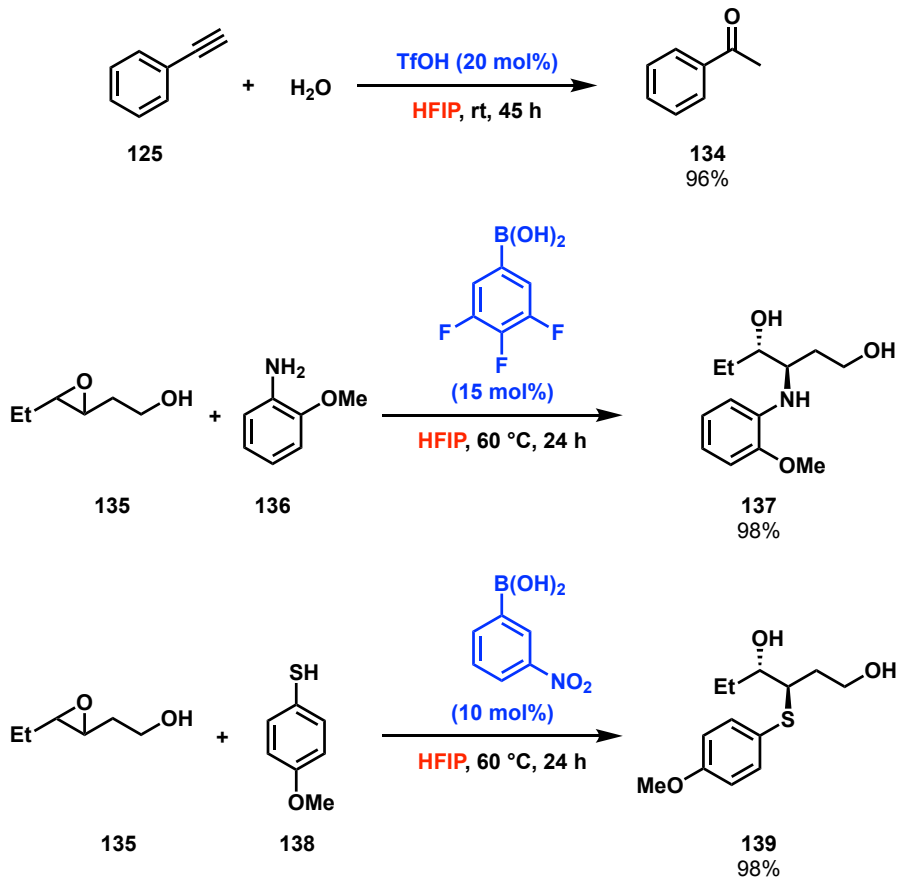


Scheme 28: Intramolecular hydroarylation of alkynes in the biphasic HFIP-cyclohexane system

1.3.3. Hydrofunctionalizations

In the past 5 years, numerous studies have been dedicated to the use of fluorinated alcohols for hydrofunctionalization reactions. In 2016, the group of Li developed a Markovnikov-type hydration protocol using triflic acid in combination with TFE or HFIP (Scheme 29, eq.1).[50] In 2018, the group of Wang developed a ring-opening hydroamination of 3,4-epoxy alcohols using a boronic acid in HFIP (Scheme 29, eq.2).[51] The amination proved to be regioselective owing to the alcohol group, which acts as a directing group enabling access to enantioenriched amino alcohols. Later, they reported that ring-opening of 3,4-epoxy alcohols was also possible with thiols and thiophenols under similar reaction conditions (Scheme 29, eq.3).[52]

[50] W. Liu, H. Wang, C.-J. Li, *Org Lett*. **2016**, *18*, 2184.
[51] J. Liu, H. Yao, C. Wang, *ACS Catal*. **2018**, *8*, 9376.
[52] H. Yao, J. Liu, C. Wang, *Org. Biomol. Chem*. **2019**, *17*, 1901.

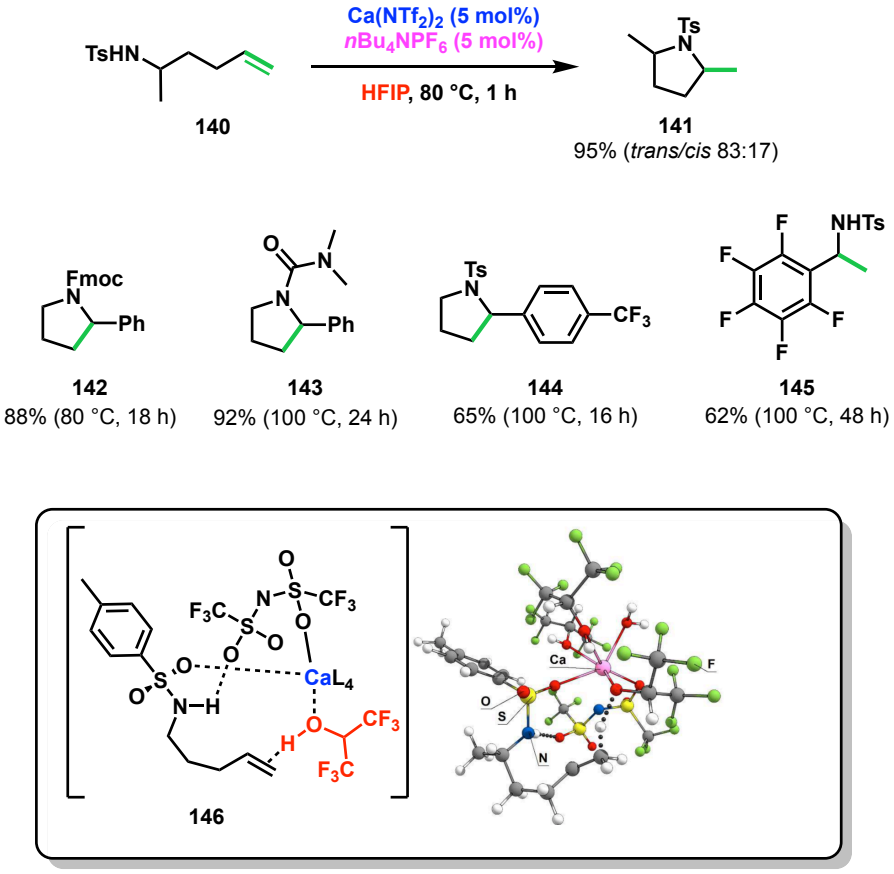


Scheme 29: Hydrofunctionalization reactions in HFIP

In 2018, Lebœuf and co-workers reported an HFIP assisted calcium(II)-catalyzed hydroamidation of unactivated alkene (Scheme 30).[53] One key parameter on this system is the HBD abilities of HFIP that facilitate the release of Lewis acids from off-cycle binding with the substrate or the product. Thanks to this ability, their promoter system overcame several limitations regarding the hydroamination of unactivated alkenes, as no rare metal was required and a large range of basic nucleophile such as urea, amides and carbamates were well-tolerated. On the other hand, substrates substituted with electron-rich functional groups on the aryl moiety furnished lower yield due to oligomerization.

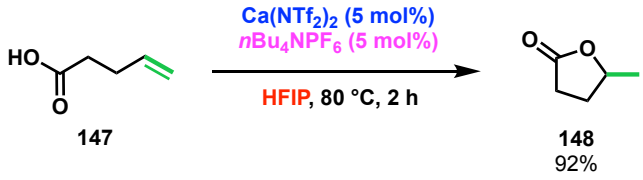
Concerning the mechanism of the reaction, the role of the ammonium salt is to promote the formation of $[CaNTf_2]^+[PF_6]^-$, which is more Lewis acidic than $CaNTf_2$. Based on DFT calculations, the authors proposed the $[(NTf_2)Ca(HFIP)^n]^+$ complex **146** as the active species for the protonation (RDS). Herein, HFIP serves a dual purpose: it rigidifies the substrate conformation, therefore inducing a good diastereoselectivity, and protonates the alkene to trigger the cyclization. The authors emphasized that the coordination of HFIP to the calcium center is critical for the reaction, as it drastically increases the acidity of HFIP.

[53] C. Qi, F. Hasenmaile, V. Gandon, D. Lebœuf, *ACS Catal.* **2018**, *8*, 1734.



Scheme 30: Calcium (II)-catalyzed hydroamidation of alkenes in HFIP

In the continuity of those studies, they demonstrated that this system was also efficient for the intramolecular hydroacyloxylation of unactivated alkenes (Scheme 31).[54] At that time, this reaction was still highly challenging because of the tendency of carboxylic acid functionalities to strongly coordinate to transition metals or Lewis acids, thus preventing the transformation.

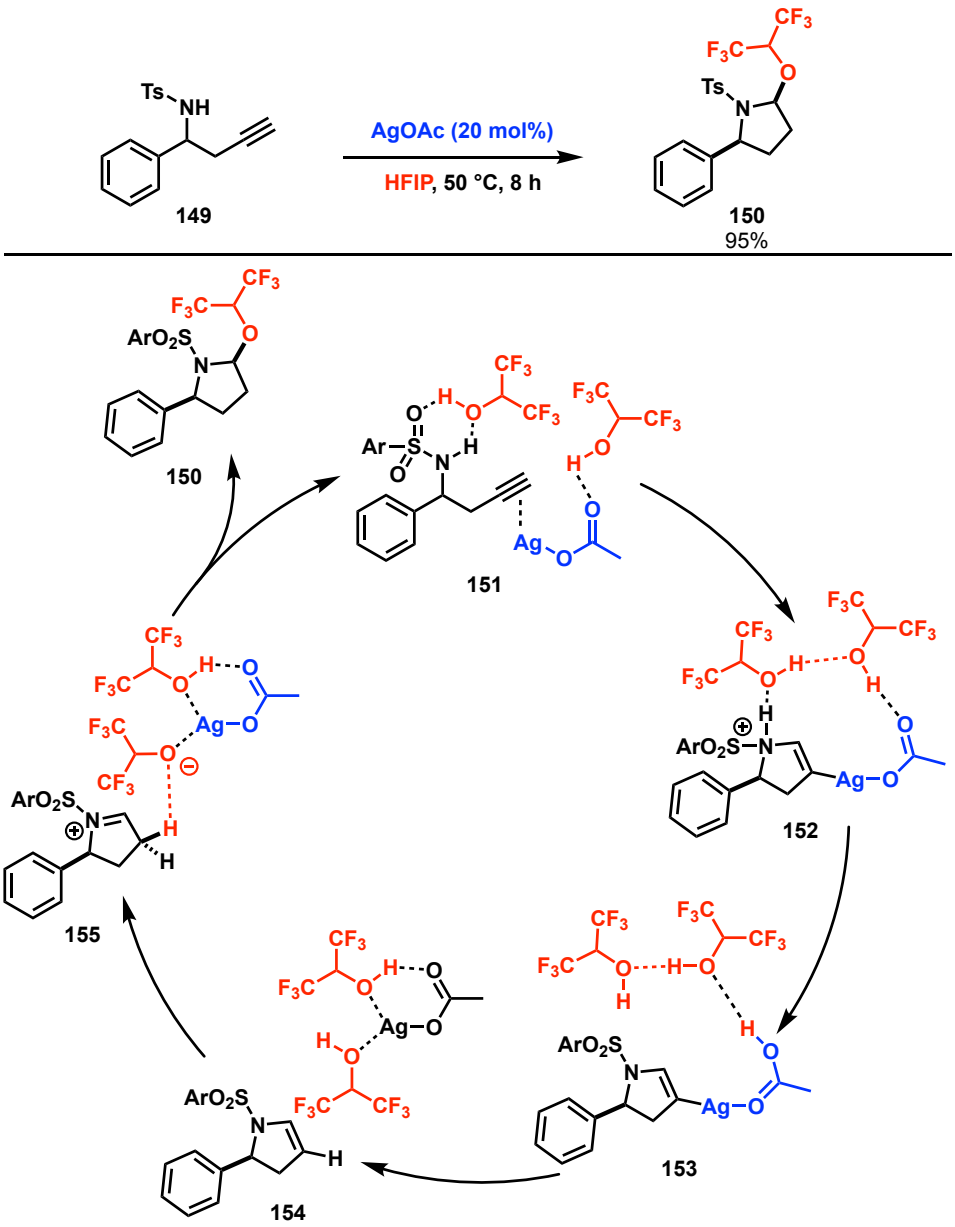


Scheme 31: Calcium (II)-catalyzed intramolecular hydroacyloxylation of unactivated alkenes in HFIP

More recently, the group of Li developed a straightforward process for the synthesis of *cis*-2,5-disubstituted pyrrolidines via *N,O*-acetals, which were formed following an intramolecular hydroamination of alkynes and a subsequent addition of HFIP (Scheme 32). HFIP plays multiple role in this reaction: it acts as a solvent, an acid, an additive, a leaving group and more surprisingly a nucleophile.[55] Remarkably, reactions with enantiopure precursors led to the formation of enantioenriched product along with a high diastereoselectivity. To probe the mechanism the authors carried out a series of control experiments and DFT calculations.

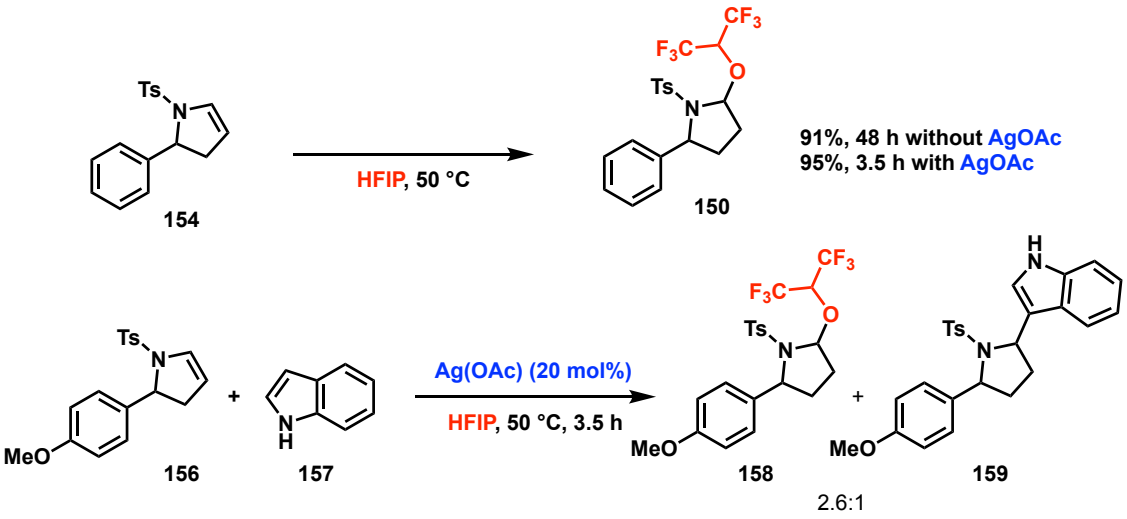
[54] C. Qi, S. Yang, V. Gandon, D. Lebœuf, *Org. Lett.* **2019**, *21*, 7405.
[55] W. Wang, X. Cao, W. Xiao, X. Shi, X. Zuo, L. Liu, W. Chang, J. Li, *J. Org. Chem*. **2020**, *85*, 7045.

(1) The first step is the classic coordination of the Ag complex to the π-system to form the complex **151**.
(2) The second step is the intramolecular hydroamination to form the complex **152**. This step has been identified as the RDS. Indeed, according to their DFT studies (with explicit inclusion of 2 HFIP molecules), the energy barrier for the cyclization step is 25.8 kcal/mol.
(3) The third step is the deprotonation of the quaternary ammonium by the HFIP aggregate to generate **153**.
(4) In the fourth step, a proto-demetalation occurred to give the intermediate **154**.
(5) In the fifth step, a protonation of the enamide moiety takes place to form iminium **155**, which dictated the addition of HFIP as the *cis* HFIP/intermediate/Ag cluster was calculated to be 1.6 kcal/mol lower than a *trans* aggregate.
(6) Finally, the nucleophilic addition of HFIP to the iminium led to the target product.



Scheme 32: Mechanism for the formation of pyrrolidine derivative in HFIP

Experimental evidence showed that intermediate **154** could undergo nucleophilic addition of HFIP in the absence of AgOAc (Scheme 33). In that case, however, the reaction is much slower. The authors concluded that the reaction of the homopropargylic sulfonamide in HFIP occurred via dihydropyrrole intermediate **155** and HFIP served as a hydroalkoxylative reagent in the addition reaction without requiring AgOAc. In addition, control experiments with intermediate **156** in the presence of indole under standard conditions showed a preferential addition of HFIP rather than that of indole, even if the bulk nucleophilicity of HFIP is lower than that of indole. This observation might be explained by the formation of a HFIP/Ag cluster that would enhance the nucleophilicity of HFIP.



Scheme 33: Mechanistic control experiments for pyrrolidine synthesis in HFIP

1.3.4. Cyclization

In the past 20 years, several cyclization reactions have been investigated in HFIP, including Nazarov cyclizations,[56] Diels-Alder cycloadditions,[57] intramolecular cyclizations[58] and a range of polycyclic cascade reactions.[59].

The Nazarov cyclization is a 4π conrotatory electrocyclization usually involving divinyl ketones for the synthesis of cyclopentenones (Scheme 34). The original version involved the use of stoichiometric amounts of Lewis or Brønsted acid, suffering from a lack of control of the selectivity regarding the position of the double bond.[60] In particular, a variant featuring TMSOTf in HFIP was developed by Minami in 1995 and enabled the use of fluorinated divinyl ketone owing to the H-bonding/cationic charge stabilizing properties of HFIP (Scheme 34,

[56] (a) T. Mietke, T. Cruchter, V. A. Larionov, T. Faber, K. Harms, E. Meggers, *Adv. Synth. Catal*. **2018**, *360*, 2093; (b) A.-S. Marques, T. Duhail, J. Marrot, I. Chataigner, V. Coeffard, G. Vincent, X. Moreau, *Angew. Chem. Int. Ed*. **2019**, *58*, 9969.

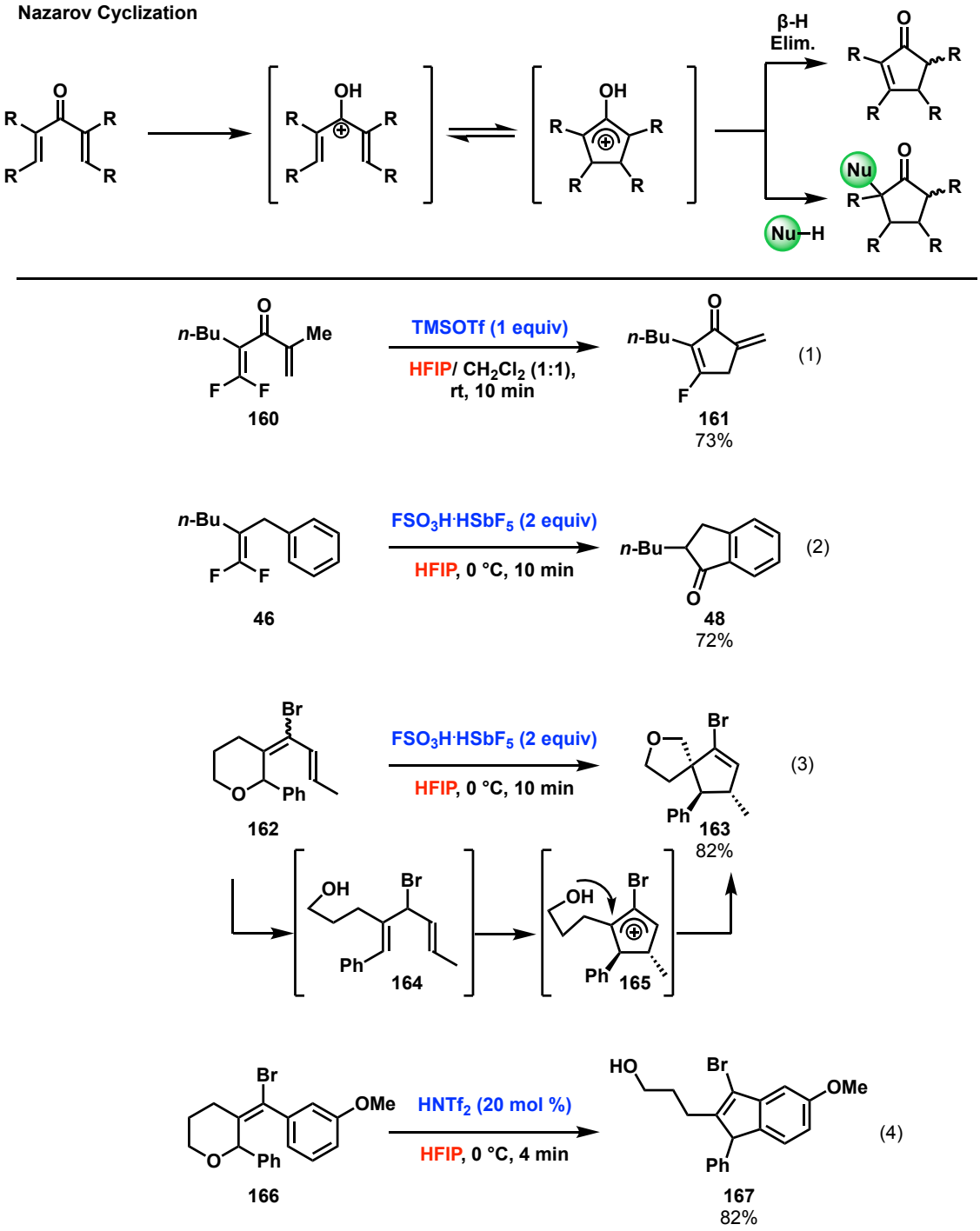
[57] C. Cativiela, J. I. García, J. A. Mayoral, L. Salvatella, *Can. J. Chem*. **1994**, *72*, 308.

[58] (a) A. M. Arnold, A. Pöthig, M. Drees, T. Gulder, *J. Am. Chem. Soc.* **2018**, *140*, 4344; (b) T. Fujita, I. Takahashi, M. Hayashi, J. Wang, K. Fuchibe, J. Ichikawa, *Eur. J. Org. Chem.* **2017**, 262; (c) P. Alonso, R. Fontaneda, P. Pardo, F. J. Fañanás, F. Rodríguez, *Org. Lett*. **2018**, *20*, 1659; (d) M. Mandal, R. Balamurugan, *Adv. Synth. Catal*. **2018**, *360*, 1453.

[59] (a) H. X. Siyang, X. Y. Ji, X. R. Wu, X. Y. Wu, P. N. Liu, *Org. Lett.* **2015**, *17*, 5220; (b) Z. Yang, H. Li, L. Zhang, M.-T. Zhang, J.-P. Cheng, S. Luo, *Chem. Eur. J.* **2015**, *21*, 14723; (c) P. Wu, M. Å. Petersen, R. Petersen, M. O. Rasmussen, K. Bonnet, T. E. Nielsen, M. H. Clausen, *Eur. J. Org. Chem.* **2015**, 5633; (d) A.-S. Marques, J. Marrot, I. Chataigner, V. Coeffard, G. Vincent, X. Moreau, *Org. Lett.* **2018**, *20*, 792; (e) T. Okamoto, M. Shibata, S. Karanjit, A. Nakayama, M. Yoshida, K. Namba, *Chem. Eur. J.* **2018**, *24*, 9508.

[60] I. N. Nazarov, I. I. Zaretskaya, *I. I.Izv. Akad. Nauk. SSSR, Ser. Khim.* **1941**, 211.

eq.1).[61] As fluorine not only possesses a α-cation-stabilizing effect but could also act as a leaving group, a better selectivity could be achieved. In 2004, the group of Ichikawa extended the scope of the defluorinative Nazarov cyclization to fluorinated aryl enones using $FSO_3H{\cdot}SbF_5$ in HFIP (Scheme 34, eq.2).[62] Such substrates are less reactive towards the Nazarov cyclization, owing to the higher energetic barrier required to break the aromaticity for ring closure. In 2017, the group of Frontier developed a halo-Nazarov cyclization method for the synthesis of

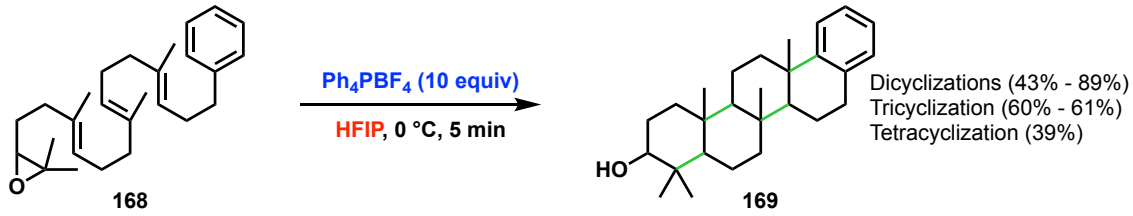


Scheme 34: Nazarov cyclization reactions in HFIP

[61] J. Ichikawa, S. Miyazaki, M. Fujiwara, T. Minami, *J. Org. Chem*. **1995**, *60*, 2320.
[62] J. Ichikawa, H. Jyono, T. Kudo, M. Fujiwara, M. Yokota, *Synthesis* **2004**, 39.

1-halocyclopentenes from a substrate bearing a halogen functionality instead of a ketone (eq. 3).[63] More recently, they extended the scope of halo-Nazarov cyclization to aryl substrates (Scheme 34, eq.4).[64] DFT computations carried out indicated that 3-halo-cationic intermediates are more kinetically accessible and thermodynamically favorable than their 3-oxy-Nazarov analogs, allowing therefore a lower catalyst loading.

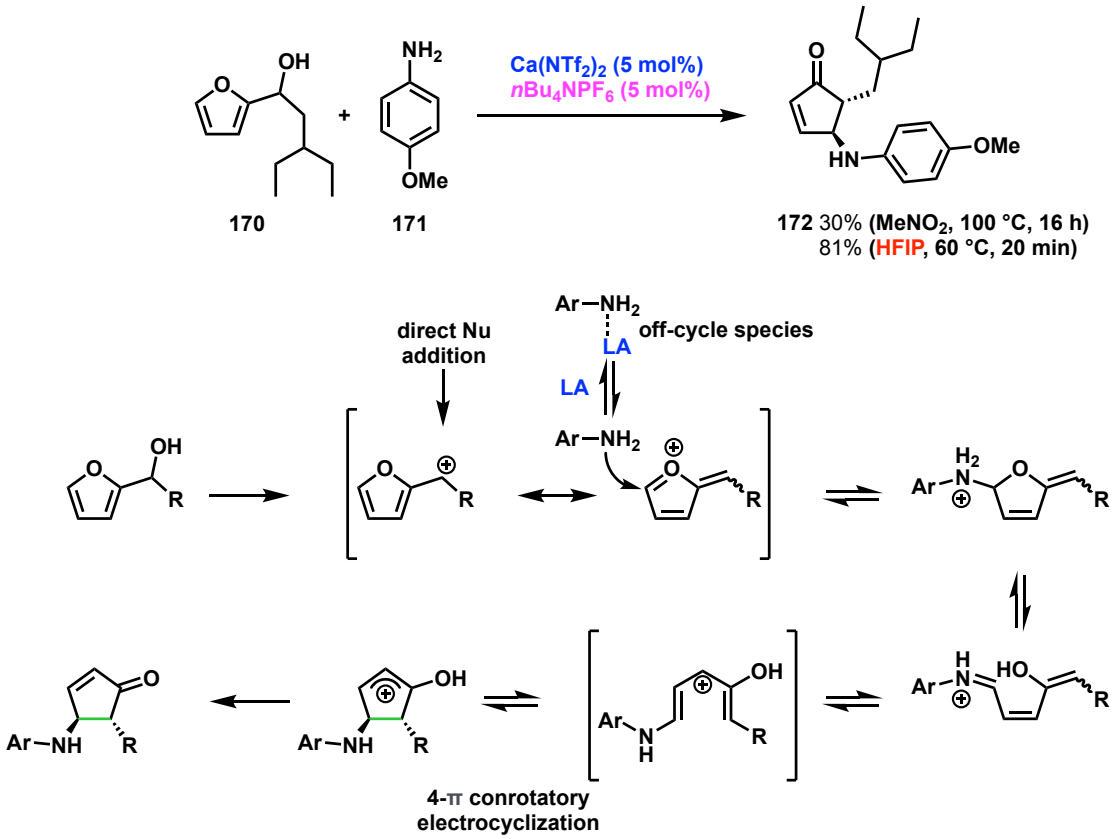
Concerning polycyclic reactions, the potential of HFIP was further illustrated in the synthesis of polycyclic terpenoids by Qu and co-workers (Scheme 35).[65] They reported the epoxide-initiated polycyclization of up to 4 double bonds in one pot, under air conditions, within 5 min. The downside of this reaction is that super-stoichiometric quantity of Ph_4PBF_4 was required.



Scheme 35: Polycyclization of terpenes in HFIP

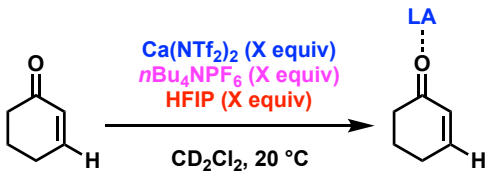
An interesting variant of the Nazarov reaction is the aza-Piancatelli cyclization, which is a useful method for the synthesis of 4-aminocyclopentenone derivatives. Over the past five years, Lebœuf and co-workers investigated the potential of HFIP with respect to the aza-Piancatelli reaction (Scheme 36).[66] In their initial studies, they devised an efficient catalytic system featuring $Ca(NTf_2)_2/n Bu_4NPF_6$ in nitromethane to promote this transformation.[67] However, they became aware that many substrates could lead to side reactions at the carbinol position, including Friedel-Crafts and deoxyamination reactions, or could decompose at high temperatures. It notably concerned 2-furylcarbinols incorporating alkene and cyclopropyl moieties or sterically hindered 2-furylcarbinols and secondary anilines.[66] Additionally, they noticed that anilines bearing strong electron-donating groups were less reactive as they could entrap the catalyst to generate an "off-cycle" species. Thus, they hypothesized that employing HFIP would favor the dissociation of the "off-cycle" species, therefore improving the reactivity of aniline derivatives such as *p*-anisidine.

[63] G. Alachouzos, A. J. Frontier, *Angew. Chem. Int. Ed.* **2017**, *56*, 15030.
[64] C. Holt, G. Alachouzos, A. J. Frontier, *J. Am. Chem. Soc.* **2019**, *141*, 5461.
[65] Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2016**, *18*, 268.
[66] D. Lebœuf, L. Marin, B. Michelet, A. Perez-Luna, R. Guillot, E. Schulz, V. Gandon, *Chem. Eur. J.* **2016**, *22*, 16165.
[67] D. Lebœuf, E. Schulz, V. Gandon, *Org. Lett.* **2014**, *16*, 6464.

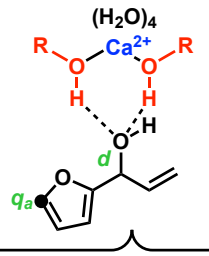


Scheme 36: aza-Piancatelli cyclization in HFIP

In order to understand the mode of activation of Ca(II)/nBu$_4$NPF$_6$ in HFIP, the authors used the Childs' method to measure the acidity of their system (Table 3). From those results, the authors deduced that the activation of furylcarbinol was triggered by an HFIP-calcium cooperative effect. In the case of some nucleophiles such as indole, the acidity of HFIP was sufficient to promote the reaction and the authors hypothesized that the role of calcium was not to directly promote the reaction as a classic Lewis acid but, instead, to increase the inherent acidity of HFIP, which was confirmed by DFT calculations.



Ca(NTf$_2$)$_2$ [equiv]	nBu$_4$NPF$_6$ [equiv]	HFIP [equiv]	H [ppm]
0	0	0	6.97
1	1	0	7.28
0	0	3	7.14
0	0	20	7.30
1	1	20	7.76

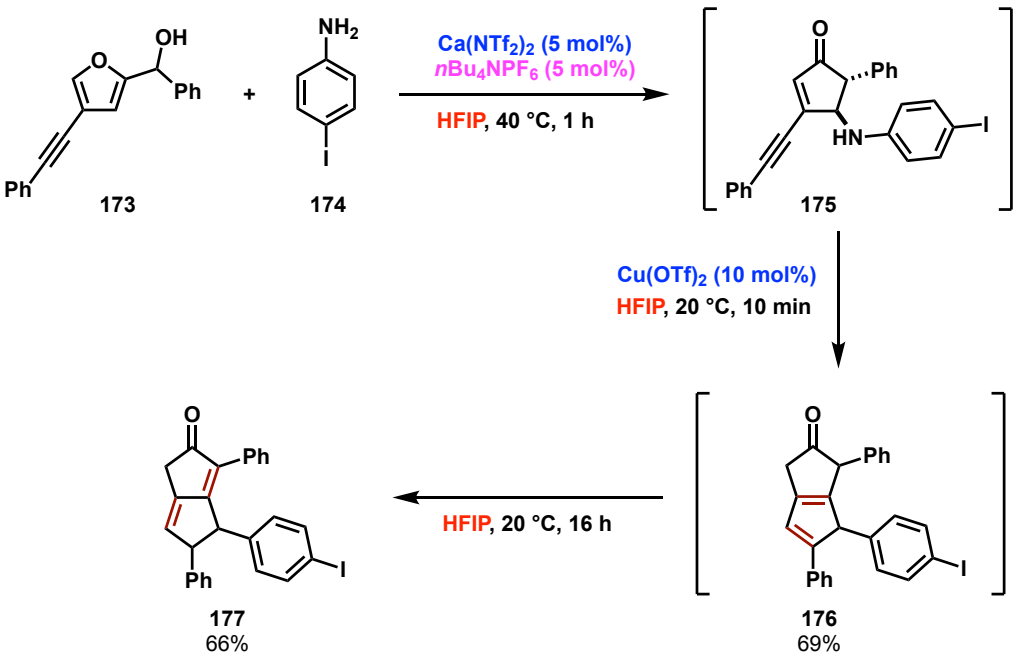


	R = H	R = iPr	R = (F$_3$C)$_2$CH
q_a	**0.087**	0.099	0.102	**0.116**
d	**1.43**	1.48	1.47	**1.51**

Table 3: Investigations on Ca(NTf$_2$)$_2$/nBu$_4$NPF$_6$ in HFIP

In 2017, the same group pushed the boundaries of the aza-Piancatelly reaction by combining this reaction with an intramolecular hydroamination in a one-pot fashion to synthetize

densely functionalized cyclopenta[*b*]pyrroles (Scheme 37).[68] When the reaction was performed in 1,2-DCE, cyclopenta[*b*]pyrrole **176** was generated following a hydroamination/isomerization process. While the use of HFIP as a solvent delivered the same compound, albeit at a lower temperature, they noticed that a prolonged reaction time led to the complete dearomatization of the product to give cyclopenta[*b*]pyrroline **177** through the activation of the carbonyl moiety by HFIP.

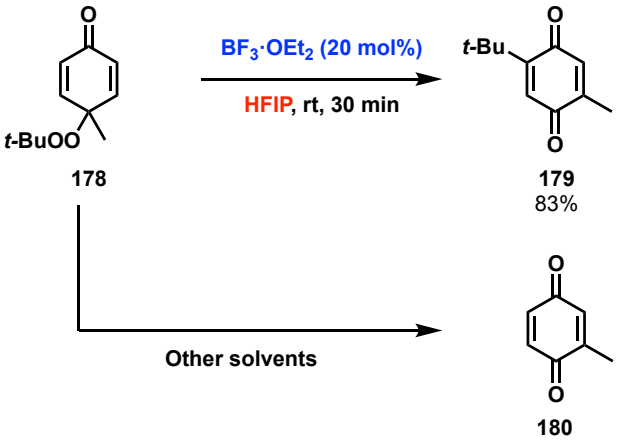


Scheme 37: Synthesis of cyclopentane[b]pyrroles in HFIP

1.3.5. Other reactions

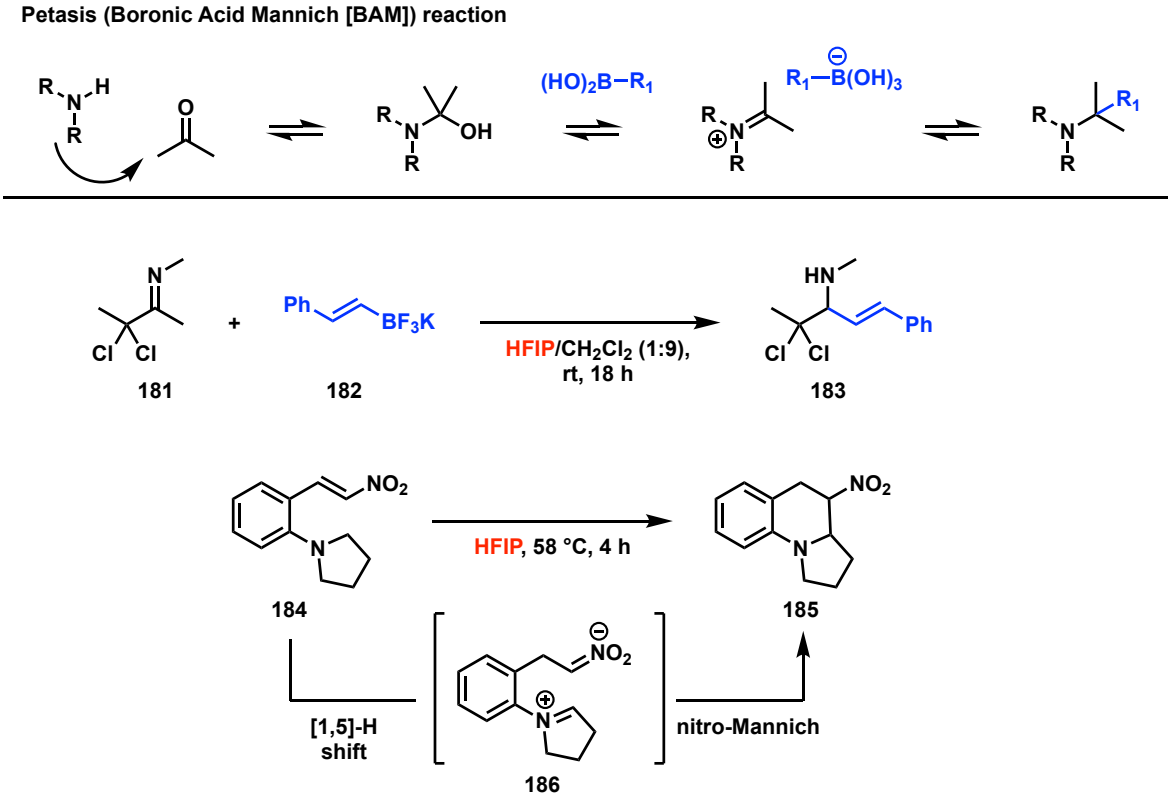
HFIP attractive properties have been used in a large variety of reactions, notably to overcome a lack of reactivity of a given substrate, to reduce side reactions or sometimes to achieve unprecedented reactivity. Komiya and co-workers discovered, for instance, an unprecedented reactivity in their attempts to synthesize vitamin K3 and K1.[69] Indeed, the precursor **178** underwent an intramolecular cyclization to furnish the benzoquinone **179** in HFIP using $BF_3{\cdot}Et_2O$ as a catalyst, while *p*-toluquinone **180** was obtained in other solvents such as DCM (Scheme 38). The authors attributed this effect to HFIP's ability to stabilizes cationic intermediate during the rearrangement. The properties of HFIP have also been used to efficiently conduct the Petasis reaction, the Schmidt reaction and the Pictet-Spengler reaction.[70]

[68] (a) L. Marin, V. Gandon, E. Schulz, D. Lebœuf, *Adv. Synth. Catal.* **2017**, *359*, 1157; (b) L. Marin, R. Guillot, V. Gandon, E. Schulz, D. Lebœuf, *Org. Chem. Front.* **2018**, *5*, 640.
[69] S.-I. Murahashi, A. Fujii, Y. Inubushi, N. Komiya, *Tetrahedron. Lett.* **2010**, *51*, 2339.
[70] N. G. Voznesenskaia, O. I. Shmatova, V. G. Nenajdenko, *Synthesis* **2019**, *52*, 263.



Scheme 38: Rearrangement in HFIP

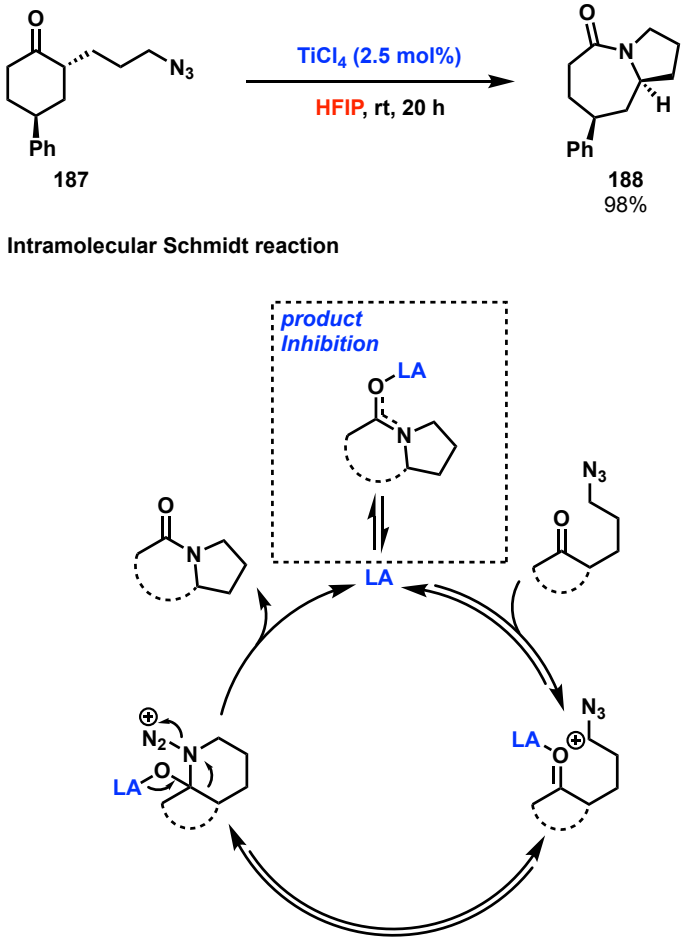
The Petasis reaction (Boronic Acid Mannich BAM reaction) is a one-step multicomponent reaction involving an organoboronic acid, an amine and a carbonyl derivative (Scheme 39). In 2017, the group of Tehrani discovered that the use of HFIP as a cosolvent could accelerate this reaction and, therefore, reduce the formation of side products.[71] The authors supposed that this acceleration was due to the ability of HFIP to stabilize/accelerate the formation of the iminium species. In a similar fashion, the group of Ware found that cyclic amines could undergo [1,5]-H nitro-Mannich reaction using HFIP as sole promoter, which was in line with Teharani assumption.[72]



Scheme 39: Mannich-Petasis reaction in HFIP

[71] S. Stas, K. A. Tehrani, *Tetrahedron* **2007**, *63*, 8921.
[72] J. C. Anderson, C.-H. Chang, M. K. Corpinot, M. Nunn, O. J. Ware, *Tetrahedron* **2019**, *75*, 130663.

The intramolecular Schmidt reaction is a method to synthesize lactams from azidoalkyl ketones. Classical methods required super-stoichiometric amount of acid to assist the transformation.[73] In 2013, the group of Aubé suggested that this lack of reactivity might be caused by a catalyst inhibition, resulting from the trapping of the catalyst by the lactam formed. Thus, they believed that the strong hydrogen bond donor ability displayed by HFIP would favor the release of the catalyst and, thus, the turn-over of the process.[74] Indeed, excellent reactivity was observed with a low catalyst loading of $TiCl_4$ in HFIP (Scheme 40).



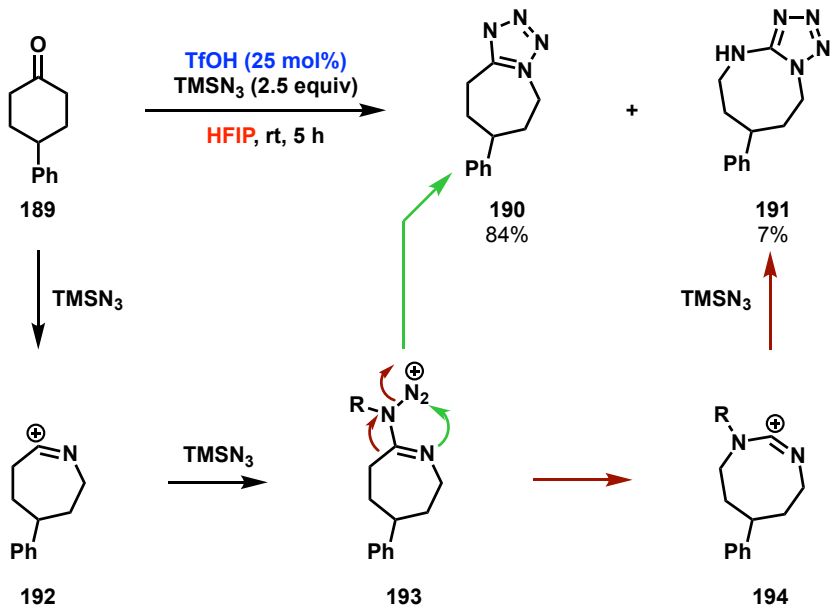
Scheme 40: Intramolecular Schmidt reaction in HFIP

In 2016, while studying the intermolecular Schmidt reaction, Aubé and co-workers found out that ketones could lead to the formation of a ring extended tetrazole using $TMSN_3$ and TfOH in HFIP (Scheme 41).[75] Interestingly, they observed another product resulting from the triple addition of trimethylsilyl azide. Concerning the role of HFIP, the authors hypothesized that HFIP might stabilize or promote the formation of the nitrilium ion **192**, which was not the case in other solvents that gave a lactam as a major product. Nevertheless, this assessment was not supported by experimental or computational evidence.

[73] (a) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449 (b) D. Lertpibulpanya, S. P. Marsden, *Org. Biomol. Chem.* **2006**, *4*, 3498

[74] H. F. Motiwala, C. Fehl, S-W. Li, E. Hirt, P. Porubsky, J. Aubé, *J. Am.Chem. Soc.* **2013**, *24*, 9000.

[75] H. F. Motiwala, M. Charaschanya, V. W. Day, J. Aubé, *J. Org. Chem.* **2016**, *81*, 1593.



Scheme 41: Modified Schmidt reaction for tetrazole synthesis

In summary, the combination of HFIP/Brønsted acid and HFIP/Lewis acid is a useful tool to overcome reactivity problems that can be met in other acid/polar solvent systems. In the different reactions described, HFIP can enhance the reactivity in different ways and often plays multiples role at the same time, including (1) stabilizing cationic intermediates, (2) preventing catalyst inhibition (*off-cycle species*) (3) assisting bond cleavage and (4) sometimes completely changing the reaction pathway. Recent computational studies and experimental evidence revealed that the formation of clusters between HFIP and Brønsted or Lewis acid was critical for the reactivity, in which HFIP is often the true active species, limiting the need to use expensive Lewis and Brønsted acids.

1.4. Alcohol Activation

1.4.1. Catalytic dehydrative substitution of alcohols

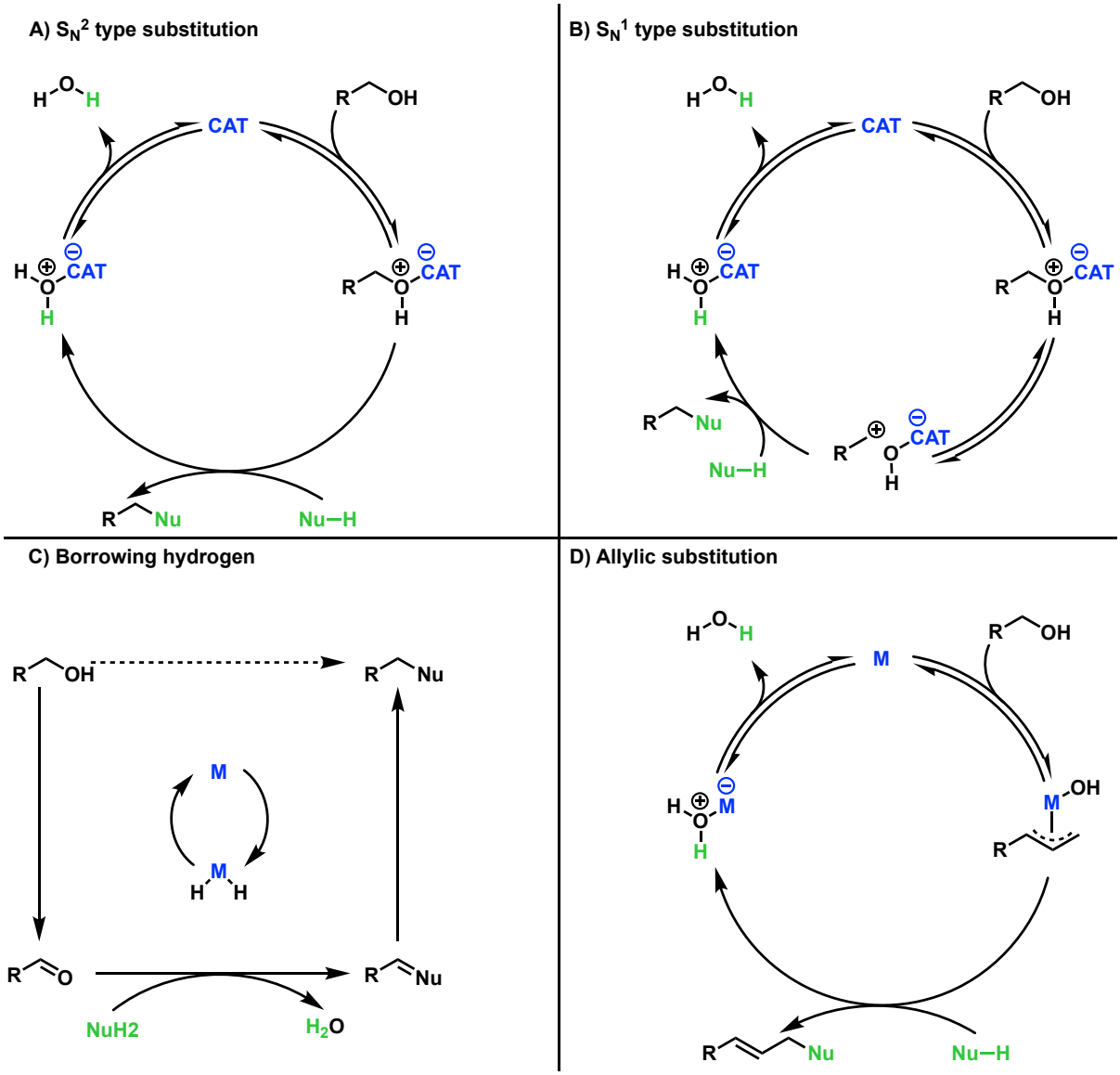
Alcohols are interesting targets for substitution as they are widely available, straightforward to prepare and tractable compounds.[76] Moreover, water is the only stoichiometric byproduct of alcohol substitution reactions. For those reasons, the ACS Green Chemistry Pharmaceutical Roundtable Institute® identified the direct substitution of alcohols as a top priority.[77] Nevertheless, due to the poor leaving group ability of the hydroxyl group, the classical approach was to convert the alcohol to a better leaving group such as a halide or to use stoichiometric amounts of acid or even using strong Brønsted acids as solvent.[78]

[76] M. Dryzhakov, E. Richmond, J. Moran, *Synthesis* **2016**, *48*, 935

[77] (a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411; (b) M. C. Brayan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weiberth, *Green Chem.* **2018**, *20*, 5082.

[78] (a) V. N. Ipatieff, H. Pines, B. S. Friedman. *J. Am. Chem. Soc.* **1938**, *60*, 2731; (b) P. F. Oesper, C. P. Smyth, M. S. Kharasch, *J. Am. Chem. Soc.* **1942**, *64*, 937; (c) M. Ouertani, J. Collin, H. B. Kagan, *Tetrahedron* **1985**, *41*, 3689; (d) J. Y. Gauthier, F. Bourdon, R. N. Young, *Tetrahedron Lett* **1986**, *27*, 15.

Nowadays, considerable advances have been made in the field of direct alcohol substitution using sub-stoichiometric amounts of catalyst.[79] Four approaches dominate, the classic S_N1 and S_N2 substitution (Scheme 42, **A** and **B**). The third pathway is the borrowing hydrogen method (Scheme 42, **C**). This approach is so named because a metal center borrows two hydrogens from the alcohol and then gives them back after addition of the nucleophile to form the final product. The overall mechanism is a nucleophilic substitution. The fourth mechanism is allylic substitution; this method takes advantage of the reactive π-allyl system to promote the substitution (Scheme 42, **D**).

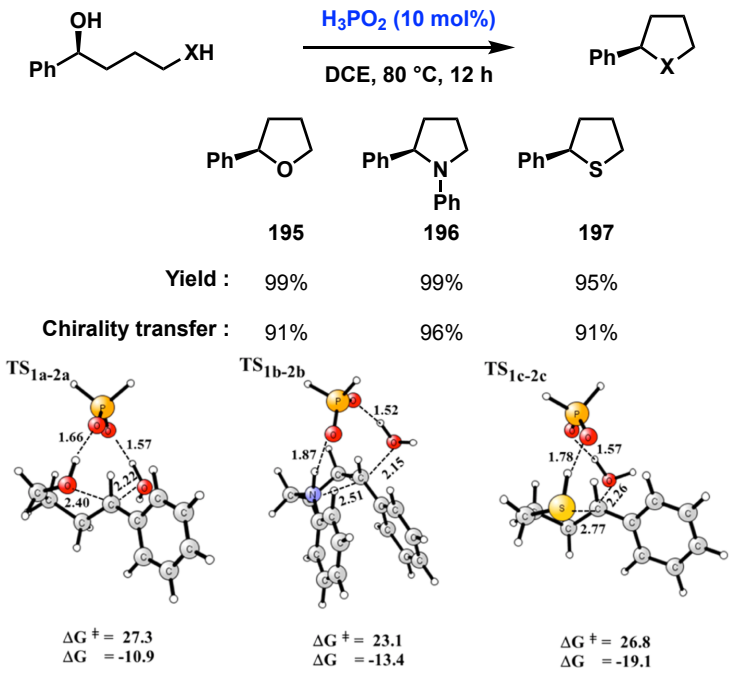


Scheme 42: General mechanism for catalytic dehydrative substitution

Only few examples of catalytic S_N2 reactions on alcohols exist in the literature. In 2015, Samec and coworkers developed a Brønsted acid catalyzed intramolecular reaction that promotes the substitution of the hydroxyl group to yield enantioenriched tetrahydrofuran, pyrrolidine and tetrahydrothiophene derivatives using phosphinic acid catalysis (Scheme 43). DFT

[79] J. E. Taylor, S. Estopiñá-Durán, *Chem. Eur. J.* **2020**, DOI 10.1002/chem.202002106.

calculations supported an S_N2 mechanism in which the phosphinic acid acted as a directing group.[80]



Scheme 43: Intramolecular cyclisation using phosphoric acid as a directing group

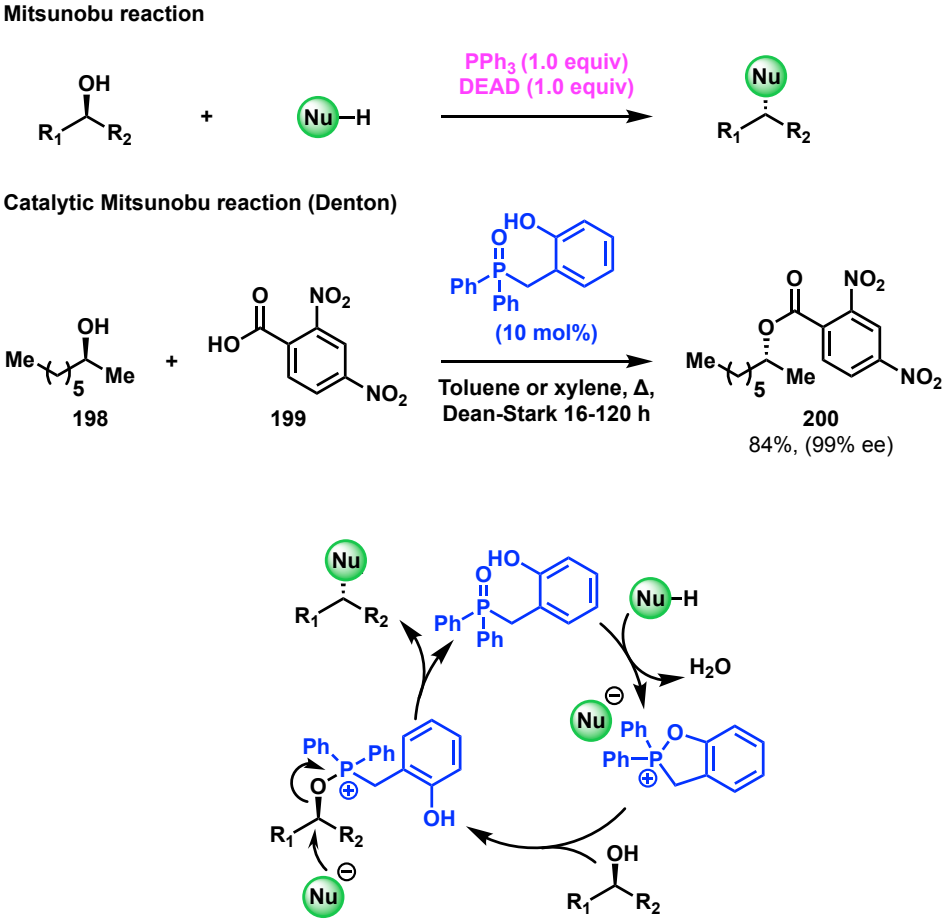
In 2019, the group of Denton report an impressive fully catalytic Mitsunobu reaction.[81] The original Mitsunobu reaction required a stoichiometric amount of an oxidant, DEAD, and a stoichiometric amount of reductant, triphenylphosphine (Scheme 44). By using an already oxidized phosphine, they succeeded to decrease the amount of phosphine required to 10%. In addition, the oxidation state of the phosphorus (V) catalyst does not change during the course of the reaction, therefore no oxidant is required. Concerning the mechanism:

(1) The nucleophile protonates the phenol group of the organocatalyst, which then undergo an intramolecular cyclization to form an oxyphosphonium salt. As the nucleophile also acts as an acid, no additional acid is required for this reaction. The downside is that the scope of nucleophile tolerated is limited to highly acidic carboxylic acids and sulfonate-bearing nucleophiles such *p*-toluene sulfonic acid.

(2) The second step is an S_N2 reaction, where the alcohol induces a ring-opening of the oxyphosphonium salt. This step breaks the strong P-O bond, which explain the high temperature required for this reaction.

(3) The subsequent addition of a nucleophile on the alkoxyphosphonium salt leads to the formation of the S_N2 product and regenerates the catalyst.

[80] A. Bunrit, C. Dahlstrand, S. K. Olsson, P. Srifa, G. Huang, A.Orthaber, P. J. R. Sjöberg, S. Biswas, F. Himo, J. S. M. Samec, *J. Am. Chem. Soc.* **2015**, *137*, 4646.
[81] R. H. Beddoe, K. G. Andrews, V. Magné, J. D. Cuthbertson, J. Saska, A. L. Shannon-Little, S. E. Shanahan, H. F. Sneddon, R. M. Denton, *Science* **2019**, *365*, 910.

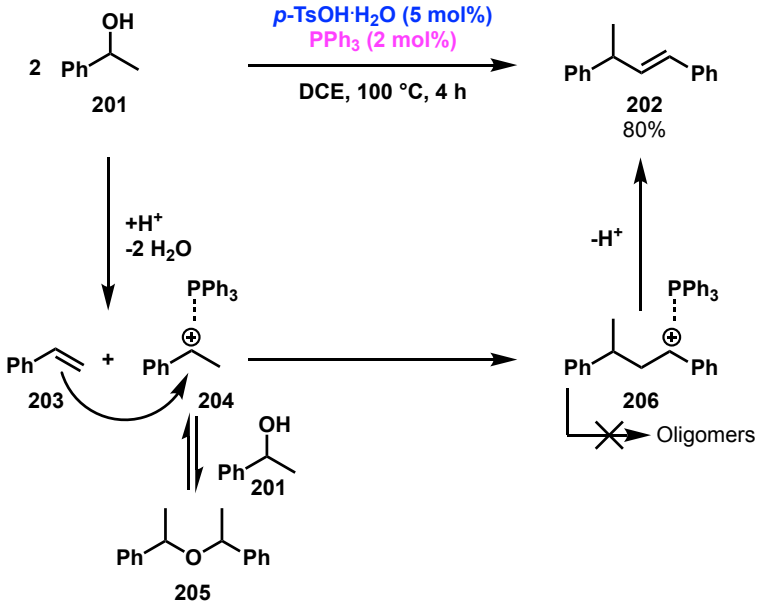


Scheme 44: Catalytic Mitsunobu reaction

An example from our group of a catalytic S_N1 reaction of highly deactivated alcohols was described in depth in the Friedel-Crafts part of this manuscript.[36] In a S_N1 reaction, the stabilization of the carbocation is critical, as this carbocation needs to exist long enough for the nucleophilic attack to occur. Thus, S_N1 reactions require substrates bearing carbocation-stabilizing groups such as phenyl and/or a stabilizing effect from the solvent or from an additive.

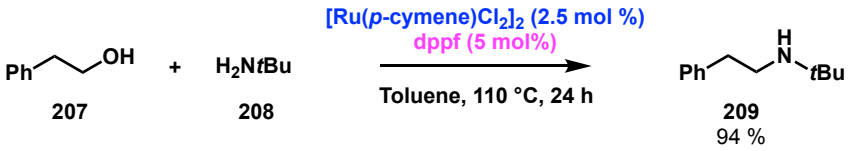
Recently, in 2019, Böld and Fleischer reported two S_N1 catalytic dehydrative reactions involving a Brønsted acid and a Lewis base for the homo-coupling of benzylic alcohol (Scheme 45).[82] According to the authors the role of PPh_3 is to avoid oligomerization.

[82] M. Böldl, I. Fleischer, *Eur. J. Org. Chem.* **2019**, 5856.



Scheme 45: Homo coupling of electron riche secondary Benzylic alcohols

The previous methods aimed at increasing the reactivity of the hydroxyl group. An alternative approach is the hydrogen borrowing strategy.[83] This method consists of using a catalytic amount of metal catalyst to remove two hydrogens from the alcohol to oxidize it into a more reactive carbonyl group. Then, the carbonyl can react with an amine nucleophile to form an imine and water. The oxidized metal species can then reduce the imine to form the amine product, thus closing the catalytic cycle. An evident downside of this reaction is that tertiary alcohols cannot be used under this strategy. Furthermore, the hydrogen borrowing strategy generally requires late transition metals such ruthenium and iridium, which restrains its application for industrial processes. As an example of a hydrogen borrowing system, the group of Williams reported an efficient $[Ru(p\text{-cymene})Cl_2]_2$ system to convert primary amines into secondary amines and secondary amines into tertiary amines using primary and secondary alcohols, respectively (Scheme 46).[84]

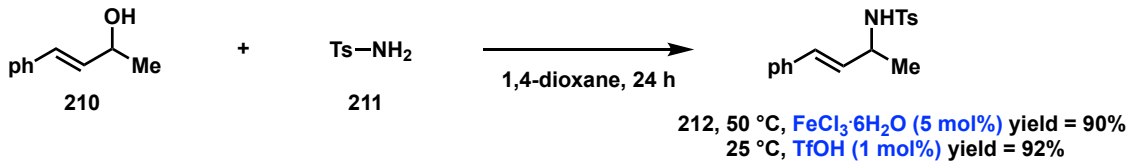


Scheme 46: Hydrogen borrowing strategy

Due to their reactive π-allyl system, allylic alcohols have been widely used for direct catalytic alcohol substitution using diverse metal salts such as copper[85], calcium[86] and later metals such

[83] A. J. A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635.
[84] M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766.
[85] (a) B. V. Rokade, K. Gadde, K. R. Prabhu, *Eur. J. Org. Chem* **2015**, 2706; (b) K. Chen, H. J. Chen, J. Wong, J. Yang, S. A. Pullarkat, *ChemCatChem* **2013**, 5, 3882.
[86] (a) T. Stopka, M. Niggemann, *Org. Lett*. **2015**, *17*, 1437; (b) D. Lebœuf, M. Presset, B. Michelet, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Chem. Eur. J.* **2015**, *21*, 11001.

as palladium[87] and platinum[88] complexes. Those metals furnish usually a better selectivity toward the nucleophilic substitution. Nevertheless, the allylic alcohol substitution is not limited to Lewis acids; in some cases, similar reactivity was obtained with Brønsted acids (Scheme 47).[89]



Scheme 47: Amination of allylic alcohols

1.4.2. Carbocation stability and alcohol reactivity.

Which electrophiles react with which nucleophiles? Mayr and co-workers have tackled this difficult issue.[90] Based on experimental data, they developed a tool for predicting the rate of a reaction between a nucleophile and an electrophile [log $K_{20°C}$ = s(E+N)], in which the electrophile is characterized by a parameter (E) and the nucleophile by two parameters (N, S) (Table 4). They also developed a rule of thumb to predict whether a nucleophile/electrophile pair can react together within a realistic experimental time: if [E+N > -5] the reaction could be expected at room temperature.

[87] (a) M. Wang, Y. Xie, J. Li, H. Huang, *Synlett* **2014**, 2781. (b) R. Shibuya, L. Lin, Y. Nakahara, K. Mashima, T. Oshima, Angew. *Chem. Int. Ed.* **2014**, *53*, 4377.
[88] X. Huo, G. Yang, D. Liu, Y. Liu, I. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6776.
[89] P. Trillo, A. Baeza, C. Najera, *Eur. J. Org. Chem.* **2012**, 2929.
[90] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66.

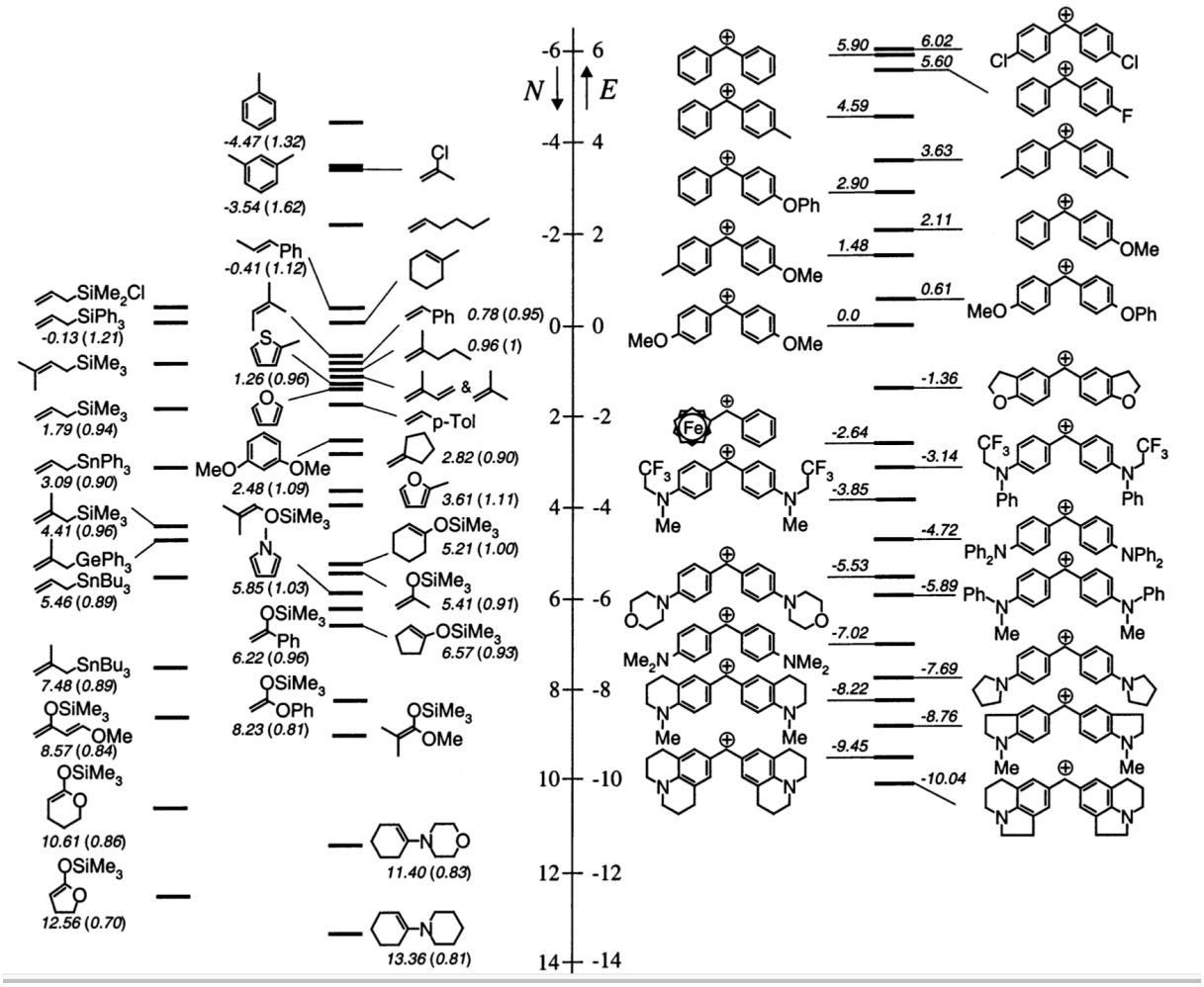
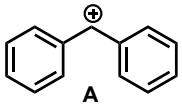


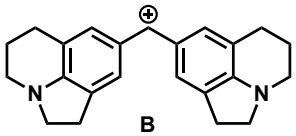
Table 4: Mayr electrophilic and nucleophilic scales

As an example of easy application of Mayr's scale:

As the scale is logarithmic, if a nucleophile reacts with **A** (electrophile on the top of the scale) within a minute, it will take 20 billion years for the same nucleophile to react with **B** (electrophile on the bottom of the scale) in the same conditions.



A ***E*** **= 5.90**

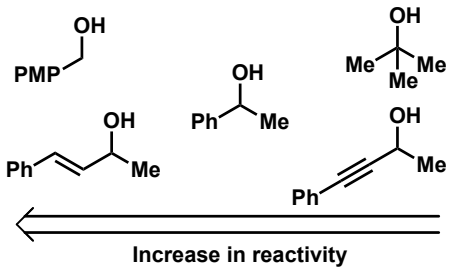


B ***E*** **= -10.04**

Scheme 48: Application of Mayr's scale

Although this method is applicable for numerous electrophile/nucleophile combinations, this method does not account for two important parameters, the ease of the carbocation formation and the possible interactions between the catalyst and the nucleophile.

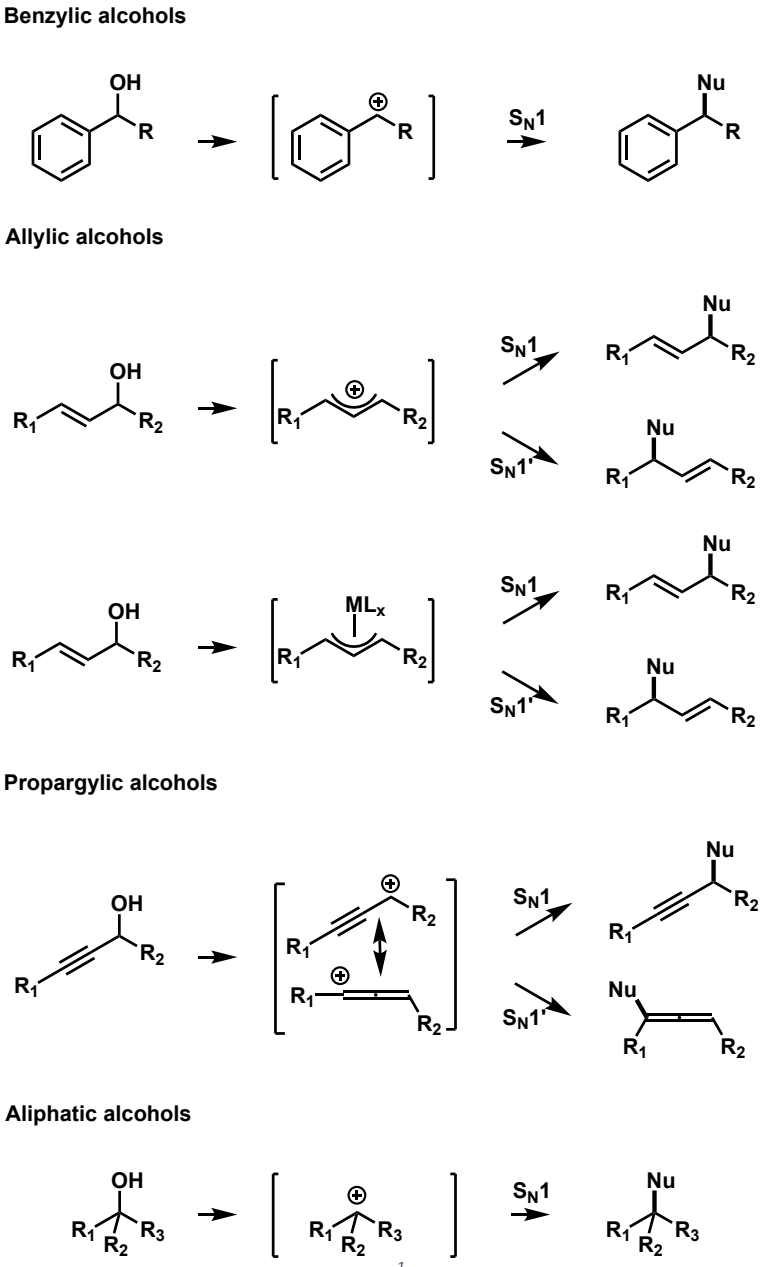
Furthermore, this approach considers the reaction of a nucleophile and a carbocation. Therefore, its application concerns S_N1 type reactions and important deviations might be observed with S_N2 reactions.
Ten years later, in 2013 Biswas and Samec reported a study aiming to map the reactivity of alcohols toward S_N1 reactions.[91] They conclude that, in the case of alcohols, the reactivity and the selectivity of the reaction is more related to "the ease" of the carbocation formation rather than the electrophilic character of the carbocation. Thus, the reactivity of alcohols starting from the less reactive to more reactive is the following: benzylic alcohols, allylic alcohols, propargylic alcohols, and then aliphatic alcohols (Scheme 49).



Scheme 49: Biswas and Samec map of alcohol reactivity

Benzylic alcohols are the most reactive thanks to the stabilization of the carbocation by the large π system of the aromatic ring (Scheme 50). The case of allylic alcohol is more complicated as two different mechanisms are possible depending if the activation occurs though coordination of a metal center on the allylic system or if a true carbocation is formed. Furthermore, if the substitution of the allylic alcohol is pseudo-symmetric (R_1 = R_2) the nucleophilic substitution leads to only one product, while in the opposite regioselectivity of the nucleophilic substitution must be considered. Propargylic alcohols are even more versatile. Dehydration reactions on propargylic alcohols leads to two possible ions, the propargylium ion and the allenylium ion, leading to allene and indene products, respectively. The ease of carbocation generation for aliphatic alcohols depends only on the hyperconjugation effect, and thus to the substitution pattern of the alcohol. Although direct alcohol substitution on aliphatic tertiary and secondary alcohols though a S_N1 mechanism is relatively easy, primary carbocation generation is not favorable thermodynamically. Therefore, no report of S_N1 reactions on primary aliphatic alcohols have been reported and this mechanism is highly unlikely for that class of substrates.

[91] S. Biswas, J. S. M. Samec, *Chem. Asian J.* **2013**, *8*, 974.



Scheme 50: Summary of S_N1-type alcohol reactivity

1.5. Thesis project

As detailed in the above subchapters, HFIP in combination with Brønsted and Lewis acids have demonstrated their versatility in a variety of reactions and possess a great potential to be exploited for quite a long time in the future. On the other hand, our group turned to the utilization of Brønsted or Lewis acid system a few years ago and commenced to benefit from the TfOH/HFIP combination for the activation of highly deactivated benzylic alcohols and mono-substituted cyclopropanes. This association proved to be efficient for conducting reactions with more versatile substrates and for the activation of less activated molecules.

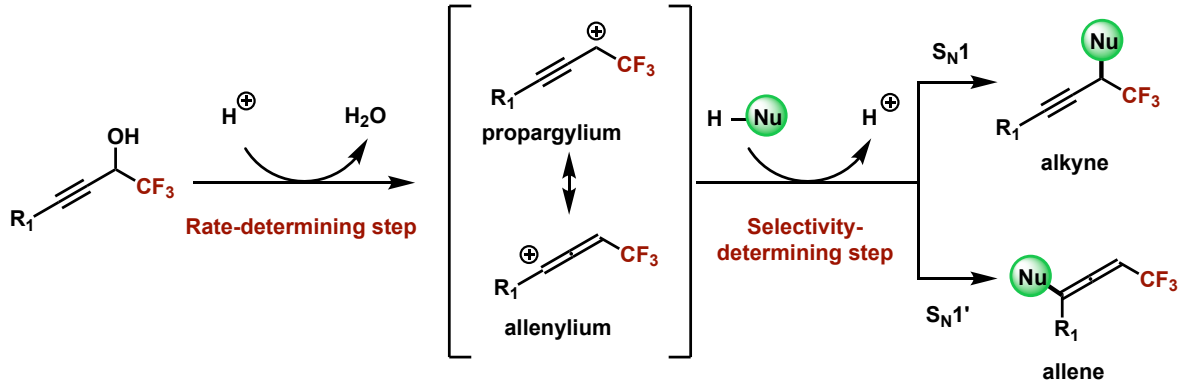
To further exploit Brønsted or Lewis acids for alcohol substitution in HFIP, in the following chapters I will present my work regarding the activation of propargylic alcohols for the synthesis of allenes, indenes, chromenes and alkenes, followed by my current progress on the direct substitution of primary aliphatic alcohols.

Part 2: Catalytic activation of trifluoromethylated propargylic alcohols

2. Catalytic activation of trifluoromethylated propargylic alcohols

2.1. Background and context

In comparison with the direct nucleophilic substitution of benzyl alcohols, that of propargylic alcohols offers a more versatile reactivity as it can give rise to two types of products, either an α-substituted alkyne or an allene (Scheme 51). Numerous examples regarding the direct substitution of this class of alcohol have been reported, using transition metal-based catalysts (ruthenium, gold, copper, etc.) as well as Brønsted acids such as TfOH.[92] On the other hand, there are only a few examples of the formation of allenes from propargylic alcohols via a carbocationic intermediate.[93]



Scheme 51: S_N1 and S_N1' reaction of propargylic alcohols

Following previous studies in our group on the Friedel-Crafts alkylation of α-trifluoromethyl benzyl alcohols in HFIP, we wondered whether this type of reactivity could be extended to their propargyl alcohol analogs. The idea of adding fluorine functional groups to a molecule is now a well-established approach in order to modulate its physiochemical and pharmaceutical properties.[94] Nearly 20-25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. Fluorine is the most electronegative element and the addition of a CF_3 group to a molecule can (1) increase its local polarity and, therefore, enhance the propensity of a molecule to bind to a host such as an enzyme center in comparison with a non-fluorinated analog, (2) decrease the size of the electron cloud of an electron-rich heteroatom or a π system, hence increasing its lipophilicity and, thus, its ability to cross biological barriers, (3) increase its biological stability owing to the strength of the C-F bound. Indeed, the CF_3 group can be used as a bioisostere of methyl or chloride to protect a molecule against biological metabolizing by enzymes such the P450 cytochrome.[95]

With respect to this project, we anticipated that the presence of a CF_3 group at the α-position of the propargylic alcohol would favor the isomerization of the propargylium cation to the allenylium cation, leading to the formation of an allene product. Interestingly, allene moieties

[92] (a) J. J. Kennedy-Smith, L. A. Young, F. D. Toste, *Org. Lett.* **2004**, *6*, 1325; (b) M. Georgy, V. Boucard, J.-M Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180; (c) G.-B. Huang, X. Wang, Y.-M. Pan, H.-S. Wang, G.-Y. Yao, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 2742; (d) S. Ponra, M. Gohain, J. H. van Tonder, B. C. B. Bezuidenhoudt, *Synlett* **2015**, 745.

[93] (a) C.-F. Xu, M. Xu, L.-Q. Yang, C.-Y. Li, *J. Org. Chem*. **2012**, *77*, 3010; (b) C. L. Ricardo, X. Mo, J. A. McCubbin, D. G. Hall, *Chem. Eur. J.* **2015**, *21*, 4218; (c) K. Huang, G. Sheng, P. Lu, Y. Wang, *J. Org. Chem*. **2017**, 82, 5294.

[94] (a) M. Schlosser, *Angew. Chem. Int. Ed.* **1998**, *37*, 1496; (b) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637.

[95] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem.* Soc. *Rev.* **2008**, *37*, 320.

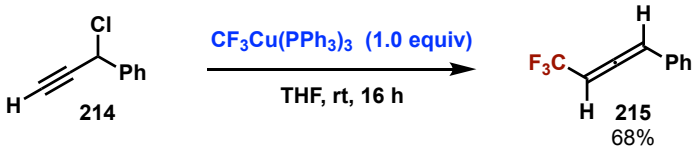
are widely spread in natural and bioactive molecules, which could make our system of potential interest in drug discovery.[96]

2.2. State of the art for the synthesis of trifluoromethylated allenes

Few examples for the preparation of trifluoromethylated allenes have been reported in the literature. The first example dates from 1974.[97] The standard method relied on the use of a stoichiometric amount of trifluoromethyl copper with a propargyl halide (Scheme 52). This method proved to be also efficient with other perfluoroalkyl copper reagents. The group of Hsu noticed that the choice of the leaving group was critical as a tosylate group furnished better yields with short perfluoroalkyl chains (CF_3 to *n*-C_3F_7), while chloride worked better for *n*-C_6F_{13} to *n*-C_8F_{17} perfluoroalkyls.

Scheme 52: Seminal example of the synthesis of CF_3-bearing allenes

In 2012, Zhao and Szabó described a copper-mediated trifluoromethylation of propargylic halides and propargylic trifluoroacetate for the synthesis of CF_3-bearing allenes (Scheme 53).[98] Control experiments conducted in the presence of a radical scavenger (TEMPO) did not affect the reactivity. Thus, the authors deduced that the reaction occurred through an ionic mechanism involving a nucleophilic transfer of the CF_3 group from the copper complex to the propargylic substrate. Additional experiments starting from an enantiomerically enriched substrate led to the formation of an enantio-enriched allene, which suggest a concerted mechanism (S_N2'-type mechanism). Nevertheless, the authors stated that a further in-depth study would be required to understand in details this transformation.



Scheme 53: Copper-mediated trifluoromethylation of propargylic halides for the synthesis of CF_3 allenes

In 2015, the group of Altman reported a ligand-controlled regioselective copper-catalyzed trifluoromethylation of propargyl acetates to generate CF_3-bearing allenes (Scheme 54).[99] The selectivity of the reaction is based on the ability of the bipyridyl ligand to control the regioselectivity of the Cu-catalyzed nucleophilic trifluoromethylation. As the trifluoromethyl source is not on the Copper, Altman's method is a good alternative to methods that required stoichiometric amount of Cu-CF_3 catalyst.

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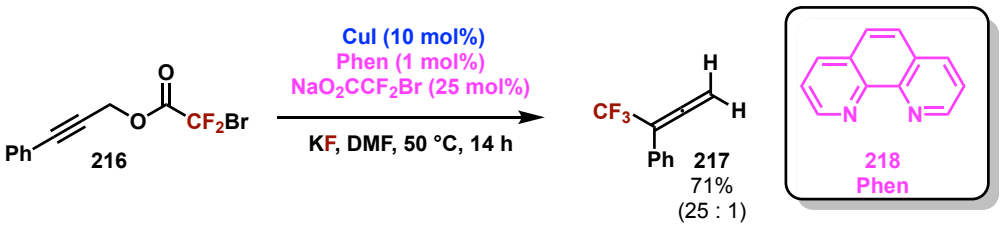
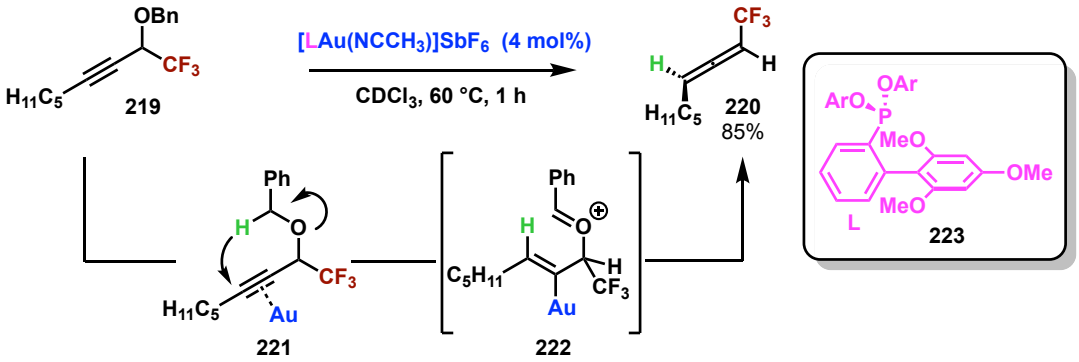
[96] A. Hoffmann-Röder, N. Krause. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.
[97] (a) P. L. Coe, N. E. J. Milner, *J. Organomet. Chem.* **1974**, *70*, 147; (b) D. J. Burton, G. A. Hartgraves, J. Hsu, *Tetrahedron Lett.* **1990**, *31*, 3699; (c) M.-H. Hung, *Tetrahedron Lett.* **1990**, *31*, 3703; (d) J.-P. Bouillon, C. Maliverney, R. Mereńyi, H. G. Viehe, *J. Chem. Soc., Perkin Trans.* 1, **1991**, 2147.
[98] T. S. N. Zhao, K. J. Szabó, *Org. Lett.* **2012**, *14*, 3966.
[99] B. R. Ambler, S. Peddi, R. A. Altman, *Org. Lett*. **2015**, *17*, 2506.



Scheme 54: Ligand-controlled regioselective copper-catalyzed trifluoromethylation for the synthesis of CF_3-bearing allenes

In 2016, Gagosz and co-workers described a method to access CF_3-bearing allenes through gold-catalyzed rearrangement of propargylic benzyl ethers (Scheme 55).[100] This reaction had the advantage of controlling the axial chirality of the allene product. In a mechanistic proposal, the authors explained that (1) the alkyne is first activated upon coordination to the gold complex and, then, (2) the metal induces a 1,5-hydride shift of the activated propargylic benzyl ether, which leads to an oxocarbenium intermediate. (3) The subsequent elimination of benzaldehyde delivers the allene product and the regeneration of the catalyst.



Scheme 55: Gold-catalyzed rearrangement of propargylic benzyl ethers for the synthesis of CF_3-bearing allenes

Unlike the above examples, the transformation that we envisioned does not require pre-activation of propargylic alcohols and has the advantage to generate water as the sole stoichiometric byproduct.

2.3. Synthesis of starting materials

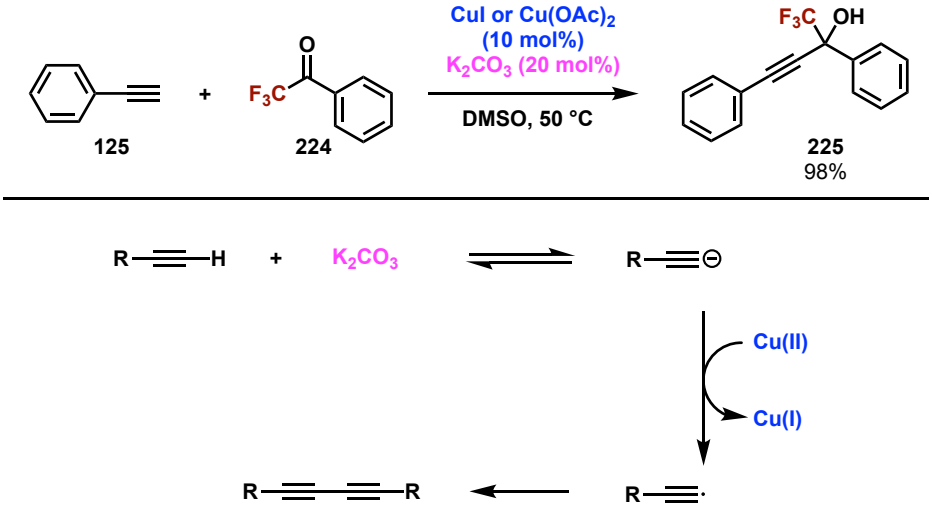
2.3.1. Synthesis of tertiary propargylic alcohols

Tertiary propargylic alcohols were synthetized according to a copper-catalyzed direct alkynylation of trifluoromethyl ketones developed by the group of Shi (Scheme 56).[101] While Cu(I) and Cu(II) catalysts could efficiently promote this reaction, the role of copper seems to go further than that of a simple Lewis acid as all other Lewis acid tested by the authors failed to trigger the reaction. Thus, they suggested that the true catalyst for this reaction might be Cu(I) as, even when a Cu(II) catalyst was used, a reductive homo-coupling of phenylacetylene was observed either in presence or absence of trifluoromethyl ketone.

However, the mechanism remains still unclear. A plausible mechanism would involve the activation of the carbonyl group of the trifluoromethyl ketone to increase its electrophilicity, combined with the activation of the alkyne by copper to lower the pK_a of the terminal hydrogen. On the other hand, conducting the reaction in the absence of phenylacetylene led

[100] A. Boreux, G. Lonca, O. Riant, F. Gagosz, *Org. Lett*. **2016**, *18*, 5162.
[101] L. Wang, N. Liu, B. Dai, X. Ma, L. Shi, *RSC Adv.* **2015**, *5*, 10089.

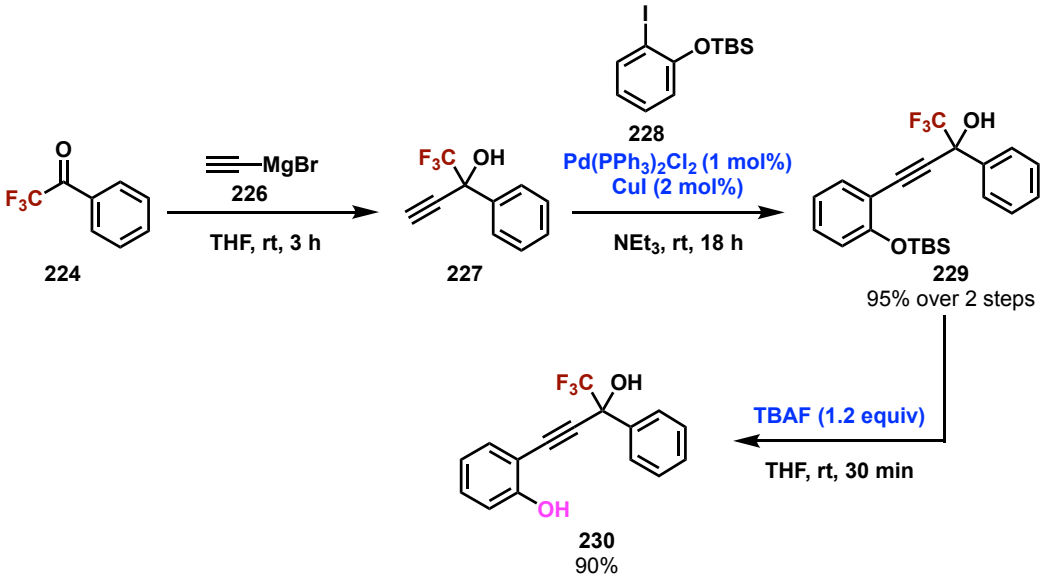
to the full conversion of trifluoromethyl ketone **224** into diol following a dimerization process, suggesting it might be an important active intermediate.



Scheme 56: Synthesis of tertiary propargylic alcohols

2.3.2. Synthesis of tertiary propargylic alcohols bearing an *o*-hydroxyl group

Tertiary propargylic alcohols bearing an *o*-hydroxyl group were synthetized according to a known three step protocol (Scheme 57).[102] The first step is a classic alkynylation of the trifluoroacetophenone **224** with a solution of ethynylmagnesium bromide to form alkyne **227**, followed by a Sonogashira cross-coupling with aryl iodide **228** bearing a *o*-OTBS group. A subsequent desilylation of the phenol led to the targeted tertiary propargylic alcohols bearing an *o*-hydroxyl group.

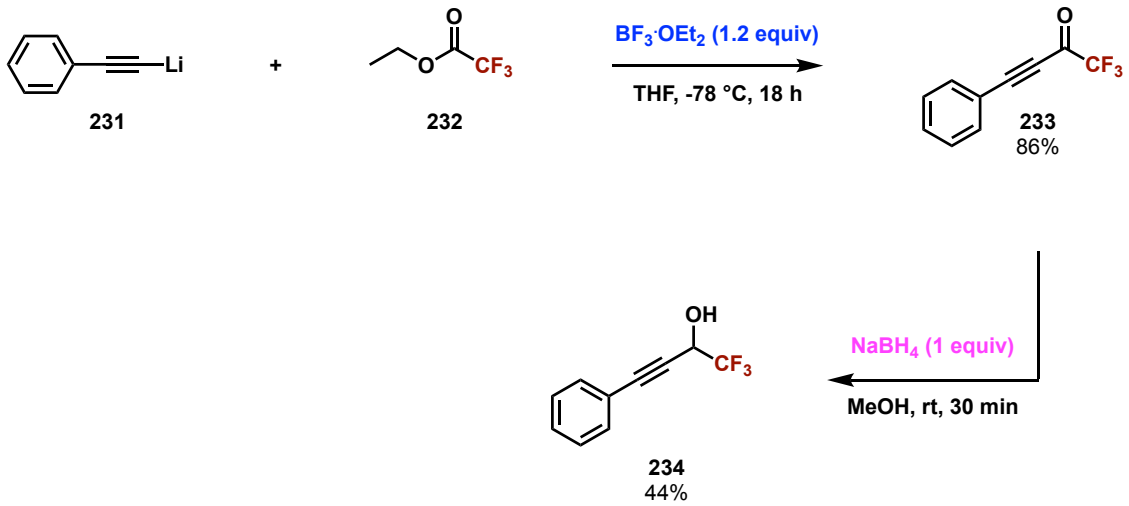


Scheme 57: Synthesis of CF_3-bearing tertiary propargylic alcohols with an o-hydroxyl group

[102] Y.-F. Qiu, Y.-Y. Ye, X.-R. Song, X.-Y. Zhu, F. Yang, B. Song, J. Wang, H.-L. Hua, Y.-T. He, Y.-P. Han, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2015**, *21*, 3480.

2.3.3. Synthesis of secondary propargylic alcohols.

Secondary propargylic alcohols were prepared via a two-step method (Scheme 58).[103] The first step is the addition of lithium acetylide to ethyl trifluoroacetate promoted by boron trifluoride etherate to provide ketone **233**. In a second step, the ketone was reduced with $NaBH_4$ to furnish the corresponding secondary propargylic alcohol.



Scheme 58: Synthesis of CF_3-bearing secondary propargylic alcohols

2.4. Synthesis of CF_3-bearing allenes

2.4.1. Reaction discovery and optimization

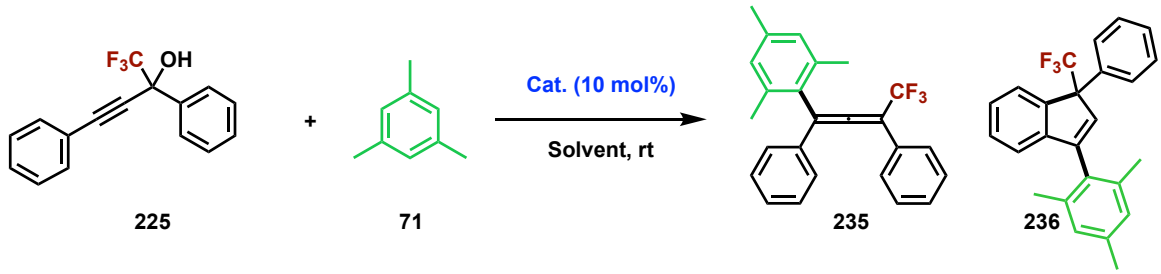
We began our investigation with a simple propargylic alcohol **225** using mesitylene as a nucleophile, which has shown excellent reactivity in the nucleophilic substitution of highly deactivated benzylic alcohols reported by our group. A series of Brønsted and Lewis acid were screened in HFIP (Table 5). Gratifyingly, triflic acid afforded the allene **235** in 85% yield at room temperature (entry 1). On the other hand, increasing the temperature to 50 °C did not only lead to the targeted allene (entry 2) but also to indene **236**. When the reaction was conducted in the presence of weaker Brønsted acids (entries 3-5), the product was either not obtained or was delivered in a lower yield due to a lack of reactivity. Stronger Brønsted acid $HSbF_6{\cdot}6H_2O$ (entry 6) led to a slightly improved reactivity, while several Lewis acids tested provided **235** in moderate yields (entries 7-11).

Regarding this reaction, the best result was obtained using $FeCl_3$ as a catalyst, yielding **235** in 93% at room temperature within 10 minutes (entry 12). Increasing the temperature to 80 °C furnished the indene **236** in 94% yield (entry 13). The use of HFIP was critical to the success of the reaction as another fluorinated solvent such as TFE only furnished the allene in 39% yield, and no reaction took place in the non-fluorinated analog of HFIP (*i*PrOH) (entries 14-15). Replacing $FeCl_3$ by $FeCl_2$ significantly decreased the efficacy of the reaction (entry 17).

Further investigations were conducted to shed light on the mode of activation of $FeCl_3$, notably whether we are in the presence of a Lewis acid catalyst or a hidden Brønsted acid catalyst. First, we rule out the hypothesis of hydrolysis of $FeCl_3$ into HCl as HCl afforded only

[103] (a) T. Kitazume, T. A. Sato, *J. Fluorine Chem*. **1985**, 30, 189; (b) L. Xiao, T. Kitazume, *Tetrahedron: Asymmetry* **1997**, *8*, 3597.

trace amounts of the allenic product. On the other hand, carrying out the reaction in the presence of a proton scavenger, 2,6-di-*tert*-butylpyridine, which does not coordinate most metal ions,[104] completely shut down the transformation. Based on previous findings from different groups, we believed that ferric ions could enhance Brønsted acidity of HFIP by forming higher order aggregates, which would act as the active catalytic species (hidden Brønsted acid catalysis).



entry	catalyst	solvent	time	allene 235 yield (%)	indene 236 yield (%)
1	TfOH	HFIP	1 h	85	<1
2[a]	TfOH	HFIP	45 min	50	43
3[a]	TFA	HFIP	24h	60	<1
4	H_3PO_4	HFIP	24h	<1	<1
5	HCl[b]	HFIP	10 min	<1	<1
6	$HSbF_6{\cdot}6H_2O$	HFIP	10 min	87	8
7	$Sc(OTf)_3$	HFIP	24 h	9	<1
8	SbF_5	HFIP	10 min	66	<1
9[a]	$AlCl_3$	HFIP	45 min	24	10
10	$ZnCl_2$	HFIP	24 h	7	<1
11	$AuCl_3$	HFIP	10 min	69	<1
12	$FeCl_3$	HFIP	10 min	93	<1
13[c]	$FeCl_3$	HFIP	24 h	<1	94
14	$FeCl_3$	*i*-PrOH	10 min	<1	<1
15	$FeCl_3$	CF_3CH_2OH	10 min	39	<1
16	$FeCl_3$	CH_2Cl_2	24 h	9	<1
17	$FeCl_2$	HFIP	24 h	41	<1

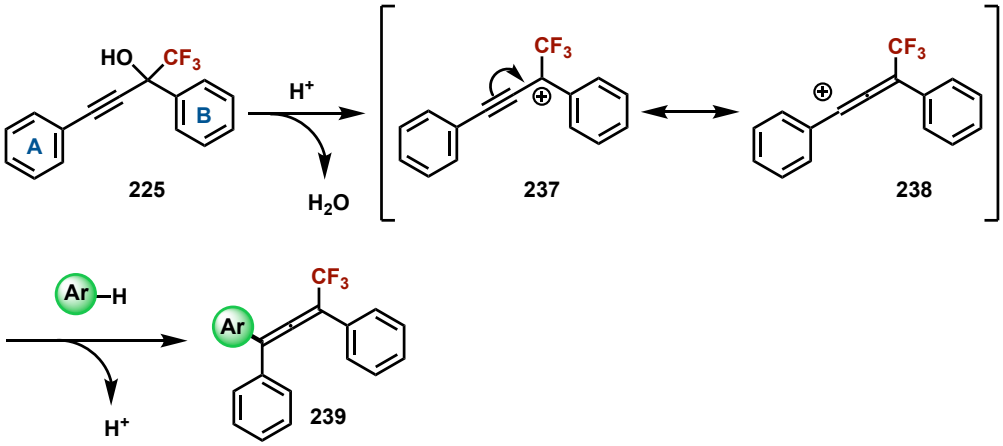
Table 5: Reaction optimization

[a] Reaction performed at 50 °C. [b] Reaction conducted in the presence of 37% aq. HCl (w/w). [c] Reaction performed at 80 °C.

[104] T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484.

2.4.2. Mechanistic proposal for the formation of allenes

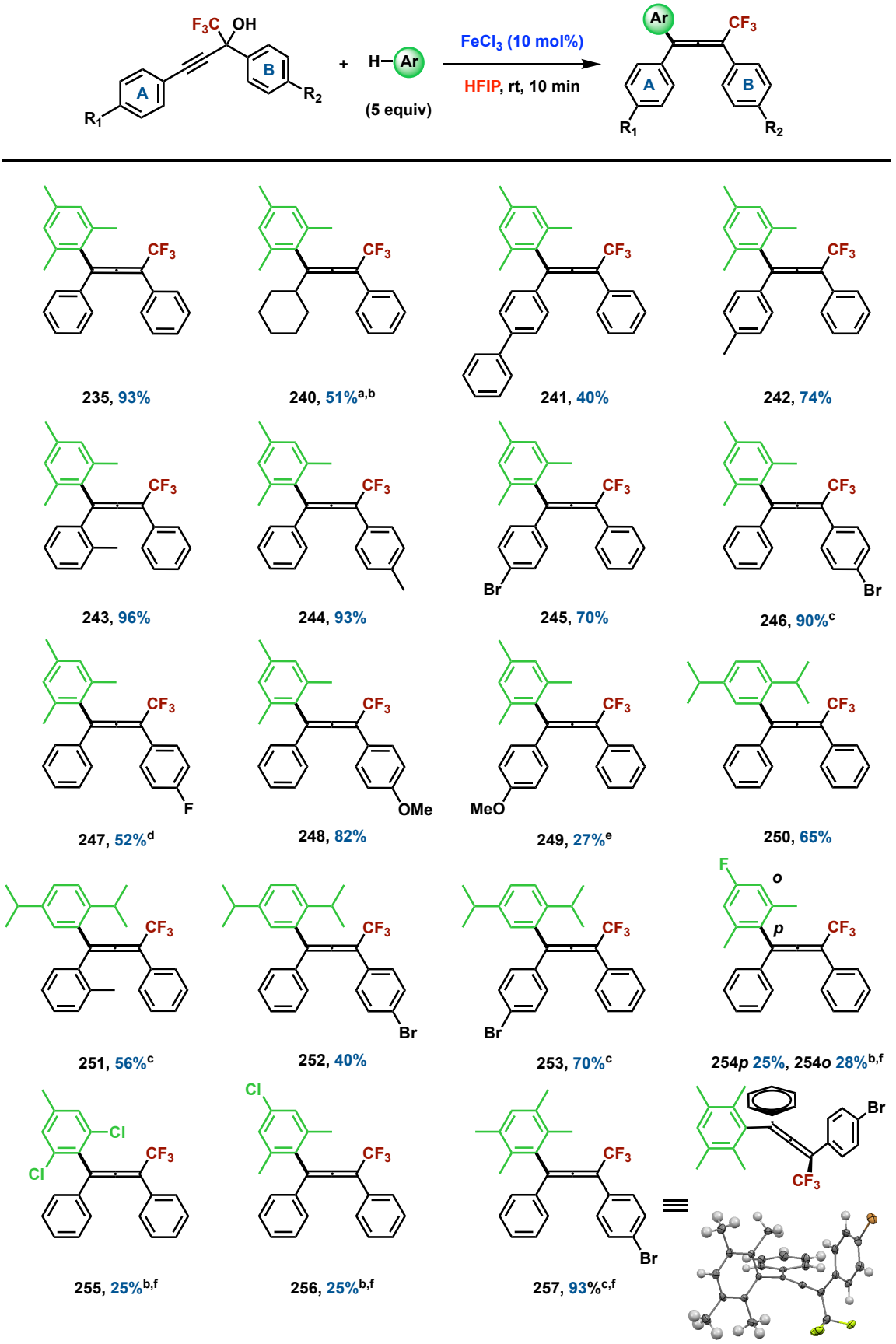
The first step of the proposed mechanism involves the classical formation of a propargylic cation that can then isomerize into the allenylium cation (Scheme 59). A subsequent trapping of this intermediate by an arene nucleophile gives the allenic product.



Scheme 59: Mechanism for the formation of the allene

2.4.3 Scope of allenes

The scope of CF_3-bearing allenes was then explored (Scheme 60). As mentioned above, our model substrate, propargylic alcohol **225**, with no substituent on phenyl rings A and B, afforded the corresponding allene **235** in 93% yield. Replacing aromatic ring A by a cyclohexyl moiety group still delivered the target product, albeit in a lower yield (**240**, 51%) while requiring a higher reaction temperature (50 °C). The same applied to a biphenyl substituent (**241**). The moderate yields obtained in both cases might be explained by the fact that the absence of a stabilizing π-system (ring A) disfavored the formation of allenylium (**240**), while the biphenyl group made the cationic intermediates more stable and thus less reactive (**241**). On the other hand, the introduction of a *p*-tolyl and *o*-tolyl group was well tolerated (**242** and **243**). The presence of moderately electron-withdrawing groups (Br or F) tended to deactivate the substrate, slowing down the reaction (reaction time increased from 1 h to 3 h). The effect of electron-donating substituents, such as methoxy, was highly dependent on its position. Located on ring B, the reaction provided the allene **248** in a good yield (82%), while, on ring A, the product **249** was obtained in a moderate yield (27%) as the allenic product was rapidly converted into indene, even after 5 min. Attempts to shorten the reaction time and lower the temperature did not improve the yields because the subsequent cyclization into indene proved to be faster than the initial formation of the allene. Lastly, the use of a sterically hindered nucleophile such as 1,4-diisopropylbenzene (**250**-**253**) or nucleophiles incorporating electron-withdrawing groups (**254**-**256**) were also less reactive with respect to the transformation.



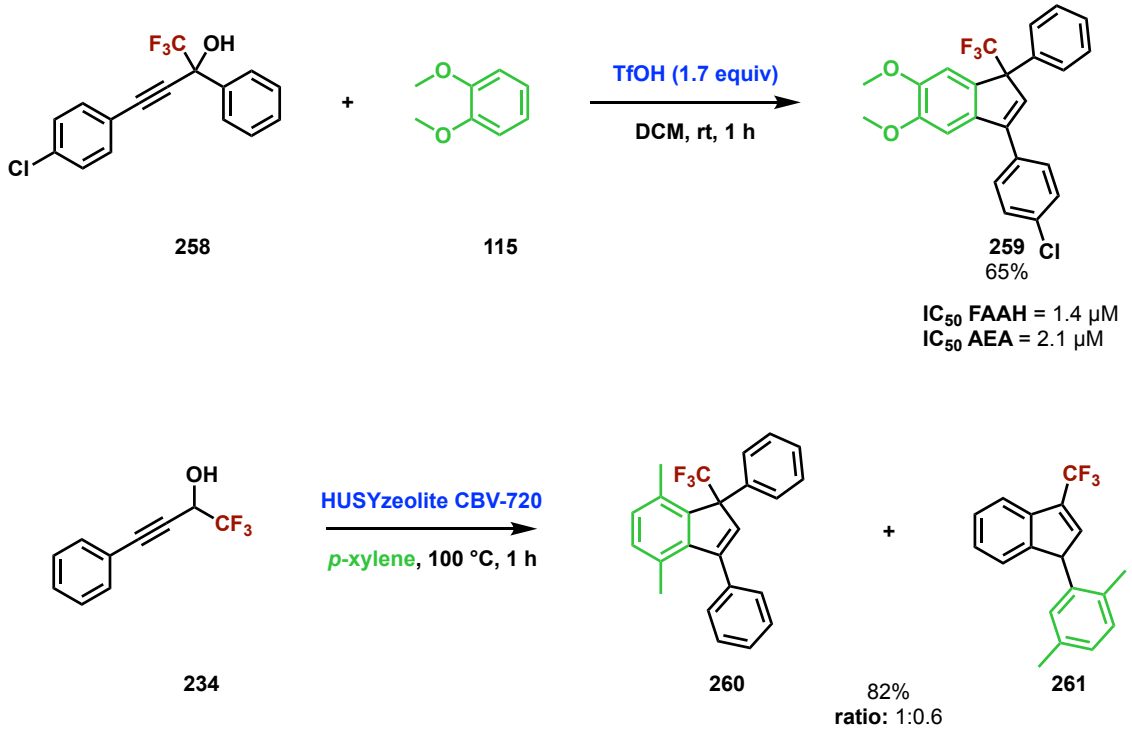
Scheme 60: Scope of CF_3-bearing allenes

[a] Reaction conducted at 50 °C. [b] Reaction for 24 h. [c] Reaction for 3 h. [d] Reaction for 1 h. [e] Reaction for 5 min. [f] Reaction conducted at 80 °C.

2.5. Synthesis of CF_3-bearing indenes

2.5.1 Formation of indenes and mechanistic proposal

CF_3-bearing indenes are not readily available compounds and only a few reports regarding their synthesis have been described in the literature.[105] Yet, CF_3-bearing indenes are interesting scaffolds for drug discovery. Indeed, the group of Vasilyev discovered that indene **259** displayed inhibitory activity towards fatty acid amide hydrolase (FAAH) and the machinery responsible for arachidonyl ethanol-amine (AEA) uptake (Scheme 61).[106] Concerning indene synthesis, Vasilyev's method required super-stoichiometric amounts of triflic acid, which might be a limitation for industrial scale-up. The same group recently reported another method to access CF_3-bearing indenes using, in this case, a heterogeneous catalyst featuring a zeolite.[107] Although the use of zeolites is typically considered as "green chemistry", this reaction displayed a few major disadvantages for industrial scale-up: (1) high temperature (100 °C), (2) the zeolite catalyst must be preactivated at 550 °C for 4 h and (3) there is a lack of selectivity regarding the cyclization of the indene. The authors rationalized the good yields obtained with this method compared to classic Brønsted acid catalysis by the ability of the zeolite to act as a cage for carbocationic intermediates, therefore preventing the formation of oligomers.



Scheme 61: Synthesis of CF_3-bearing indenes

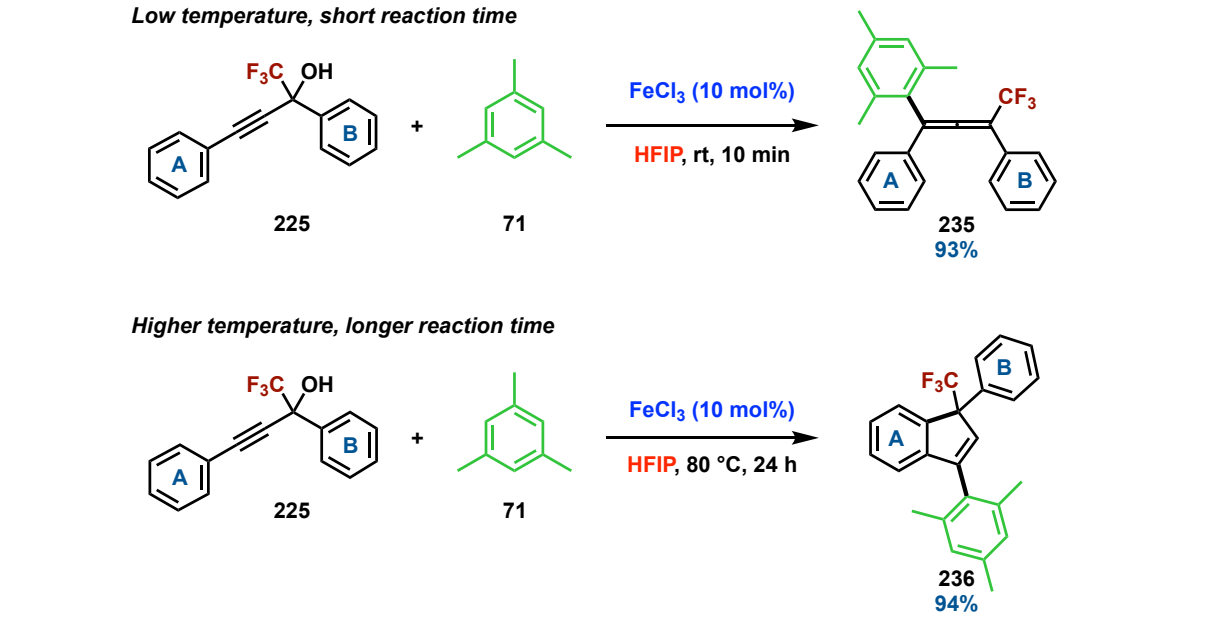
Regarding the standard protocol for the reaction between propargylic alcohol **225** and mesitylene in HFIP employing $FeCl_3$ as a catalyst, we emphasized that conducting the reaction

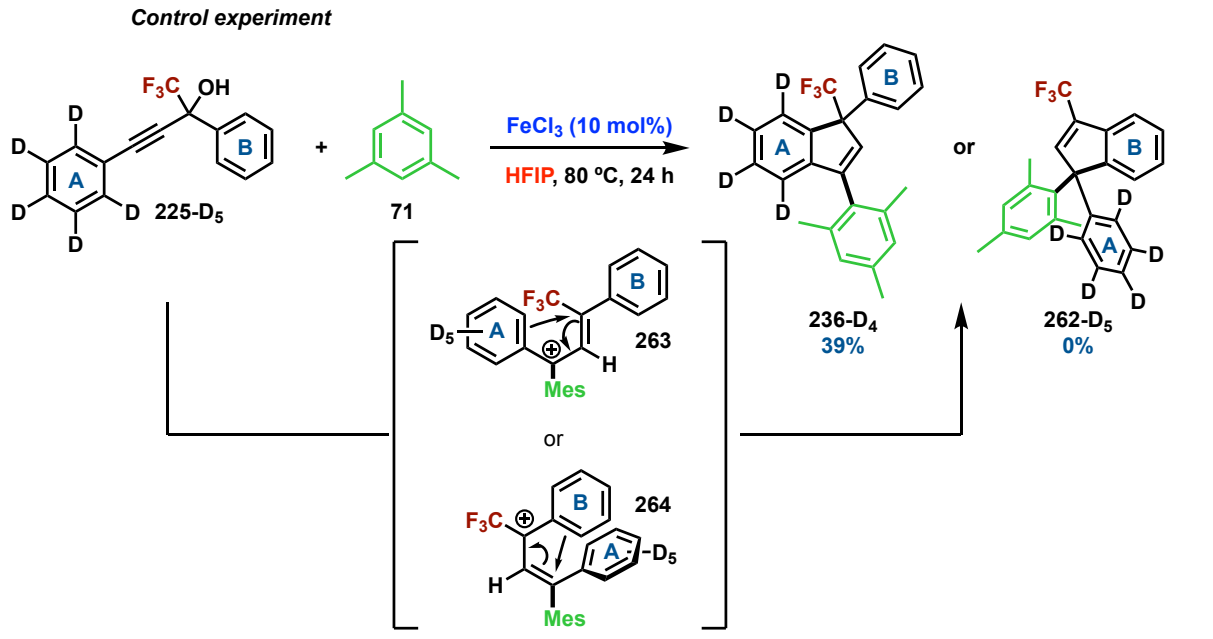
[105] (a) H-J. Tang, Y-F. Zhang, Y-W. Jiang, C. Feng, *Org. Lett.* **2018**, *20*, 5190; (b) A. N. Kazakova, R. O. Iakovenko, I. A. Boyarskaya, A. Y. Ivanov, M. S. Avdontceva, A. A. Zolotarev, T. L. Panikorovsky, G. L. Starova, V. G. Nenajdenko, A. V. Vasilyev, *Org. Chem. Front.* **2017**, *4*, 255.

[106] R. O. Iakovenko, A. Chicca, D. Nieri, I. Reynoso-Moreno, J. Gertsch, M. Krasavin, A. V. Vasilyev, *Tetrahedron* **2019**, *5*, 624.

[107] S. K. Nursahedova, A. V. Zerov, I. A. Boyarskaya, E. V. Grinenko, V. G. Nenajdenko, A. V. Vasilyev, *Org. Biomol. Chem.* **2019**, *17*, 1215.

at rt for a short reaction time led to the allene product. However, interestingly, a prolonged heating at a higher temperature (80 °C) enabled the formation of another product, an indene derivative (Scheme 62). To determine whether phenyl ring A or ring B underwent the cyclization, we prepared deuterated substrate **225**-D_5, which was subjected to the standard reaction conditions. Analysis of the resulting ^1H and ^2H NMR spectra as well as the HRMS of the resulting product was consistent with the formation of **236**-D_4 indene, thereby implying that phenyl ring A was involved in the cyclization. Of note, subjecting the isolated allene product to the standard reaction conditions also led to the indene, confirming its role as intermediate in the formation of the indene.

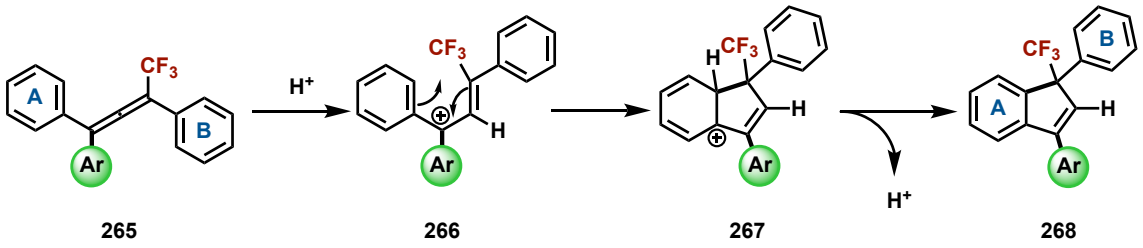




Scheme 62: Allene vs indene

Based on these results, we proposed the following mechanism (Scheme 63): after formation of the allenic product, the electron-rich π-system of the allene can be protonated to generate

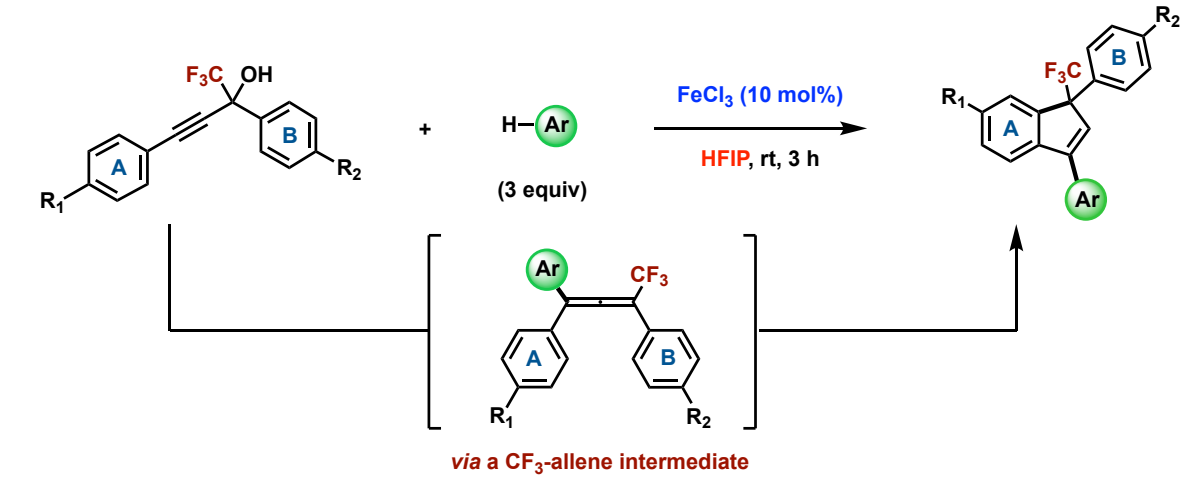
an allyl cation. A Nazarov-type electrocyclization would then occur to form **267** before a subsequent rearomatization, finally furnishing the indene.

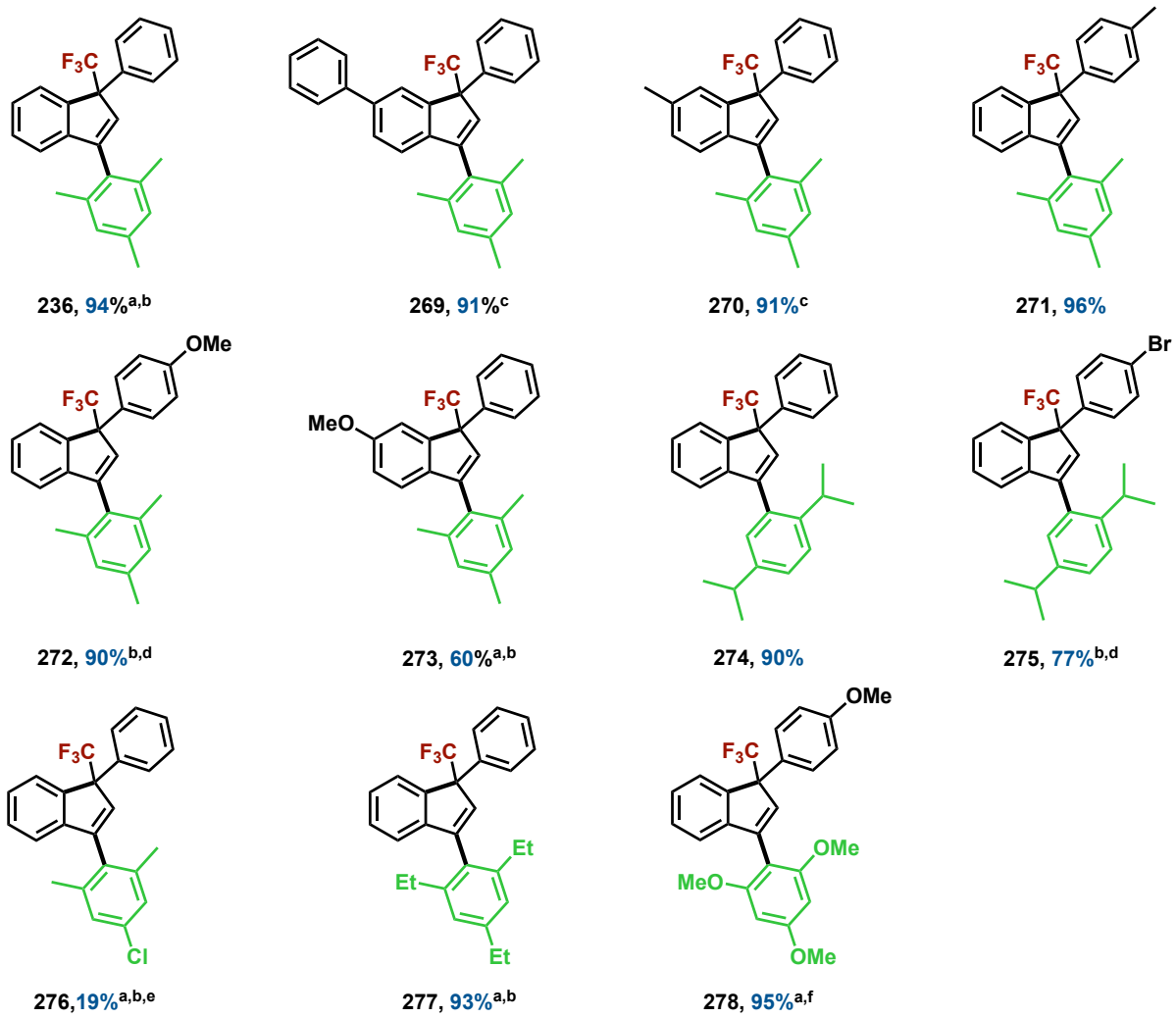


Scheme 63: Mechanistic proposal for the formation of the indene

2.5.2 Scope of indenes

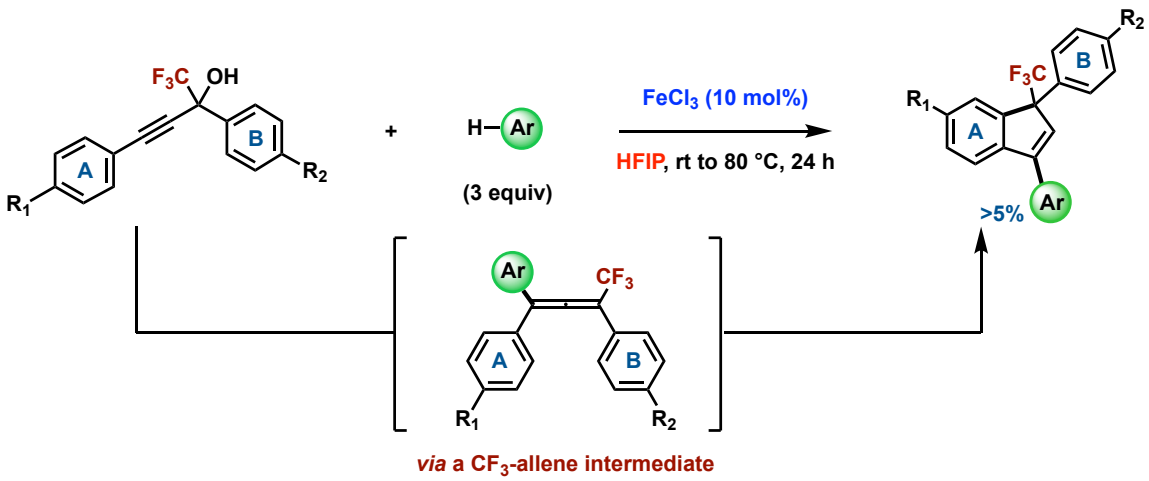
The scope of indenes was then investigated (Scheme 64). Propargylic alcohols with no substituent at the phenyl ring A and ring B furnished the corresponding indenes in high yields (up to 94%) when mesitylene, 1,4-diisopropylbenzene and even bulkier 1,3,5-triethylbenzene were used as nucleophiles. In addition, the reaction was compatible with the presence of electron-donating groups (Ph, Me and MeO) at the *para*-position of phenyl ring A to furnish the target products in good to high yields (up to 91%). In the same vein, introducing electron-donating and -withdrawing groups at the *para*-position of phenyl ring B did not prevent the reaction, providing compounds **262** and **275** in 90% and 77% yields, respectively. Of note, increasing the temperature to 120 °C was necessary with the more nucleophilic 1,3,5-trimethoxybenzene **278**, giving the indene in high yield (95%). Indeed, as mentioned in the introduction for the reactivity of cyclopropanes, this nucleophile can be easily protonated under the reaction conditions to form an off-cycle species, which might slow down the reaction. Unfortunately, chloro-bearing nucleophiles such as **276** were less efficient in this transformation. In general, our efforts to prepare indenes from propargylic alcohols using weaker arene nucleophiles were ineffective (allenes **254**), due both to the reduced ability of the nucleophile to capture the propargylic carbocation and the subsequent deactivating effect of the electron-poor arene on the cyclization of the allene intermediate (Scheme 65). Even under harsher reaction conditions, propargylic alcohols bearing a bromide or fluoride functionality on the phenyl ring A or ring B did not give access to the desired indenes, stopping at the allene intermediates (**245**, **246**, **247**, **253** and **256**) previously described in Scheme 10.

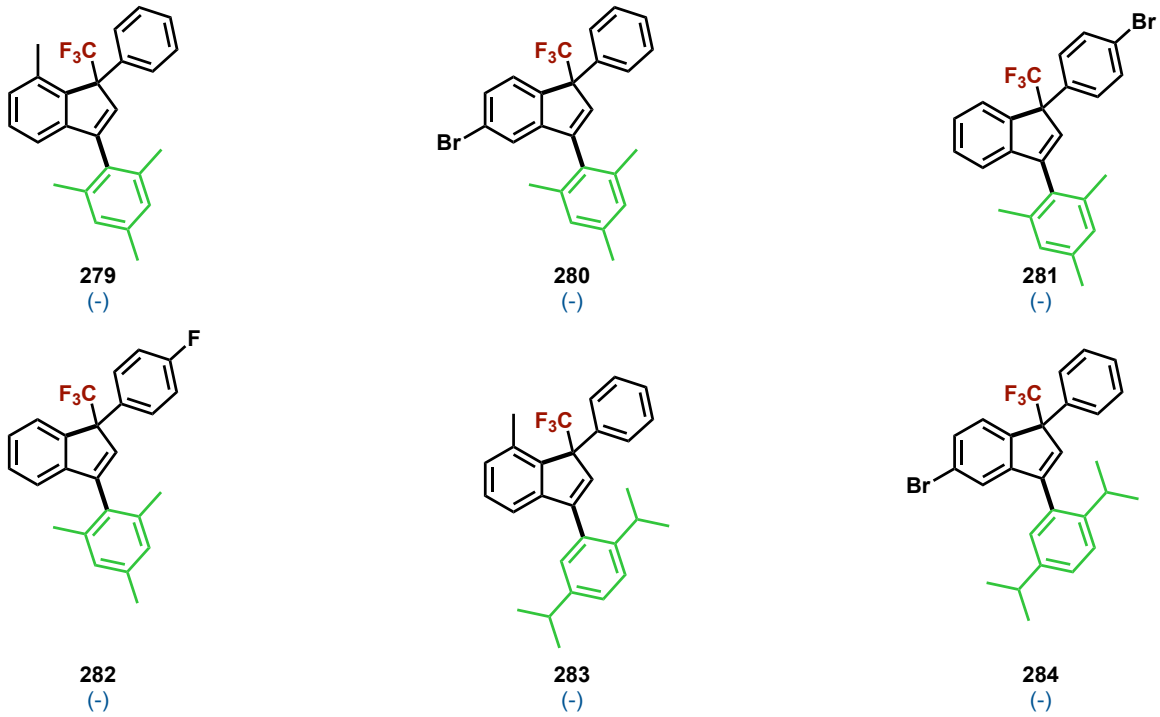




Scheme 64: Scope of CF_3-bearing indenes

[a]Reaction for 24 h. [b] Reaction performed at 80 °C. [c] Reaction performed at 50 °C for 6 h. [d] Reaction for 1 h. [e] the other region-isomer was observed by ^{1}H NMR but not purified. [f] Reaction performed at 120 °C.



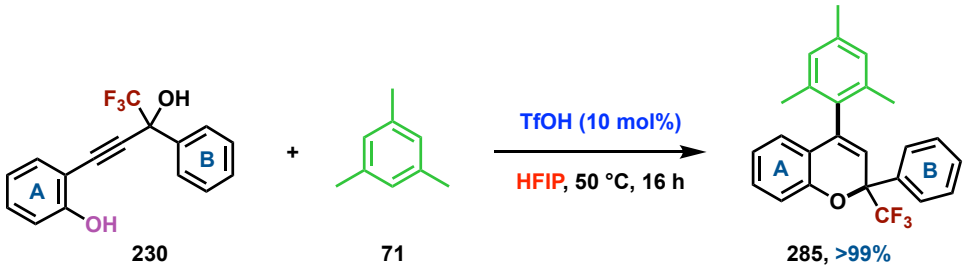


Scheme 65: Unsuccessful propargylic alcohols for the formation of indenes

2.6. Synthesis of CF_3-bearing chromenes

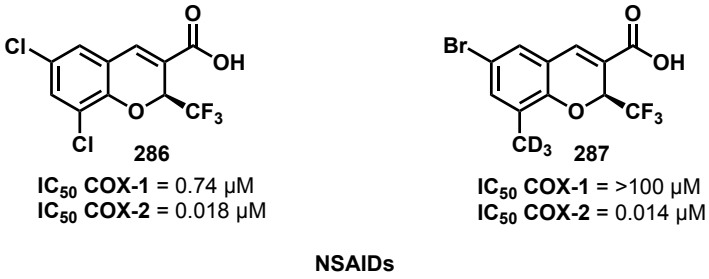
2.6.1. Formation of chromenes and mechanistic proposal

Inspired by the results obtained with the formation of indenes, we hypothesized that propargylic alcohols bearing an additional nucleophile at the *ortho*-position of phenyl ring could undergo an intramolecular cyclization to afford a bicyclic derivative (Scheme 66). Indeed, propargylic alcohols substituted with an *o*-hydroxyl group on ring A led to the formation of chromene **285**. In the studied case, better results were obtained with TfOH as a catalyst rather than with $FeCl_3$, affording compound **285** in nearly quantitative yield.



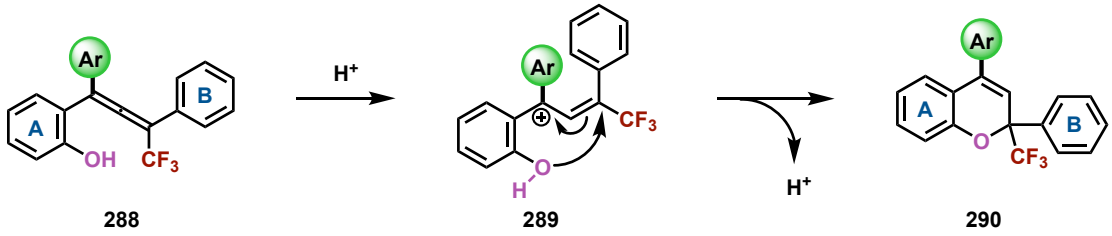
Scheme 66: Activation of tertiary propargylic alcohols bearing an o-hydroxyl group at ring A

Chromenes are an attractive class of molecules as they exhibit important biological activities. In particular, CF_3-bearing chromenes have been used for the development of non-steroidal anti-inflammatory agents (NSAIDs) (Scheme 67).[108] Indeed, they have been found to be efficient for the specific inhibition of COX-2, one of the two isoforms of cyclooxygenase that is an enzyme expressed in response to inflammatory stimuli. Inhibition of one of those isoforms of the cyclooxygenase is sufficient to generate an efficient anti-inflammatory response. Nevertheless, the gastrointestinal tissue needs a basal level of expression of COX-1 for its homeostasis and platelet clotting ability. Thus, a specific inhibition of COX-2 is required to avoid detrimental effects on the gastrointestinal system.



Scheme 67: CF_3-bearing chromenes as anti-inflammatory agents

Concerning the mechanism, as for the synthesis of the indene, once the allene intermediate is formed and then protonated (Scheme 68), a S_N2' nucleophilic addition of the hydroxyl group takes place to lead to the chromene.

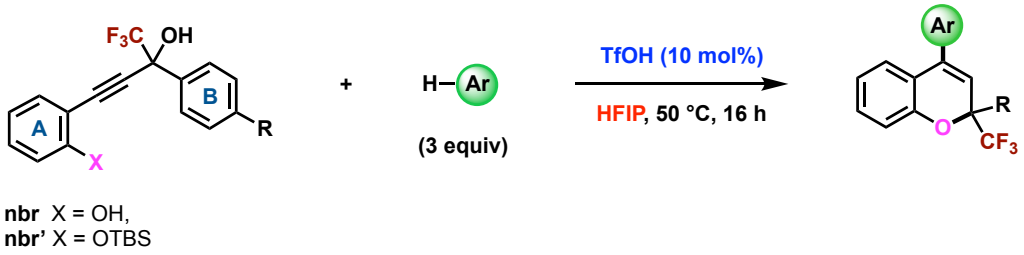


Scheme 68: Mechanistic proposal for the formation of the chromene

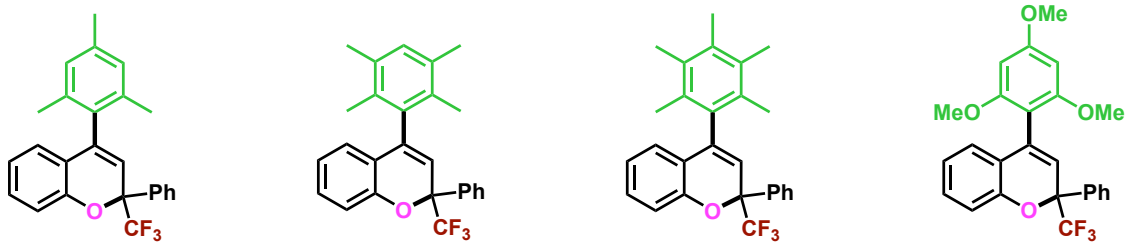
[108] a) J. L. Wang, J. Carter, J. R. Kiefer, R. G. Kurumbail, J. L. Pawlitz, D. Brown, S. J. Hartmann, M. J. Graneto, K. Seibert, J. J. Talley, *Bioorg. Med. Chem. Lett*. **2010**, 20, 7155; (b) L. Xing, B. C. Hamper, T. R. Fletcher, J. M. Wendling, J. Carter, J. K. Gierse, S. Liao, *Bioorg. Med. Chem. Lett*. **2011**, 21, 993; (c) Y. Zhang, M. D. Tortorella, Y. Wang, J. Liu, Z. Tu, X. Liu, Y. Bai, D. Wen, X. Lu, Y. Lu, J. J. Talley, *ACS Med. Chem. Lett*. **2014**, 5, 1162; (d) K. R. Reddy, P. S. Rao, G. J. Dev, Y. Poornachandra, C. G. Kumar, P. S. Rao, B. Narsaiah, *Bioorg. Med. Chem. Lett.* **2014**, 24, 1661; (e) Y. Zhang, Y. Wang, C. He, X. Liu, Y. Lu, T. Chen, Q. Pan, J. Xiong, M. She, Z. Tu, X. Qin, M. Li, M. D. Tortorella, J. J. Talley, *J. Med. Chem*. **2017**, 60, 4135.

2.6.2. Scope of CF3-bearing chromenes

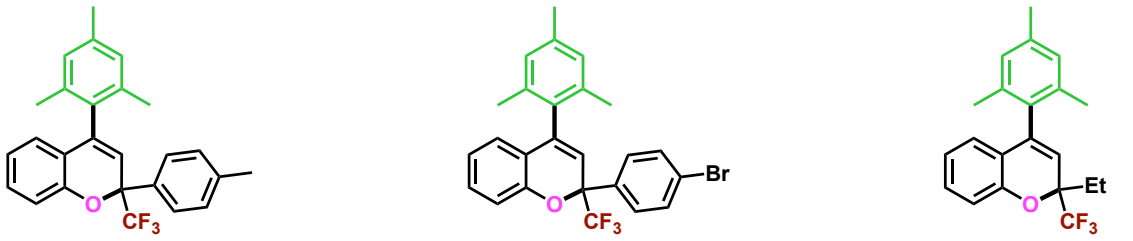
With respect to the scope, bulky nucleophiles such as durene and pentamethylbenzene are well-tolerated under the reaction conditions (Scheme 69). As for the case with indenes, the use of 1,3,5-trimethoxybenzene slowed down the reaction but still afforded the corresponding chromene **293** (43%). Additionally, the reaction proved to be compatible with the presence of electron-donating and -withdrawing groups at the *para*-position of the phenyl ring B. Importantly, the presence of an aromatic ring at the α-position of the CF_3 group was not necessary as substrate **296** incorporating an alkyl group (ethyl) underwent the cyclization to give the target product in 77% yield. Propargylic alcohol with a *o*-hydroxyl protected with a *tert*-butyl-dimethylsilyl group showed a similar reactivity as its non-protected analog, which might be explained by the highly acidic reaction conditions that could favor the *in situ* deprotection of the phenol.



nbr X = OH,
nbr' X = OTBS



285, >99% **291**, 86% **292**, >99% **293**, 43%



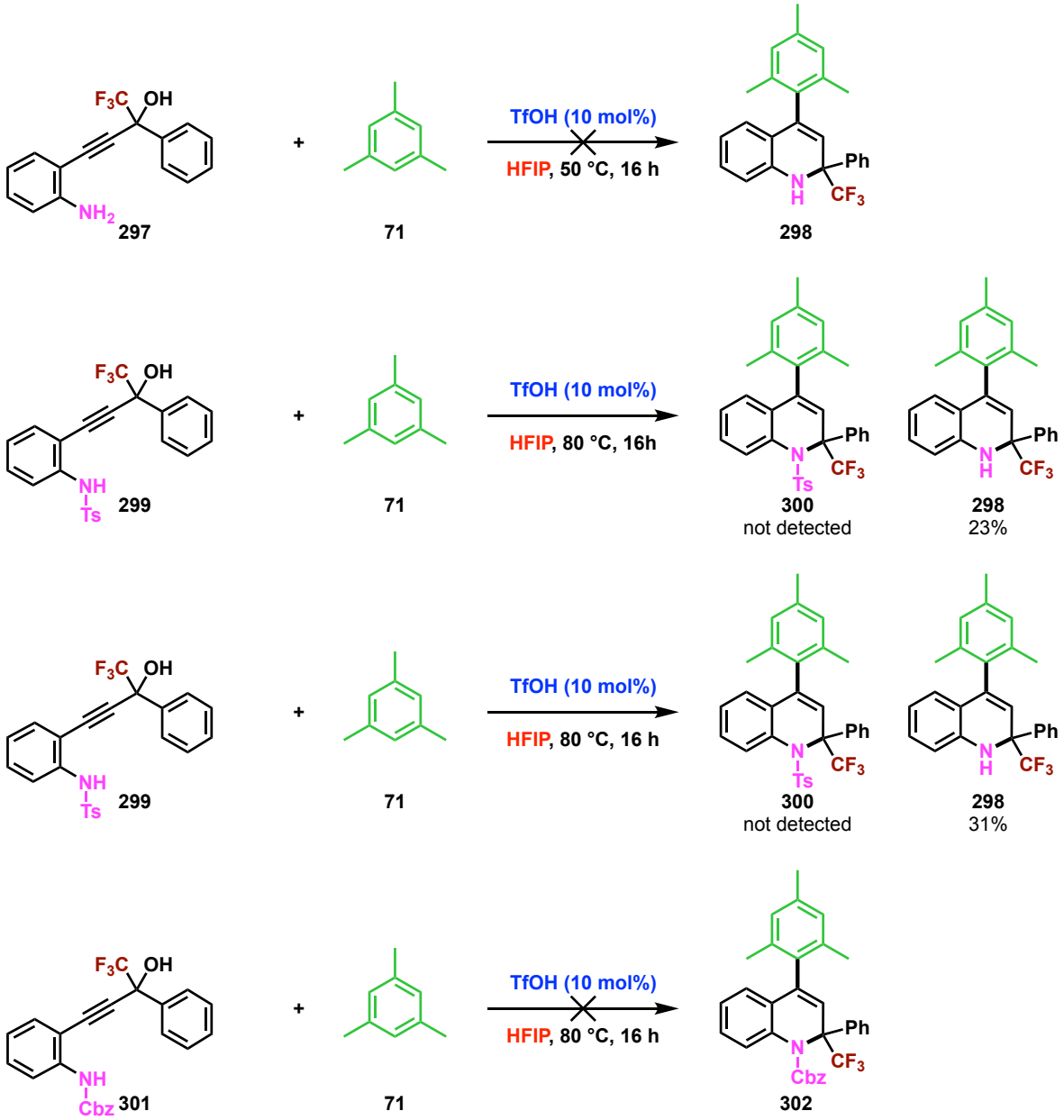
294, 70%
294', 71%[a] **295**, 75% **296**, 77%

Scheme 69: Scope of CF_3-bearing chromenes

[a] Reaction performed on 1 mmol scale.

On the other hand, further attempts with propargylic alcohols bearing amine functionalities failed to give efficiently the desired cyclic products (Scheme 70). Precursor **297** substituted with an *o*-NH_2 did not provide the corresponding cyclic product under the standard conditions used for the synthesis of chromenes. ^{1}H NMR and TLC showed a rapid degradation of the starting material. An *N*-tosyl-protected substrate did not furnish either product at rt.

Nevertheless, 23% of deprotected cyclic product was isolated by increasing the temperature to 80 °C. In order to improve the reactivity, another protecting group (carboxybenzyl) was tested at 80 °C but neither the protected nor unprotected product was detected. This reaction will require more optimizations to obtain the desired reactivity.

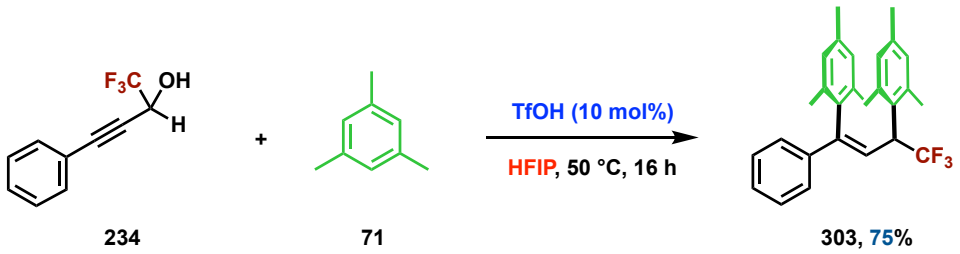


Scheme 70: Attempts towards the cyclization o-amine substituted tertiary propargylic alcohols

2.7. Synthesis of CF_3-bearing alkenes

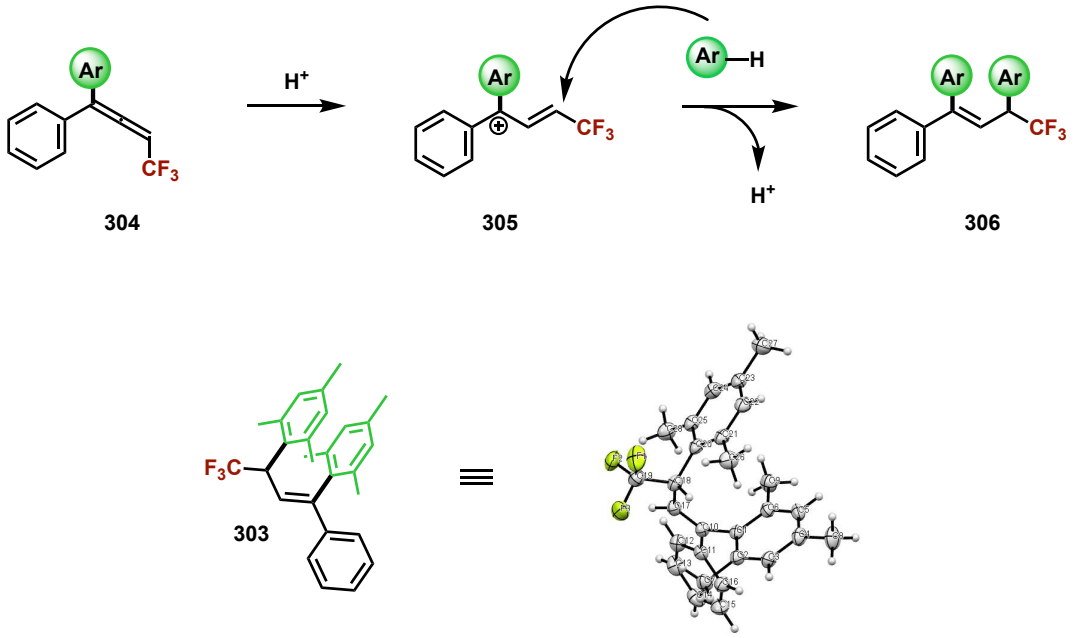
2.7.1. Formation of alkenes and mechanistic proposal

Lastly, we investigated the reactivity of secondary propargylic alcohols. Due to their lower steric hindrance, we observed a different reactivity than tertiary propargylic alcohols as they underwent a double addition of aromatic nucleophiles to give access to bis-arylated alkenes under identical reaction conditions (Scheme 71).



Scheme 71: Formation of CF_3-bearing alkenes

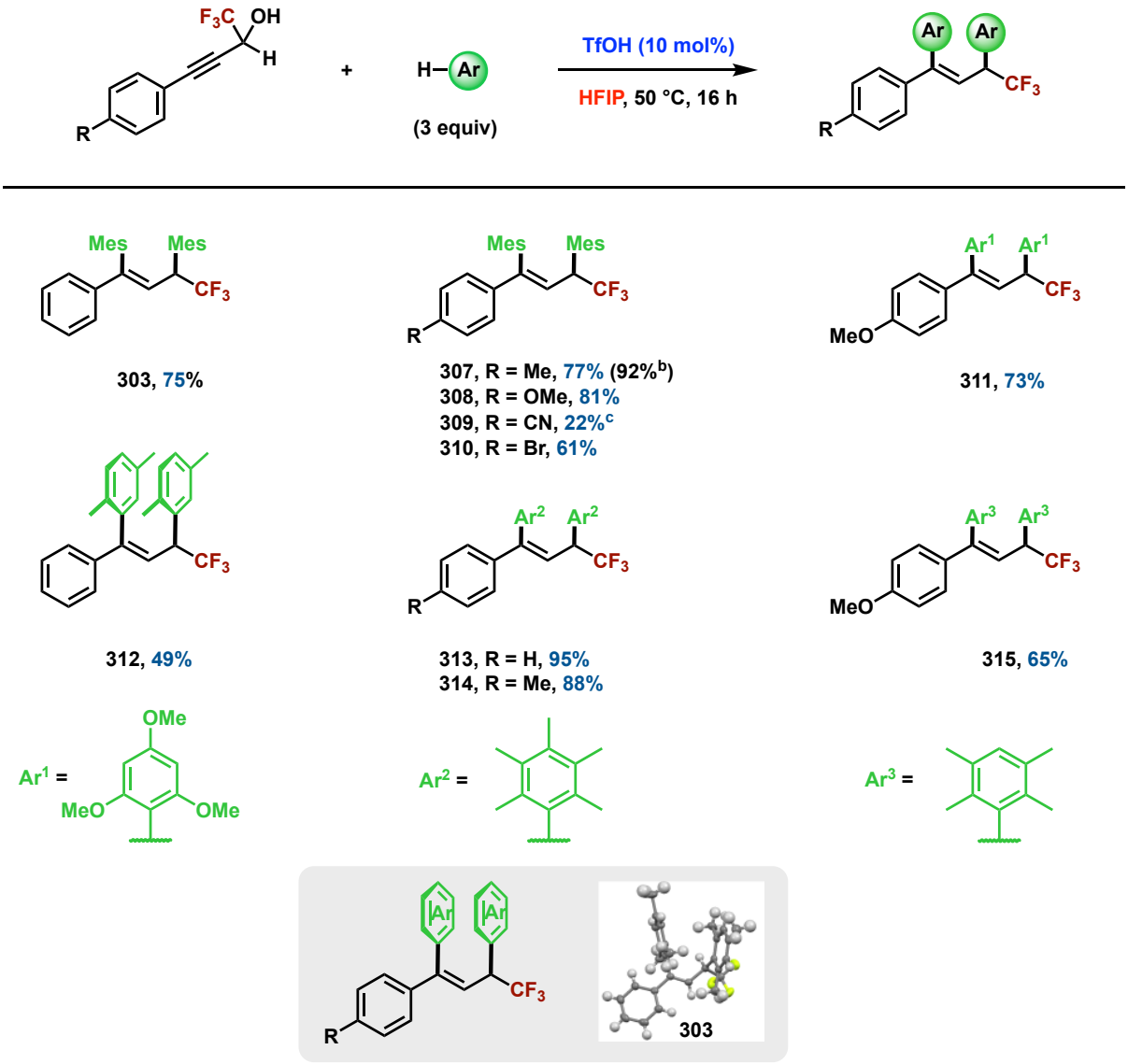
Regarding the mechanism, we assumed that, following the formation of the allene and its subsequent protonation, a second addition of nucleophile occurred to provide the corresponding alkene (Scheme 72). The structure as well as the *Z* geometry were probed by X-ray crystallography. We noticed that the preferred conformation was the one in which the two mesityl groups were aligned. Interestingly, in solution it was possible to distinguish two different rotamers in the reaction product by ^{1}H NMR when *p*-xylene was used as a nucleophile.



Scheme 72: Mechanistic proposal for the formation of the alkene

2.7.2. Scope of Alkenes.

We first explored the influence of the *para*-substitution on the phenyl ring (Scheme 73). The reaction could be achieved in good yields in the case of electron-donating groups (Me and MeO, 77% and 81%, respectively). However, in the case of electron-withdrawing groups (Br and CN), a significant decrease of the reactivity was observed. A plausible explanation might be the destabilization of the carbocation intermediate after the protonation. Additionally, due to its Lewis base character, the cyano group could also buffer the Brønsted acid catalyst and prevent the reaction. The electron-rich 1,3,5-trimethoxybenzene (**311**) also afforded the desired alkene in 73% yield. Other methyl-substituted arenes nucleophiles such as *p*-xylene (**312**), pentamethylbenzene (**313-314**) and durene (**315**) were also tested and led to the corresponding alkenes in good to high yields (up to 95%).



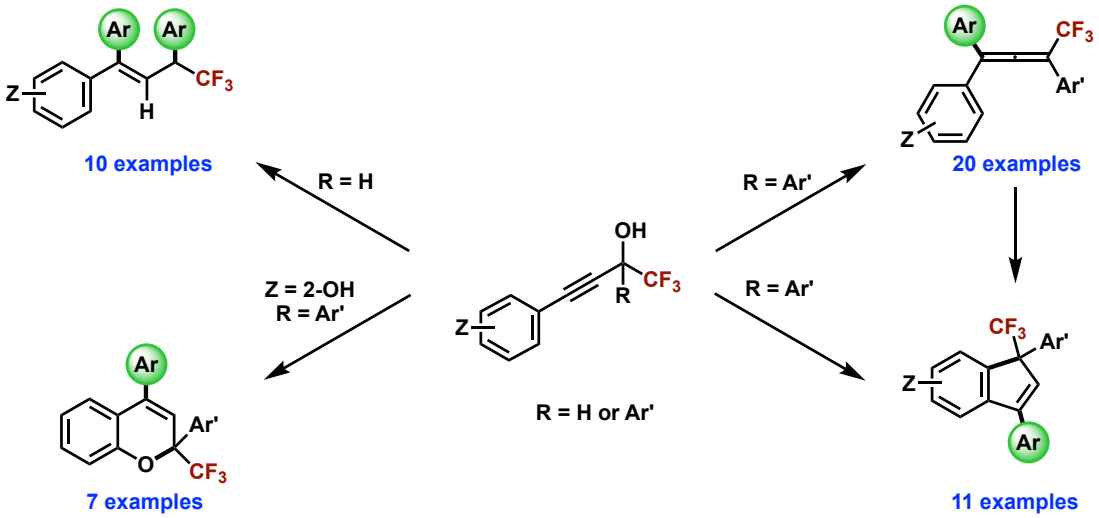
Scheme 73: Scope of CF_3-bearing alkenes

[a]Isolated yield after column chromatography. [b]Performed on 1 mmol scale. [c]Reaction heated at 100 °C for 88 h. Mes = mesityl.

2.8. Conclusion

In summary, we have described a method for straightforward access to trifluoromethylated compounds such as allenes and indenes from tertiary propargylic alcohols, chromenes from *o*-hydroxyl substituted tertiary propargylic alcohols and alkenes from secondary propargylic alcohols (Scheme 74). Mechanistic experiments suggest that the role of $FeCl_3$ is to activate HFIP upon coordination to generate a Brønsted acid, which would be the true catalytic species. Moreover, it had been determined that the formation of indenes resulted from an intramolecular rearrangement of allenes. Regarding the reactivity of *o*-hydroxyl substituted tertiary propargylic alcohols, an intramolecular cyclization was observed, leading to the corresponding chromenes. Attempts to use *o*-amine and *o*-tosylamine as nucleophile were unfortunately not successful to obtain the nitrogen-bearing analog. The use of other *o*-substituted tertiary propargylic alcohols such *o*-sulfide-bearing substrate could be an interesting alternative to extend the scope of the transformation. Finally, we can change the

course of the transformation by employing secondary propargylic alcohols to furnish alkene derivatives via a bis-arylation process.



Scheme 74: Summary of the reactivity of CF_3-bearing propargylic alcohols

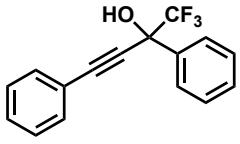
2.9. Experimental Section

2.9.1 General information

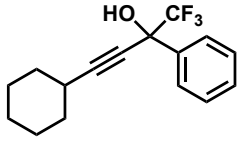
All Friedel-Crafts reactions were performed in 10 mL glass pressure tubes under an atmosphere of air. Elevated temperatures were achieved by way of a stirrer-hotplate, metal heating block and thermocouple. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 µm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel 60 F254 (Merck), cut to size. Visualization was accomplished with UV light. ^{1}H NMR spectra were recorded on a Bruker UltraShield Plus 400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard (residual $CHCl_3$ at 7.26 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker UltraShield Plus 400 (100 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F NMR spectra were recorded on a Bruker UltraShield Plus 400 (376.5 MHz) spectrometer at ambient temperature and are reported in ppm using trifluoroacetic acid as external standard (peak at –76.55 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, qd = quartet of doublets, dt = doublet of triplets, dm = doublet of multiplets, td = triplet of doublets, quintd = quintet of doublets), coupling constants (in Hz) and integration. In cases where compounds were isolated as mixtures of regioisomers, signals corresponding to protons of the major regioisomer were integrated as integer values matching the number of protons in the molecule. Non-integer integration values correspond to signals of protons of minor regioisomers or to overlapping signals of regioisomers. GC/MS analysis was conducted on a GC System 7820A (G4320) connected to a MSD block 5977E (G7036A) using Agilent High Resolution Gas Chromatography Column HP-5MS UI, 30 m×0.250 mm×0.25 µm. High resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and CI), MicroTOF-Q Bruker (ESI), and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer). **Materials:** All commercial materials were purchased from Sigma-Aldrich, Alfa Aesar and FluoroChem, and were used as received, without further purification.

2.9.2. Preparation of tertiary propargylic alcohols

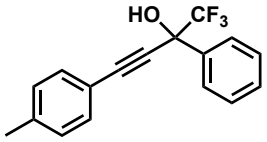
General procedure A for tertiary propargylic alcohols synthesis: Trifluoromethyl phenyl ketone (5.0-10 mmol, 1.0 equiv) and phenyl acetylene (1.5 equiv) were diluted in 10-15 mL DMSO. CuI (0.10 equiv) and K_2CO_3 (0.20 equiv) were added and the reaction mixture was heated at 50-70 ^{o}C for 24 h. The reaction mixture was then treated with brine, extracted with CH_2Cl_2, dried with anhydrous sodium sulfate and concentrated at reduced pressure. The product was then purified by silica gel column chromatography.



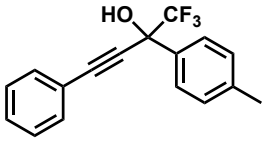
1,1,1-Trifluoro-2,4-diphenylbut-3-yn-2-ol **225** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[109] Isolated 2.55 g, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86–7.79 (m, 2H), 7.57–7.52 (m, 2H), 7.48–7.42 (m, 3H), 7.42–7.32 (m, 3H), 3.10 (s, 1H).



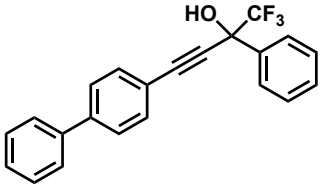
4-Cyclohexyl-1,1,1-trifluoro-2-phenylbut-3yn-2-ol **316** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[110] Isolated 1.32 g, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.82-7.68 (m, 2H), 7.43-7.39 (m, 3H), 2.92 (s, 1H), 2.54 (sept. *J* = 4 Hz, 1H), 1.90-1.29 (m, 10H).



1,1,1-Trifluoro-2-phenyl-4-(p-toluyl)but-3-yn-2-ol **317** was prepared according to general procedure A and isolated as a pale yellow oil. Spectral data are in agreement with the literature.[111] Isolated 2.55 g, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86-7.78 (m, 2H), 7.52–7.36 (m, 5H), 7.17 (d, *J* = 7.8 Hz, 2H), 3.08 (s, 1H), 2.38 (s, 3H).



1,1,1-Trifluoro-4-phenyl-2-(p-toluyl)but-3-yn-2-ol **318** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[112] Isolated 0.93 g, 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 8.1 Hz, 2H), 7.48–7.43 (m, 2H), 7.35–7.25 (m, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 2.98 (s, 1H), 2.31 (s, 3H).



4-((1,1'-Biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol **319** was prepared according to general procedure A and isolated as a yellow solid. Isolated 2.01 g, 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.86-7.80 (m, 2H), 7.63-7.57 (m, 6H), 7.48-7.42 (m, 4H), 7.38 (t, *J* = 7.4 Hz, 2H), 3.09 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 142.5, 140.2, 135.4, 132.7, 129.7, 129.1, 128.4, 128.1, 127.4, 127.3, 127.2, 123.5 (q, *J* = 283.9 Hz), 119.9, 88.1, 85.1, 73.5 (q, *J* =

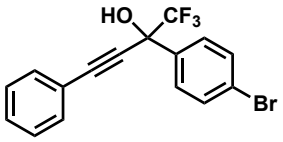
[109] J. B. Geri, M. M. Wade Wolfe, N. K. Szymczak *Angew. Chem. Int. Ed.* **2018**, 57, 1381

[110] Y. Zheng, Y. Tan, K. Harms, M. Marsch,R. Riedel, L. Zhang. *J. Am. Chem. Soc*. **2017**, 139, 4322.

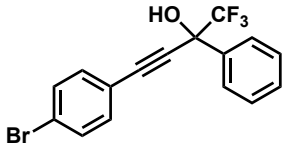
[111] F. M. Irudayanathan, J. Kim, K. H. Song, S. Lee. *Asian J. Org. Chem.* **2016**, 5, 1148

[112] R. Motoki, M. Kanai, M. Shibasaki. *Org. Lett*. **2007**, 9, 2997

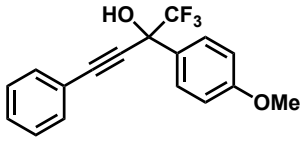
32.3 Hz), ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH - ext. st.): δ (ppm) –80.9 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M+H–H_2O]^+$: Calcd for $C_{22}H_{15}F_3O$ 335.1042; Found 335.1054 (3.5 ppm).



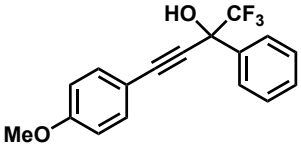
4-(4-Bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol **320** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[13] Isolated 2.70 g, 90% yield. R_f = 0.43 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.6 Hz, 2H), 7.58-7.50 (m, 4H), 7.44-7.35 (m, 3H), 3.26 (s, 1H).



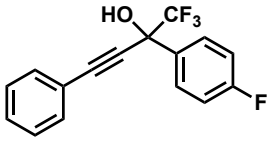
4-(4-Bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol **321** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[13] Isolated 1.56 g, 52% yield. R_f = 0.44 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75-7.69 (m, 2H), 7.46-7.41 (m, 2H), 7.39-7.34 (m, 3H), 7.34-7.28 (m, 2H), 3.09 (s, 1H).



1,1,1-Trifluoro-2-(4-methoxyphenyl)-4-phenylbut-3-yn-2-ol **322** was prepared according to general procedure A and isolated as pale yellow solid. Spectral data are in agreement with the literature.[113] Isolated 1.92 g, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, *J* = 8.8 Hz, 2H), 7.57-7.50 (m, 2H), 7.43–7.32 (m, 3H), 6.96 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.10 (s, 1H).



1,1,1-Trifluoro-2-(4-methoxy-phenyl)-4-phenylbut-3-yn-2-ol **323** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature. [15] Isolated 2.73 g, 91% yield. R_f = 0.36 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (dt, *J* = 8.8 Hz, 3.0 Hz, 2H), 7.56-7.51 (m, 2H), 7.45-7.33 (m, 3H), 6.93-6.10 (m, 2H), 3.84 (s, 3H), 3.10 (s, 1H).



1,1,1-Trifluoro-2-(4-fluorophenyl)-4-phenylbut-3-yn-2-ol **324** was prepared according to general procedure A and isolated as a yellow oil. Spectral data are in agreement with the literature.[13] Isolated 2.85 g, 95% yield. R_f = 0.40 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400

[113] (a) T. Kitazume, T. Sato, *J. Fluorine Chem*. **1985**, 30, 189. (b) L. Xiao, et al. *Tetrahedron: Asymmetry* **1997**, *8*, 3597.

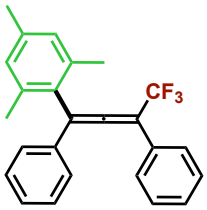
MHz, $CDCl_3$): δ (ppm) 7.83-7.76 (m, 2H), 7.56-7.50 (m, 2H), 7.45-7.34 (m, 3H), 7.16-7.08 (m, 2H), 3.29 (s, 1H).

2.9.3. Preparation of allenes

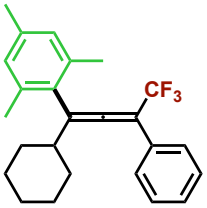
General procedure B: To a 10 mL reaction tube was added the catalyst (10 mol%), HFIP (0.50 M relative to propargylic alcohol), propargylic alcohol (0.17-0.40 mmol, 1.0 equiv), followed by the arene nucleophile (5.0 equiv). The mixture was allowed to stir at 25 °C until judged complete by TLC (9:1 Petroleum ether:EtOAc), typically after 10 min. The reactions typically turn an opaque black. The crude reaction mixture was directly transferred for silica gel chromatography.

General procedure C: To a 10 mL reaction tube was added the catalyst (10 mol%), HFIP (0.5-1.0 M relative to propargylic alcohol), and propargylic alcohol (0.17-0.40 mmol, 1.0 equiv), followed by the arene nucleophile (5.0 equiv). The reactions typically turn an opaque black. After completion of the reaction as judged by TLC, the crude reaction mixture was directly transferred for silica gel chromatography.

Characterization data for allenes

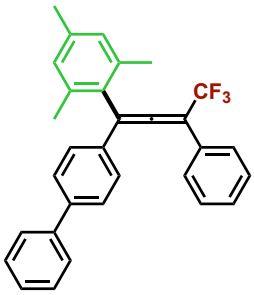


1-Mesityl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **231** was prepared according to general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (100 mg, 0.363 mmol) and mesitylene (253 µL, 1.82 mmol, 5.0 equiv) with 5.9 mg (0.036 mmol) of $FeCl_3$ in 0.73 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 128 mg (93% yield) of white solid. R_f = 0.83 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 7.5 Hz, 2H), 7.43–7.12 (m, 8H), 6.94 (s, 2H), 2.32 (s, 3H), 2.17 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 205.1 (q, *J* = 3.5 Hz), 138.1, 137.1, 133.3, 130.2, 129.9, 129.2, 128.9, 128.7, 128.6, 128.5, 127.6, 126.7, 123.7 (q, *J* = 275.1 Hz), 114.1, 104.0 (q, *J* = 34.3 Hz), 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH - ext. st.): δ (ppm) –62.5 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{21}F_3$ 378.1590; Found 378.1596 (1.5 ppm).

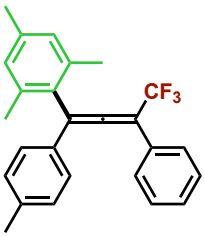


1-Cyclohexyl-1-mesityl-3-phenyl-4,4,4-trifluoro-1,2-butadiene **240** was prepared according to general procedure B from 4-cyclohexyl-1,1,1-trifluoro-2-phenylbut-3yn-2-ol (49 mg, 0.17 mmol) and mesitylene (70 µL, 0.50 mmol, 3.0 equiv) with 2.7 mg (0.017 mmol) of $FeCl_3$, in 0.33 mL of HFIP. The reaction mixture was stirred at 50 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 33 mg (51% yield) of the product. ^{1}H NMR

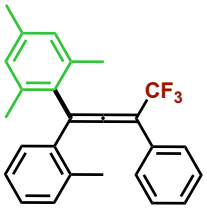
(400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.89 (s, 2H), 2.41-2.15 (m, 10H), 2.03-1.91 (m, 2H), 1.87-1.75 (m, 2H), 1.75-1.66 (m, 1H), 1.43-1.18 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.5 (q, *J* = 4.0 Hz), 137.2, 131.9, 130.9, 128.7, 128.0, 127.32, 127.31, 124.1 (q, *J* = 272.7 Hz), 118.1, 102.2 (q, *J* = 33.8 Hz), 43.4, 32.1, 31.9, 26.7, 26.7, 26.2, 21.1. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –58.1 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{27}F_3$ 384.2059; Found 384.2059 (–0.1 ppm).



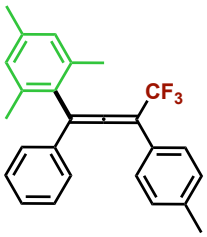
1-Mesityl-1-(1,1'-biphenyl-4-yl)-4,4,4-trifluoro-3-phenyl-1,2-butadiene **241** was prepared according to general procedure B from 4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (59 mg, 0.17 mmol) and mesitylene (71 µL, 0.51 mmol, 3.0 equiv) with 2.7 mg (0.017 mmol) of $FeCl_3$, in 0.34 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 31 mg (40% yield) of the product with 95% purity (the rest is the corresponding indene that started to form quickly). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67-7.56 (m, 4H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.43-7.30 (m, 6H), 6.99 (s, 2H), 2.36 (s, 3H), 2.23 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 205.3 (q, *J* = 3.9 Hz), 141.5, 140.6, 138.1, 137.2, 132.2, 130.2, 129.9, 129.0, 128.9, 128.8, 128.6, 127.9, 127.7, 127.7, 127.2, 127.1, 123.7 (q, *J* = 273.3 Hz), 113.9, 104.1 (q, *J* = 34.1 Hz), 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –58.1 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{31}H_{25}F_3$ 454.1903; Found 454.1903 (0.1 ppm).



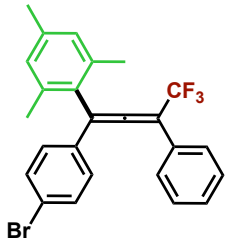
1-Mesityl-4,4,4-trifluoro-1-(p-toluyl)-3-phenyl-1,2-butadiene **242** was prepared according to general procedure B from 1,1,1-trifluoro-2-phenyl-4-(*p*-tolulyl)but-3-yn-2-ol (85 mg, 0.29 mmol) and mesitylene (117 µL, 0.84 mmol, 5.0 equiv) with 4.6 mg (0.028 mmol) of $FeCl_3$, in 0.57 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 84 mg (74% yield) of the product. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 7.6 Hz, 2H), 7.50-7.31 (m, 3H), 7.33-7.22 (m, 4H), 7.07 (s, 2H), 2.46 (s, 3H), 2.44 (s, 3H), 2.32 (6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 205.0 (q, *J* = 4.0 Hz), 138.7, 138.0, 137.1, 130.4, 130.3, 130.0, 128.9, 128.7, 128.5, 127.6, 127.1, 126.1, 123.8 (q, *J* = 273.5 Hz), 114.1, 103.9 (q, *J* = 34.2 Hz), 21.4, 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –59.2 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3$ 392.1746; Found 392.1750 (1.0 ppm).



1-Mesityl-3-phenyl-3-(2-toluyl)-4,4,4-trifluoro-1,2-butadiene **243** was prepared according to general procedure B from 1,1,1-trifluoro-4-phenyl-2-(*o*-tolulyl)but-3-yn-2-ol (91 mg, 0.31 mmol) and mesitylene (188 µL, 1.57 mmol, 5.0 equiv) with 5.1 mg (0.031 mmol) of $FeCl_3$, in 0.63 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 118 mg (96% yield) of white solid. R_f = 0.87 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 7.6 Hz, 2H), 7.46–7.33 (m, 3H), 7.33–7.23 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.00 (s, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 2.54 (s, 3H), 2.39 (s, 3H), 2.24 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 205.4 (q, *J* = 4.3 Hz), 137.8, 137.6, 136.9, 132.6, 132.3, 131.7, 130.7, 128.9, 128.8, 128.4, 128.3, 128.2, 128.0, 126.5, 123.8 (q, *J* = 274.6 Hz), 112.5, 101.5 (q, *J* = 34.5 Hz), 22.0, 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –58.2 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3$ 392.1746; Found 392.1747 (0.2 ppm).

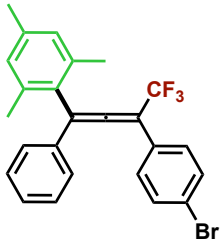


1-Mesityl-1-phenyl-3-toluyl-4,4,4-trifluoro-1,2-butadiene **244** was prepared according to general procedure B from 1,1,1-trifluoro-4-phenyl-2-(*p*-tolulyl)but-3-yn-2-ol (100 mg, 0.346 mmol) and mesitylene (241 µL, 1.73 mmol, 5.0 equiv) with 3.5 mg (0.022 mmol) of $FeCl_3$, in 0.69 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 122 mg (93% yield) of a colorless oil. R_f = 0.93 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (d, *J* = 8.0 Hz, 2H), 7.40–7.32 (m, 3H), 7.32–7.27 (m, 2H), 7.21 (d, *J* = 8.0, 2H), 7.00 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H), 2.23 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 204.8 (q, *J* = 3.8 Hz), 138.5, 138.0, 137.1, 133.4, 129.6, 129.1, 128.7, 128.5, 127.5, 127.1, 127.1, 126.7, 123.8 (q, *J* = 275.2 Hz), 113.9, 103.8 (q, *J* = 34.3 Hz), 21.3, 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –58.3 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3$ 392.1746; Found 392.1744 (–0.6 ppm).

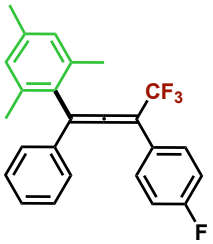


1-(4-Bromophenyl)-1-mesityl-3-phenyl-4,4,4-trifluoro-1,2-butadiene **245** was prepared according to general procedure B from 4-(*p*-bromophenyl)-1,1,1-trifluoro-2-phenyl-but-3-yn-2-ol (86 mg, 0.24 mmol) and mesitylene (146 µL, 1.05 mmol, 5.0 equiv) with 3.4 mg (0.021

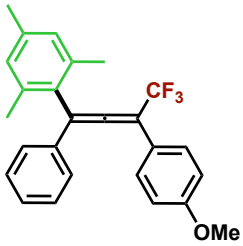
mmol) of $FeCl_3$, in 0.5 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 78 mg (70% yield) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52-7.41 (m, 4H), 7.41-7.29 (m, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.95 (s, 2H), 2.32 (s, 3H), 2.15 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 204.9 (q, *J* = 3.8 Hz), 138.3, 137.0, 132.3, 129.8, 129.3, 128.9, 128.8, 128.7, 128.1, 127.6, 127.6, 123.5 (q, *J* = 273.5 Hz), 122.7, 113.3, 104.3 (q, *J* = 34.3 Hz), 21.1, 20.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.): δ (ppm) –62.5 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{20}{}^{79}BrF_3$ 456.0695; Found 456.0700 (1.1 ppm).



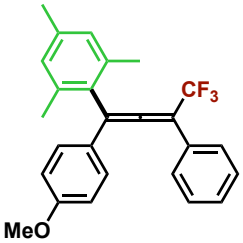
3-(4-Bromophenyl)-1-mesityl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **246** was prepared according to general procedure B from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (100 mg, 0.286 mmol) and mesitylene (199 µL, 1.43 mmol, 5.0 equiv) with 4.3 mg (0.029 mmol) of $FeCl_3$, in 0.57 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 118 mg (90% yield) of a colorless oil. R_f = 0.82 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 8.6 Hz, 2H), 7.38–7.28 (m, 5H), 7.25–7.18 (m, 2H), 6.95 (s, 2H), 2.33 (s, 3H), 2.16 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 205.0 (q, *J* = 3.8 Hz), 138.2, 137.0, 132.9, 132.1, 129.6, 129.3, 129.2, 129.2, 128.8, 127.1, 126.7, 123.5 (q, *J* = 275.0 Hz), 122.7, 114.6, 103.2 (q, *J* = 34.6 Hz), 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.): δ (ppm) –62.5 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{20}{}^{79}BrF_3$ 456.0695; Found 456.0699 (0.9 ppm).



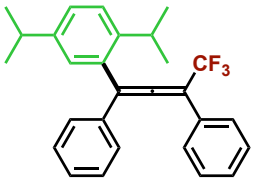
3-(4-Fluorophenyl)-1-mesityl-1-phenyl-4,4,4-trifluoro-1,2-butadiene **247** was prepared according to modified general procedure B from 1,1,1-trifluoro-2-(*p*-fluorophenyl)-4-phenyl-but-3-yn-2-ol (72 mg, 0.21 mmol) and mesitylene (146 µL, 1.05 mmol, 5.0 equiv) with 3.4 mg (0.021 mmol) of $FeCl_3$, in 0.42 mL of HFIP. The reaction mixture was stirred at ambient temperature for 1 h. Purification by flash column chromatography over silica (petroleum ether) gave 50 mg (52% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56-7.48 (m, 2H), 7.44-7.33 (m, 3H), 7.33-7.27 (m, 2H), 7.16-7.07 (m, 2H), 7.02 (s, 2H), 2.39 (s, 3H), 2.23 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 204.8 (q, *J* = 3.6 Hz), 162.9 (d, *J* = 246.9 Hz), 138.2, 137.0, 133.1, 129.7, 129.5 (d, *J* = 8.1 Hz), 129.2, 128.8, 128.7, 126.6, 126.2 (d, *J* = 3.3 Hz), 123.6 (q, *J* = 273.3 Hz), 116.1 (d, *J* = 21.7 Hz), 114.3, 103.1 (q, *J* = 34.6 Hz), 21.3, 20.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.): δ (ppm) –62.8 (s, 3F), –116.0 (m, 1F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{20}F_4$ 396.1496; Found 396.1500 (1.0 ppm).



1-Mesityl-3-(4-methoxyphenyl)-1-phenyl-trifluoro-1,2-butadiene **248** was prepared according to modified general procedure B from 1,1,1-trifluoro-2-(4-metoxyphenyl)-4-phenylbut-3-yn-2-ol ol (71 mg, 0.25 mmol) and mesitylene (102 µL, 0.735 mmol, 3.0 equiv) with 4.0 mg (0.025 mmol) of $FeCl_3$, in 0.98 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether/EtOAc 40:1 to 30:1) gave 79 mg (82% yield) of colorless oil. R_f = 0.81 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.42 (d, *J* = 8.5 Hz, 2H), 7.38–7.21 (m, 5H), 6.96 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.34 (s, 3H), 2.18 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 204.5 (q, *J* = 3.5 Hz), 159.8, 138.0, 137.1, 133.5, 130.1, 129.1, 128.9, 128.7, 128.5, 126.6, 123.8 (q, *J* = 275.0 Hz), 122.2, 114.3, 113.8, 103.6 (q, *J* = 34.5 Hz), 55.4, 21.2, 20.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –59.1 (s, 3F). HRMS (APPI$^+$-Orbitrap): *m/z* $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3O$ 408.1696; Found 408.1708 (2.9 ppm).

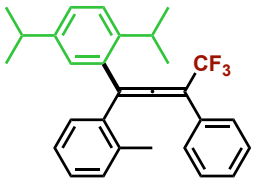


1-Mesityl-4-(4-methoxyphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene **249** was prepared according to modified general procedure B from 1,1,1-trifluoro-4-(4-metoxyphenyl)-2-phenylbut-3-yn-2-ol ol (73 mg, 0.24 mmol) and mesitylene (84 µL, 0.74 mmol, 2.5 equiv) with 3.9 mg (0.024 mmol) of $FeCl_3$, in 0.48 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica gave 26 mg (27% yield) of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 7.6 Hz, 2H), 7.41-7.29 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.33 (s, 3H), 2.19 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 204.8 (q, *J* = 3.9 Hz), 160.0, 137.9, 137.1, 130.5, 130.1, 128.8, 128.7, 128.4, 128.0, 127.6, 127.6, 125.3, 123.7 (q, *J* = 273.3 Hz), 114.6, 113.7, 103.8 (q, *J* = 34.1 Hz), 55.5, 21.2, 20.3. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –59.3 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M+H]^{+\cdot}$ calculated for $C_{26}H_{24}F_3O$ 409.1774; found 409.1768 (–1.5 ppm).

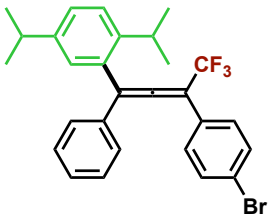


1-(2,5-Diisopropylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **250** was prepared according to general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (104 mg, 0.376 mmol) and diizopropyl benzene (356 µL, 1.88 mmol, 5.0 equiv) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 0.75 mL of HFIP. The reaction mixture was stirred at ambient temperature

for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 103 mg (65% yield) of a colorless oil. R_f = 0.82 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, *J* = 7.9 Hz, 2H), 7.35–7.27 (m, 2H), 7.25–7.14 (m, 8H), 7.20–7.12 (m, 1H), 2.94 (sept, *J* = 6.8 Hz, 1H), 2.83 (sept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.5 (q, *J* = 3.6 Hz), 146.7, 145.0, 134.7, 132.0, 130.1, 128.9, 128.9, 128.5, 128.5, 128.3, 127.3, 127.3, 127.2, 126.2, 123.6 (q, *J* = 273.6 Hz), 116.4, 103.9 (q, *J* = 34.1 Hz), 33.7, 30.4, 24.4, 24.1, 24.1, 24.1. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –58.7 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z* $[M]^{+\cdot}$ Calcd for $C_{28}H_{27}F_3$ 420.2059; Found 420.2062 (0.7 ppm).

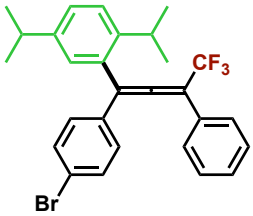


1-(2,5-Diisopropylphenyl)-3-phenyl-3-(2-toluyl)-4,4,4-trifluoro-1,2-butadiene **251** was prepared according to modified general procedure B from 1,1,1-trifluoro-4-phenyl-2-(*o*-tolulyl)but-3-yn-2-ol (63 mg, 0.22 mmol) and diisopropylbenzene (123 µL, 0.647 mmol, 3.0 equiv) with 3.5 mg (0.022 mmol) of $FeCl_3$, in 0.86 mL of HFIP. The reaction mixture was stirred at ambient temperature for 3 h. Purification by flash column chromatography over silica (petroleum ether) gave 63 mg (58% yield) of colorless oil. R_f = 0.84 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 7.7 Hz, 2H), 7.41–7.34 (m, 2H), 7.34–7.28 (m, 2H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 4.0 Hz, 2H) 7.18–7.13 (m, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 3.00 (sept, *J* = 6.8 Hz, 1H), 2.87 (sept, *J* = 6.9 Hz, 1H) 2.30 (s, 3H), 1.30–1.16 (d, *J* = 7.0 Hz, 6H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.7 (q, *J* = 3.6 Hz), 146.6, 144.8, 137.0, 134.7, 134.0, 131.3, 130.6, 129.7, 128.8, 128.3, 128.3, 128.2, 127.4 (q, *J* = 1.1 Hz), 127.0, 126.3, 126.2, 123.8 (q, *J* = 274.8 Hz), 115.2, 101.4 (q, *J* = 34.1 Hz), 33.6, 30.0, 24.2, 24.1, 21.5. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –60.5 (s, 3F). HRMS (APPI$^+$-Obitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{29}H_{29}F_3$ 434.2216; Found 434.2226 (2.3 ppm).

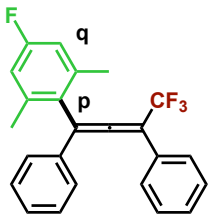


1-(4-Bromophenyl)-1-(2,5-diisopropylphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene **252** was prepared according to general procedure B from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (10.2 mg, 0.28 mmol) and diisopropylbenzene (267 µL, 1.411 mmol, 5.0 equiv) with 4.5 mg (0.028 mmol) of $FeCl_3$, in 0.56 mL of HFIP. The reaction mixture was stirred at ambient temperature for 10 min. Purification by flash column chromatography over silica (petroleum ether) gave 56 mg (40% yield) of yellow solid. R_f = 0.87 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55–7.47 (m, 2H), 7.44–7.28 (m, 7H), 7.25–7.19 (m, 2H), 7.14–7.08 (m, 1H), 2.98 (sept, *J* = 6.8 Hz, 1H), 2.90 (sept, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.4 (q, *J* = 4.2 Hz), 146.8, 145.0, 134.3, 132.1, 131.7, 129.1, 129.0, 128.8, 128.7, 128.2, 127.4, 127.3, 126.3, 123.3 (q, *J* = 275.0 Hz), 122.7, 117.0, 103.1 (q, *J* = 34.8 Hz), 33.7, 30.4, 24.4, 24.1.

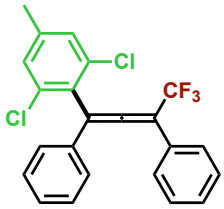
^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –58.8 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{26}{}^{79}BrF_3$ 498.1165; Found 498.1168 (0.6 ppm).



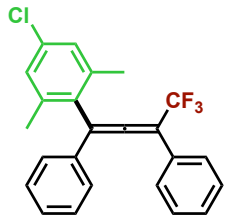
1-(4-Bromophenyl)-1-(2,5-diisopropylphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene **253** was prepared according to general procedure B from 4-(4-bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (111 mg, 0.314 mmol) and diisopropylbenzene (297 µL, 1.568 mmol, 5.0 equiv) with 4.7 mg (0.031 mmol) of $FeCl_3$, in 0.63 mL of HFIP. The reaction mixture was stirred at ambient temperature for 3 h. Purification by flash column chromatography over silica (petroleum ether) gave 111 mg (70% yield) of a colorless oil. R_f = 0.88 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 7.7 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.42–7.36 (m, 2H), 7.36–7.31 (m, 2H), 7.31–7.27 (m, 1H), 7.15-7.10 (m, 3H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.92 (sept, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 206.3 (q, *J* = 3.9 Hz), 146.9, 145.0, 133.8, 132.1, 131.6, 129.7, 129.0, 128.8, 128.7, 128.2, 127.5, 127.3, 126.3, 123.4 (q, *J* = 273.5 Hz), 122.7, 115.7, 104.3 (q, *J* = 34.2 Hz), 33.7, 30.4, 24.4, 24.1, 24.1, 24.1. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –60.8 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{26}{}^{79}BrF_3$ 498.1165; Found 498.1175 (2.0 ppm).



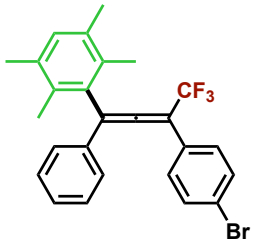
1-(2-(5-Fluoro-m-xylenyl))-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **254** was prepared according to modified general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (104 mg, 0.376 mmol) and 5-fluoro-*m*-xylene (142 µL, 1.13 mmol, 3.0 equiv) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 1.50 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 37 mg (25% yield) of colorless oil. R_f = 0.84 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 7.4 Hz, 2H), 7.40–7.29 (m, 6H), 7.25–7.20 (m, 2H), 6.84 (d, *J* = 9.4 Hz, 2H), 2.20 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.1 (q, *J* = 3.8 Hz), 162.4 (d, *J* = 244.7 Hz), 139.7 (d, *J* = 7.2 Hz), 132.9, 129.9, 129.3, 129.0, 128.8, 128.7, 128.6 (d, *J* = 2.0 Hz), 127.6 (q, *J* = 1.1 Hz), 126.6, 123.6 (q, *J* = 273.5 Hz), 114.6 (d, *J* = 21.0 Hz), 113.5, 104.3 (q, *J* = 34.3 Hz), 20.6. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –60.1 (s, 3F), –115.9 (s, 1H). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{24}H_{18}F_4$ 382.1339; Found 382.1348 (2.4 ppm).



(1-(2,6-Dichloro-4-methylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **255** was prepared according to modified general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (108 mg, 0.392 mmol) and 3,5-dichlorotoluene (190 mg, 1.18 mmol, 3.0 equiv) with 6.4 mg (0.039 mmol) of $FeCl_3$, in 1.57 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 31 mg (23% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 7.1 Hz, 2H), 7.41–7.30 (m, 7H), 7.24–7.19 (m, 3H), 2.27 (s, 3H). 7.56 (d, *J* = 7.1 Hz, 2H), 7.41–7.30 (m, 7H), 7.24–7.19 (m, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.3 (q, *J* = 3.9 Hz), 141.1, 135.3, 134.7, 132.1, 131.0, 129.3, 129.1, 129.0, 128.9, 127.7(q, *J* = 1.2 Hz), 127.3, 126.5, 123.4 (q, *J* = 273.9 Hz), 112.8, 106.6 (q, *J* = 34.2 Hz), 20.6. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –60. (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{23}H_{15}Cl_2F_3$ 418.0497; Found 418.0500 (0.7 ppm).



(1-(2,4-Dichloro-5-methylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **256** was prepared according to modified general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (108 mg, 0.392 mmol) and 3,5-dichlorotoluene (190 mg, 1.18 mmol, 3.0 equiv) with 6.4 mg (0.039 mmol) of $FeCl_3$, in 1.57 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 17 mg (10% yield) of white solid^{1}H NMR (500 MHz, CDCl3) δ (ppm) 7.57 (d, J = 7.1 Hz, 2H), 7.43 – 7.31 (m, 7H), 7.25 – 7.20 (m, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 205.3 (q, *J* = 3.9 Hz), 141.1, 135.3, 134.7, 132.1, 131.0, 129.3, 129.1, 129.0, 128.9, 127.7(q, *J* = 1.2 Hz), 127.3, 126.5, 123.4 (q, *J* = 273.9 Hz), 112.8, 106.6 (q, *J* = 34.2 Hz), 20.6. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –60.8 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z* $[M]^{+\cdot}$ Calcd for $C_{23}H_{15}Cl_2F_3$ 418.0497; Found 418.0500 (0.7 ppm).

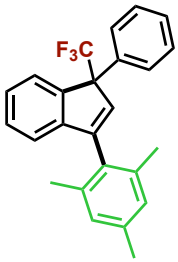


3-(4-Bromophenyl)-1-durenyl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene **257** was prepared according to modified general procedure B 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (101 mg, 0.284 mmol) and durene (114 mg, 0.85 mmol, 3.0 equiv.) with 2.9 mg (0.028 mmol) of $FeCl_3$, in 1.13 mL of HFIP. The reaction mixture was heated at 80 °C for 3 h. Purification by flash column chromatography over silica (petroleum ether) gave 125 mg (93% yield) of white solid. R_f = 0,90 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.39–7.30 (m, 5H), 7.24–7.17 (m, 2H), 7.03 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 205.0 (q, *J* = 3.6 Hz), 134.6, 134.2, 133.2, 132.6, 132.5, 132.1, 131.7, 129.4, 129.2, 128.8, 126.9,

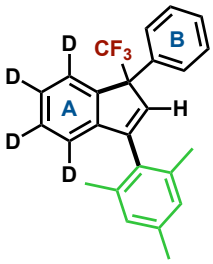
123.6 (q, J = 275.2 Hz), 122.7, 115.8, 103.2 (q, J = 34.8 Hz), 20.2 (2C), 17.5, 16.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –59.0 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{22}{}^{79}BrF_3$ 470.0851; Found 470.0862 (2.3 ppm).

2.9.4. Preparation of Indenes

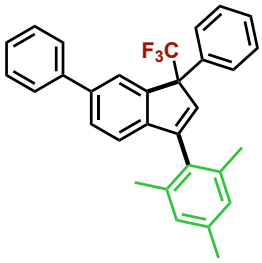
Characterization data for indenes



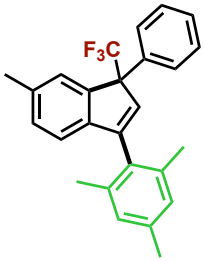
3-Mesityl-1-phenyl-1-(trifluoro-methyl)-1H-indene **235** was prepared according to general procedure C from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (106 mg, 0.382 mmol) and mesitylene (160 µL, 1.15 mmol, 3.0 equiv) with 6.2 mg (0.038 mmol) of $FeCl_3$, in 1.50 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 137 mg (94% yield) of a colorless oil. R_f = 0.80 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68–7.61 (m, 1H), 7.61–7.55 (m, 2H), 7.38–7.29 (m, 5H), 6.98 (s, 1H), 6.94 (s, 1H), 6.93–6.90 (m, 1H), 6.44 (s, 1H), 2.35 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 147.1, 145.0, 143.5, 137.6, 136.9, 136.5, 135.0, 133.4, 130.5, 128.9, 128.8, 128.4, 128.2, 128.1, 127.8, 126.9 (q, J = 280.6 Hz), 126.7, 125.4, 121.4, 64.8 (q, J = 26.6 Hz), 21.3, 20.3, 20.0. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –68.2 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{25}H_{21}F_3$ 378.1590; Found 378.1593 (0.8 ppm).



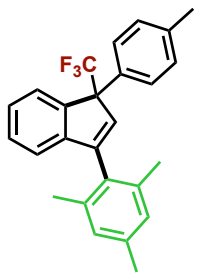
4,5,6,7-Tetradeutero-3-mesityl-1-phenyl-1-(trifluoro-methyl)-1H-indene **235-D$_4$** was prepared according to general procedure C from 1,1,1-trifluoro-2-phenyl-4-pentadeuterophenyl-but-3-yn-2-ol (68.4 mg, 0.243 mmol) and mesitylene (102 µL, 0.73 mmol, 3.0 equiv) with 3.9 mg (0.024 mmol) of $FeCl_3$ in 0.97 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 37 mg (39% yield) of a colorless oil. R_f = 0.80 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62–7.56 (m, 2H), 7.41–7.29 (m, 3H), 6.99 (s, 1H), 6.95 (s, 1H), 6.45 (s, 1H), 2.36 (s, 3H), 2.17 (s, 3H), 2.07 (s, 3H). ^{2}H NMR (600 MHz, CH_2Cl_2): δ (ppm) 7.71 (br. s, 1D), 7.38 (br. s, 2D), 6.94 (br. s, 1D). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{18}D_4F_3$ 383.1919; Found 383.1918 (0.3 ppm).



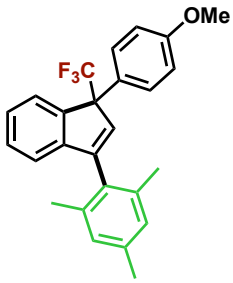
3-Mesityl-1,6-diphenyl-1-(trifluoromethyl)-1H-indene **269** was prepared according to modified general procedure C from 4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (70 mg, 0.20 mmol) and mesitylene (84 µL, 0.60 mmol, 3.0 equiv) with 3.3 mg (0.020 mmol) of $FeCl_3$, in 0.41 mL of HFIP. The reaction mixture was heated at 50 °C for 6 h. Purification by flash column chromatography over silica (petroleum ether) gave 82 mg (91% yield) of the product (in 90% purity). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (s, 1H), 7.68-7.57 (m, 4H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.47-7.40 (m, 2H), 7.38-7.30 (m, 4H), 7.03-6.93 (m, 3H), 6.46 (s, 1H), 2.35 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 146.9, 144.4, 144.2, 144.1, 140.1, 137.7, 136.9, 136.5, 135.0, 133.7, 130.5, 129.0, 128.9, 128.5, 128.3, 128.2, 128.0, 127.8, 127.5, 127.4, 126.9 (q, *J* = 280.8 Hz), 124.4, 121.6, 65.4 (q, *J* = 26.6 Hz), 21.3, 20.4, 20.1. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –65.9 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z* $[M]^{+\cdot}$ Calcd for $C_{31}H_{25}F_3$ 454.1903; Found 454.1904 (0.2 ppm).



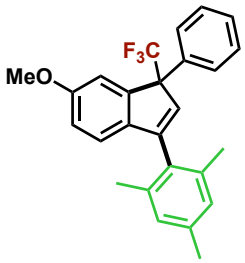
3-Mesityl-6-methyl-1-phenyl-1-(trifluoromethyl)-1H-indene **270** was prepared according to modified general procedure C from 1,1,1-trifluoro-2-phenyl-4-(*p*-toluyl)but-3-yn-2-ol (80 mg, 0.28 mmol) and mesitylene (117 µL, 0.84 mmol, 3.0 equiv) with 4.5 mg (0.028 mmol) of $FeCl_3$, in 0.55 mL of HFIP. The reaction mixture was heated at 50 °C for 6 h. Purification by flash column chromatography over silica (petroleum ether) gave 98 mg (91% yield) of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (d, *J* = 7.3 Hz, 2H), 7.52 (s, 1H), 7.44-7.33 (m, 3H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.04 (s, 1H), 7.00 (s, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.43 (s, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 147.0, 143.9, 142.4, 137.5, 136.9, 136.7, 136.5, 135.3, 132.5, 130.7, 129.6, 128.8, 128.4, 128.2, 128.0, 127.8, 127.0 (q, *J* = 280.9 Hz), 126.3, 121.1, 64.7 (q, *J* = 26.3 Hz), 21.8, 21.2, 20.3, 20.0. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) –66.0 (s, 3F). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{24}F_3$ 393.1825; Found 393.1815 (2.5 ppm).



3-Mesityl-1-toluyl-1-(trifluoromethyl)-1H-indene **271** was prepared according to general procedure C from 1,1,1-trifluoro-4-phenyl-2-(*p*-tolulyl)but-3-yn-2-ol (93 mg, 0.32 mmol) and mesitylene (133 µL, 0.96 mmol, 3.0 equiv) with 5.1 mg (0.032 mmol) of $FeCl_3$, in 1.27 mL of HFIP. The reaction mixture was stirred at ambient temperature for 3 h. Purification by flash column chromatography over silica (petroleum ether) gave 120 mg (96% yield) of colorless oil. R_f = 0.83 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67–7.64 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.34–7.28 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 1H), 6.95 (s, 1H), 6.93–6.90 (m, 1H), 6.44 (s, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.16 (s, 3H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ (ppm) 146.9, 144.9, 143.6, 137.9, 137.6, 136.9, 136.5, 133.5, 131.9, 130.6, 129.5, 128.8, 128.4, 128.2, 127.7, 126.9 (q, *J* = 282.5 Hz), 126.6, 125.4, 121.3, 64.5 (q, *J* = 26.7 Hz), 21.2, 21.1, 20.3, 20.0. ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.): δ (ppm) –68.4 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3$ 392.1746; Found 392.1747 (0.3 ppm).

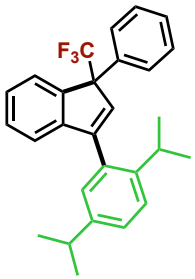


3-Mesityl-1-(4-methoxyphenyl)-1-(trifluoromethyl)-1H-indene **272** was prepared according to modified general procedure C from 1,1,1-trifluoro-2-(4-metoxyphenyl)-4-phenylbut-3-yn-2-ol (109 mg, 0.356 mmol) and mesitylene (149 µL, 1.07 mmol, 3.0 equiv) with 5.8 mg (0.036 mmol) of $FeCl_3$, in 1.42 mL of HFIP. The reaction mixture was heated at 80 °C for 1 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 40:1 to 30:1) gave 131 mg (90% yield) of yellow oil. R_f = 0.58 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69–7.63 (m, 1H), 7.54–7.48 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.98 (s, 1H), 6.94 (s, 1H), 6.91 (dd, *J* = 5.5, 3.2 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.43 (s, 1H), 3.80 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 159.3, 146.8, 144.9, 143.6, 137.6, 136.9, 136.5, 133.5, 130.6, 129.1, 128.8, 128.4, 128.2, 126.7, 126.9 (q, *J* = 282.5 Hz), 126.6, 125.4, 121.4, 114.1, 64.2 (q, *J* = 26.8 Hz), 55.4, 21.2, 20.3, 20.0. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –66.6 (s, 3F). HRMS (APPI$^+$-Orbitrap): *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3O$ 408.1696; Found 408.1697 (0.2 ppm).

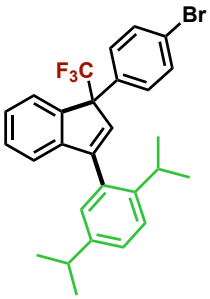


3-Mesityl-5-methoxy-1-phenyl-1-(trifluoromethyl)-1H-indene **273** was prepared according to general procedure C from 1,1,1-trifluoro-4-metoxyphenyl-2-phenylbut-3-yn-2-ol (106 mg, 0.345 mmol) and mesitylene (144 µL, 1.03 mmol, 3.0 equiv) with 5.6 mg (0.035 mmol) of $FeCl_3$, in 1.03 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 40:1 to 30:1) gave 84 mg (60% yield) of acolorless oil. R_f = 0.74 (petroleum ether/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56

(d, *J* = 7.8 Hz, 2H), 7.35–7.25 (m, 3H), 7.19 (s, 1H), 6.95 (s, 1H), 6.91 (s, 1H), 6.80 (s, 2H), 6.28 (s, 1H), 3.78 (s, 3H), 2.31 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 159.1, 146.7, 145.4, 137.8, 137.5, 136.9, 136.5, 135.2, 131.4, 130.8, 128.8, 128.4, 128.2, 128.1, 127.7, 126.9 (q, *J* = 282.5 Hz), 121.8, 113.5, 112.7, 64.7 (q, *J* = 26.7 Hz), 55.7, 21.2, 20.3, 20.0. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –74.9 (s, 3F). HRMS ($APPI^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}F_3O$ 408.1696; Found 408.1695 (–0.2 ppm).

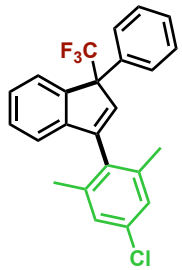


3-(2,5-Diisopropylphenyl)-1-phenyl-1-(trifluoromethyl)-1H-indene **274** was prepared according to general procedure C from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (104 mg, 0.375 mmol) and diizopropyl benzene (213 µL, 1.13 mmol, 3.00 equiv) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 0.75 mL of HFIP. The reaction mixture was stirred at ambient temperature for 3 h. Purification by flash column chromatography over silica (petroleum ether) gave 142 mg (90% yield) of a white solid. R_f = 0.91 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37–7.20 (m, 11H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 2.94–2.85 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 7.4 Hz, 3H), 0.66 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 148.5, 143.7, 141.8, 141.1, 141.0, 138.1, 136.4 (q, *J* = 2.1 Hz), 134.8, 131.9, 128.7 (q, *J* = 2.0 Hz), 128.2, 128.1, 127.9, 127.8, 126.7, 126.8 (q, *J* = 283.5 Hz), 126.1, 125.7, 121.5, 64.4 (q, *J* = 26.4 Hz), 29.3, 27.1, 24.3, 23.9, 23.6, 23.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –63.7 (s, 3F). HRMS ($APPI^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{27}F_3$ 420.2059; Found 420.2061 (1.9 ppm).

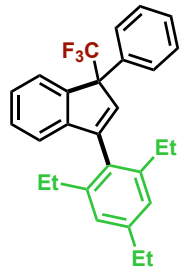


1-(4-Bromophenyl)-3-(2,5-diisopropylphenyl)-1-(trifluoromethyl)-1H-indene **275** was prepared according to modified general procedure C from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (102 mg, 0.288 mmol) and diisopropylbenzene (164 µL, 0.87 mmol, 3.0 equiv) with 4.7 mg (0.029 mmol) of $FeCl_3$, in 1.15 mL of HFIP. The reaction mixture was heated at 80 °C for 1 h. Purification by flash column chromatography over silica (with petroleum ether) gave 111 mg (77% yield) of yellow solid. R_f = 0.88 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.57–7.29 (m, 8H), 7.22–7.12 (m, 3H), 6.11 (s, 1H), 2.88 (sept, *J* = 6.4 Hz, 2H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ (ppm) 148.5, 143.7, 141.8, 141.1, 141.0, 138.1, 136.4 (q, *J* = 1.7 Hz), 134.8, 131.9, 128.7 (q, *J* = 1.7 Hz), 128.2, 128.1, 127.9, 127.8, 126.8 (q, *J* = 281.8 Hz), 126.7, 126.1, 125.7, 121.5, 64.4 (q, *J* = 26.4 Hz), 29.4, 27.1, 24.3, 23.9,

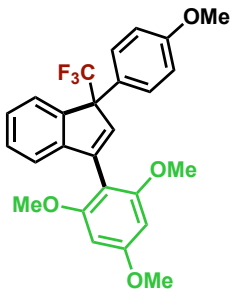
23.6, 23.4z.[19]F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –64.5 (s, 3F). HRMS (APPI$^+$-Orbitrap): *m/z* for $C_{28}H_{26}{}^{81}BrF_3$ $[M]^{+\cdot}$: calculated 500.1150; found 500.1145 (–1.0 ppm).



3-(4-(1-Chloro-3,5-dimethylphenyl))-1-phenyl-1-(trifluoro-methyl)-1H-indene **276** was prepared according to a modification of general procedure B from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (113 mg, 0.410 mmol) and 5-chloro-*m*-xylene (165 µL, 1.23 mmol, 3.0 equiv) with 6.1 mg (0.041 mmol) of $FeCl_3$, in 1.6 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 31 mg (19 % yield) of a white solid. R_f = 0.31 (petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.64 (d, *J* = 6.8 Hz, 1H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.37–7.27 (m, 5H), 7.16 (s, 1H), 6.98 (s, 1H), 6.95–6.91 (m, 1H), 6.51 (s, 1H), 2.33 (s, 3H), 2.05 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 144.7, 144.4, 143.2, 139.3, 138.6, 134.8, 134.6, 133.8, 129.7, 129.3, 128.9, 128.8, 128.2, 127.8, 127.7, 126.7, 126.7 (q, *J* = 281.1 Hz), 125.5, 121.4, 65.0 (q, *J* = 26.8 Hz), 21.1, 20.6. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –67.7 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ calculated for $C_{24}H_{18}{}^{35}ClF_3$ 398.1044; found 398.1050 (1.5 ppm).



1-Phenyl-3-(2,4,6-triethylphenyl)-1-(trifluoromethyl)-1H-indene **277** was prepared according to general procedure C from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (117 mg, 0.424 mmol) and 1,3,5-triethylbenzene (239 µL, 1.27 mmol, 3.0 equiv) with 6.9 mg (0.042 mmol) of $FeCl_3$, in 1.69 mL of HFIP. The reaction mixture was heated at 80 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 127 mg (71% yield) of colorless oil. R_f = 0.88 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67–7.62 (m, 1H), 7.57 (d, *J* = 6.9 Hz, 2H), 7.36–7.29 (m, 5H), 7.03 (s, 1H), 7.00 (s, 1H), 6.96–6.91 (m, 1H), 6.48 (s, 1H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.57–2.27 (m, 4H), 1.30 (t, *J* = 7.6 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ (ppm) 146.4, 146.1, 144.3, 143.3, 143.3, 142.9, 134.9, 133.9, 129.4, 128.9, 128.8, 128.1, 127.8, 126.9 (q, *J* = 282.5 Hz), 126.7, 125.7, 125.5, 125.3, 121.6, 64.8 (q, *J* = 26.7 Hz), 28.9, 27.0, 26.9, 16.3, 16.2, 15.6. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –67.9 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{27}F_3$ 420.2059; Found 420.2055 (–1.2 ppm).

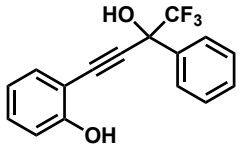


3-(2,4,6-Trimethoxyphenyl)-1-(4-methoxyphenyl)-1-(trifluoromethyl)-1H-indene **278** was prepared according to a modification of general procedure C from 1,1,1-trifluoro-2-(4-metoxyphenyl)-4-phenylbut-3-yn-2-ol (258 mg, 0.841 mmol) and 1,3,5-trimethoxybenzene (424 mg, 2.52 mmol, 3.0 equiv) with 13.6 mg (0.084 mmol) of $FeCl_3$, in 3.4 mL of HFIP. The reaction mixture was heated at 120 °C for 24 h in a high-pressure reaction tube. Purification by flash column chromatography over silica (petroleum ether/EtOAc 40:1 to 30:1) gave 364 mg (95% yield) of a yellow solid. R_f = 0.21 (petroleum ether/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.64–7.58 (m, 3H), 7.30 (td, *J* = 1.0, 7.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.58 (s, 1H), 6.26 (s, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 3.76–3.70 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ (ppm) 161.5, 159.4, 159.3, 159.1, 145.4, 143.5, 139.8, 135.3 (q, *J* = 1.8 Hz), 129.1 (q, *J* = 1.8 Hz), 128.2, 127.4, 127.0 (q, *J* = 282.4 Hz), 125.8, 124.7, 121.9, 113.9, 104.8, 91.2, 91.1, 63.9 (q, *J* = 26.8 Hz), 56.2, 55.9, 55.5, 55.3. ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –66.7 (s, 3F). HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{24}F_3O_4$ 457.1621; Found 457.1611 (–2.2 ppm).

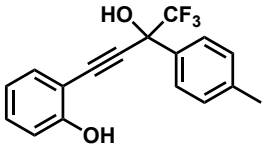
2.9.5 Preparation of tertiary propargylic alcohols for synthesis of chromenes

General procedure D:[114] **Step 1.** To a 0.5 M solution of ethynyl magnesium bromide (10 mmol) in THF was slowly added aryl trifluoromethyl ketone (10 mmol) in THF (20 mL). After 3 h at ambient temperature the reaction mixture was quenched first with water and then with saturated NH_4Cl(aq). The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford colored oil (2-aryl-1,1,1-trifluoro-3-butyn-2-ol - compound **A**) that was engaged in the next step without further purification. **Step 2.** To a solution of 2-iodophenol (10 mmol) and imidazole (20 mmol) in dry THF (20 mL) was added *tert*-butyldimethylsilyl chloride (20 mmol) in one portion and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was then diluted with CH_2Cl_2 and filtered through celite. The residue was purified by flash column chromatography (petroleum ether) to provide the desired product (1-iodo-2-(*tert*-butyldimethylsilyloxy)benzene - compound **B**). **Step 3.** To a stirred solution of compound **B** (10 mmol) in Et_3N (20 mL) under argon were sequentially added $Pd(PPh_3)_2Cl_2$ (1 mol %) and CuI (2 mol %) at ambient temperature. Then compound **A** (1.3 equiv) was added and the mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl (aq), extracted with Et_2O, dried over Na_2SO_4, and was purified by flash column chromatography (petroleum ether/EtOAc 9:1). To the isolated product (10 mmol) in THF (20 mL) was added tetra-*n*-butyl ammonium fluoride (1.2 equiv) at room temperature for 30 min. The reaction was quenched by adding water and extracted with EtOAc, dried over Na_2SO_4. The crude material was purified by column chromatography (petroleum ether/EtOAc 10:1) to give the pure propargylic alcohol that was used for subsequent synthesis of chromenes.

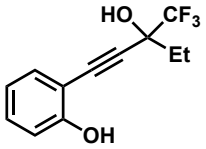
[114] Qiu Y.-F. et al. *Chem. Eur. J.* **2015**, 21, 3480.



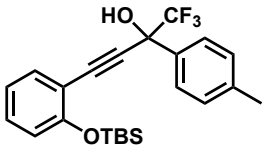
2-(4,4,4-Trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol **235** was prepared according to general procedure D using 2,2,2-trifluoro-1-phenylethan-1-one (1.4 mL, 10 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 263 mg (90% yield) of light yellow yellow solid. Mp: 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85-7.76 (m, 2H), 7.47-7.44 (m, 3H), 7.42 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 6.98 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.92 (td, *J* = 7.6, 1.1 Hz, 1H), 5.57 (s, 1H), 3.16 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 157.4, 135.0, 132.5, 132.0, 129.9, 128.6, 127.2, 123.4 (q, *J* = 285.6 Hz), 120.8, 115.5, 107.4, 91.6, 82.9, 73.7 (q, *J* = 32.8 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –81.1 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M+H]^{+}$ Calcd for $C_{16}H_{12}O_2F_3$ 293.0784; Found 293.0783 (–0.2 ppm).



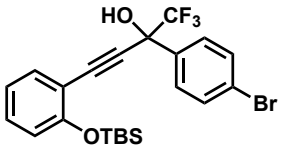
2-(4,4,4-Trifluoro-3-hydroxy-3-(p-tolyl)but-1-yn-1-yl)phenol **325** was prepared according to general procedure D using 2,2,2-trifluoro-1-(p-tolyl)ethan-1-one (1.5 mL, 10 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 110 mg (36% yield) of brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.2 Hz, 2H), 7.41 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36–7.30 (m, 1H), 7.22-7.25 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 5.61 (s, 1H), 3.19 (s, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 157.4, 140.0, 132.4, 132.2, 131.9, 129.3, 127.1, 123.5 (q, *J* = 285.8 Hz), 120.8, 115.5, 107.5, 91.8, 82.7, 73.6 (q, *J* = 31.6 Hz), 21.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –81.1 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{17}H_{13}O_2F_3$ 306.0862; Found 305.0862 (–0.1 ppm).



2-(3-Hydroxy-3-(trifluoromethyl)pent-1-yn-1-yl)phenol **326** was prepared according to general procedure D using 1,1,1-trifluorobutan-2-one (1 g, 8 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 54 mg (22% yield, 70% purity (remainder is 1,1,1-trifluorobutan-2-one) of brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.90 (td, *J* = 7.6, 1.0 Hz, 1H), 5.57 (s, 1H), 2.70 (s, 1H), 1.98 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 157.0, 132.4, 131.7, 124.3 (q, *J* = 285.2 Hz), 120.7, 115.4, 107.6, 90.4, 82.2, 73.2 (q, *J* = 31.1 Hz), 28.4, 7.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –82.1 (s, 3F). HRMS (APPI^{+}-Orbitrap) $[M]^{+\cdot}$ Calcd *m/z*: for $C_{12}H_{11}O_2F_3$ 244.0711; Found 244.0705 (–2.5 ppm).



4-(2-((Tert-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro-2-(p-tolyl)but-3-yn-2-ol **327** was prepared according to general procedure D using 2,2,2-trifluoro-1-(p-tolyl)ethan-1-one (1.5 mL, 10 mmol), without deprotection step. Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 362 mg (86% yield) of brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69 (d, *J* = 8.1 Hz, 2H), 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28–7.19 (m, 3H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.02 (s, 1H), 2.38 (s, 3H), 0.97 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 156.9, 139.3, 134.3, 132.5, 130.7, 128.9, 127.2, 123.1 (q, *J* = 285.3 Hz), 121.1, 119.2, 113.4, 87.8, 85.5, 73.3 (q, *J* = 31.9 Hz), 25.6, 21.3, 18.3, –4.2. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –78.9 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M+H]^{+\cdot}$ calculated for $C_{23}H_{28}O_2F_3Si$ 421.1805; Found 421.1797 (–2.0 ppm).

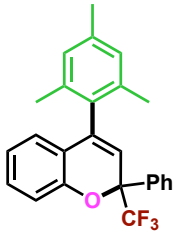


2-(4-Bromophenyl)-4-(2-((tert-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro-but-3-yn-2-ol **328** was prepared according to general procedure D using 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (2.5 g, 10 mmol), without deprotection step. Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 427 mg (88% yield) of brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28–7.25 (m, 1H), 6.93 (td, *J* = 7.6, 1.0 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.09 (s, 1H), 0.95 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 157.0, 134.9, 134.6, 131.7, 131.2, 129.4, 124.1, 123.4 (q, *J* = 286.4 Hz), 121.4, 119.8, 113.4, 87.4, 86.4, 73.4 (q, *J* = 32.8 Hz), 25.8, 18.5, –3.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –81.0 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z* $[M]^{+\cdot}$ Calcd for $C_{22}H_{25}O_2{}^{79}BrF_3Si$ 485.0754; Found 485.0756 (0.4 ppm).

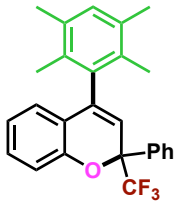
2.9.6. Preparation of Chromenes

General procedure E for synthesis of CF_3-chromenes and CF_3-alkenes. To a solution of propargylic alcohol (0.25 mmol) in HFIP (125 µL), aryl nucleophile was added (0.75 mmol) and TfOH (2.2 µL, 10 mol%). The reaction was stirred at 50 °C for 16 h. The crude reaction mixture was directly transferred for silica gel chromatography.

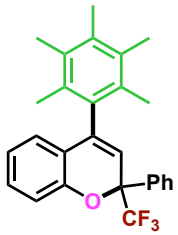
Characterization data for chromenes.



4-Mesityl-2-phenyl-2-(trifluoromethyl)-2H-chromene **285** was prepared according to general procedure E from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (73 mg, 0.25 mmol) and mesitylene (105 µL, 0.750 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 101 mg (quantitative yield) of white solid. Mp: 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, *J* = 7.5 Hz, 2H), 7.41–7.33 (m, 3H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 10.0 Hz, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 2.33 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 151.7, 137.9, 137.5, 136.9, 133.2, 130.6, 129.3, 128.7, 128.6, 128.5, 127.1, 125.7, 125.0 (q, *J* = 284.6 Hz), 122.5, 120.9, 118.3, 116.9, 80.4 (q, *J* = 30.1 Hz), 21.4, 20.1, 19.9. ^{19}F NMR (376.5 MHz, $CDCl_3$ CF_3CO_2H, - ext. st.): δ (ppm) –80.3 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M–H]^{+}$ for $C_{25}H_{20}OF_3$ Calcd 393.1461; Found 393.1460 (–0.1 ppm).

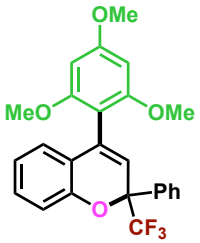


2-Phenyl-4-(2,3,5,6-tetramethylphenyl)-2-(trifluoromethyl)-2H-chromene **291** was prepared according to general procedure E from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (73 mg, 0.25 mmol) and durene (102 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 88 mg (86% yield) of white solid. Mp: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 (d, *J* = 7.3 Hz, 2H), 7.42–7.33 (m, 3H), 7.22–7.18 (m, 1H), 7.12 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.01 (s, 1H), 6.77 (td, *J* = 7.5, 1.1 Hz, 1H), 6.53 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.99 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.05 (s, 3H), 1.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 151.6, 139.0, 137.5, 136.2, 134.3, 134.1, 132.8, 132.6, 131.5, 130.5, 129.3, 128.6, 127.2, 126.0, 124.3 (q, *J* = 284.6 Hz), 122.4, 121.3, 118.0, 116.8, 80.4 (q, *J* = 30.5 Hz), 20.4, 20.3, 16.8, 16.6. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.3 (s, 3F). HRMS (APPI^{+}-Obitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}OF_3$ 408.1696; Found 408.1698 (0.6 ppm).

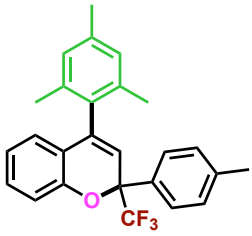


4-(2,3,4,5,6-Pentamethylphenyl)-2-phenyl-2-(trifluoromethyl)-2H-chromene **292** was prepared according to general procedure E from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (72.5 mg, 0.25 mmol) and pentamethyl-benzene (111 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 132 mg (quantitative yield) of white solid. Mp: 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (d, *J* = 7.3 Hz, 2H), 7.44–7.30 (m, 3H), 7.23–7.17 (m, 1H), 7.12 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.77 (td, *J* = 7.5, 1.2 Hz, 1H), 6.56 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.00 (s, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H), 1.95 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 151.6, 139.6, 137.5, 136.1, 133.8, 133.2, 132.9, 132.4, 132.2, 130.5, 129.3, 128.6, 127.2, 126.2, 124.4 (q, *J* = 284.6 Hz), 122.4, 121.6, 118.1, 116.8, 80.5 (q, *J*

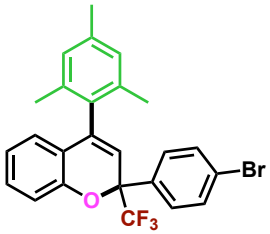
= 30.5 Hz), 18.1, 17.8, 17.2, 16.9, 16.8. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.2 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{27}H_{25}OF_3$ 422.1852; Found 422.1855 (0.7 ppm).



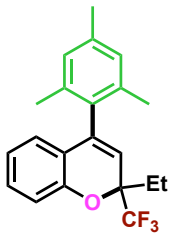
2-Phenyl-2-(trifluoromethyl)-4-(2,4,6-trimethoxyphenyl)-2H-chromene **293** was prepared according to general procedure E from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (73 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (116 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether/EtOAc 97:3) gave 47 mg (43% yield) of white solid. Mp: 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (d, *J* = 7.4 Hz, 2H), 7.38-7.32 (m, 3H), 7.11 (t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.20 (d, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 161.8, 159.6, 159.4, 151.4, 137.6, 131.7, 129.6, 129.2, 128.2, 127.9, 125.8, 124.7 (q, *J* = 283.8 Hz), 122.4, 122.0, 120.5, 116.8, 107.3, 91.3, 91.2, 56.3, 56.1, 55.7 (quaternary carbon **a** displayed a very weak signal). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –79.9 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{22}O_4F_3$ 443.1465; Found 443.1464 (–0.2 ppm).



4-Mesityl-2-(p-tolyl)-2-(trifluoromethyl)-2H-chromene **294** was prepared according to general procedure E from 2-(4,4,4-trifluoro-3-hydroxy-3-(*p*-tolyl)but-1-yn-1-yl)phenol (77 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 55 mg (54% yield) of white solid. **294** was also prepared according to general procedure E from 4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro-2-(*p*-tolyl)but-3-yn-2-ol (105 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 290 mg (71% yield) of white solid. Mp: 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (d, *J* = 8.1 Hz, 2H), 7.21–7.17 (m, 3H), 7.09 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 6.76 (td, *J* = 7.5, 1.2 Hz, 1H), 6.54 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.00 (s, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 151.7, 139.2, 137.8, 137.7, 136.9, 134.5, 133.3, 130.5, 129.3, 128.7, 128.4, 127.1, 125.6, 124.2 (q, *J* = 284.6 Hz), 122.4, 121.0, 118.5, 116.9, 80.4 (q, *J* = 30.5 Hz), 24.5, 21.4, 20.1, 19.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.5 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{23}OF_3$ 408.1698; Found 408.1696 (–0.7 ppm).



2-(4-Bromophenyl)-4-mesityl-2-(trifluoromethyl)-2H-chromene **295** was prepared according to general procedure E from 2-(4-bromophenyl)-4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro-but-3-yn-2-ol (121 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 89 mg (75% yield) white solid. Mp: 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 4H), 7.23–7.18 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 6.9 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.55 (dd, *J* = 1.2, 7.7 Hz, 1H), 5.97 (s, 1H), 2.33 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 151.4, 138.4, 138.0, 136.8, 136.7, 136.5, 133.0, 131.9, 130.8, 128.9, 128.7, 128.5, 125.8, 124.1 (q, *J* = 284.6 Hz), 123.8, 122.7, 120.8, 117.7, 116.9, 80.1 (q, *J* = 30.5 Hz), 21.4, 20.1, 19.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.5 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z* $[M]^{+\cdot}$ Calcd for $C_{25}H_{21}OBrF_3$ 473.0722; Found 473.0716 (–1.3 ppm).



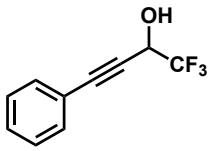
2-Ethyl-4-mesityl-2-(trifluoromethyl)-2H-chromene **296** was prepared according to general procedure E from 2-(3-hydroxy-3-(trifluoromethyl)pent-1-yn-1-yl)phenol (61 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 67 mg (77% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14 (td, *J* = 8.0, 1.6 Hz, 1H), 6.94 (s, 1H), 6.92 (s, 1H), 6.90 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.73 (td, *J* = 7.5, 1.1 Hz, 1H), 6.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.26 (s, 1H), 2.33 (s, 3H), 2.17–2.07 (m, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 1.83 (dq, *J* = 14.2, 7.3 Hz, 1H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 153.4, 139.7, 137.7, 137.1, 136.3, 133.5, 130.4, 128.7, 128.4, 125.5, 125.0 (q, *J* = 284.6 Hz), 121.8, 119.8, 117.4, 115.8, 80.7 (q, *J* = 30.5 Hz), 27.9, 21.4, 20.2, 19.8, 7.8. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –83.0 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{21}H_{21}OF_3$ 346.1539; Found 346.1538 (–0.3 ppm).

2.9.7. Preparation of secondary propargylic alcohols

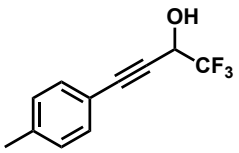
General procedure F for preparation of secondary propargylic alcohols. Secondary propargylic alcohols were prepared via two-step Kitazume/Sato sequence.[115] To a mixture of alkyne (10 mmol) and anhydrous THF (30 mL) at –78 °C was added *n*-BuLi (10 mmol, 2.5 M solution) for 5 min. After 20 min stirring at –78 °C, ethyl trifluoroacetate (10 mmol), boron

[115] (a) T. Kitazume, T. A. Sato, *J. Fluorine Chem*. **1985**, 30, 189. (b) L. Xiao, et al. *Tetrahedron: Asymmetry* **1997**, *8*, 3597.

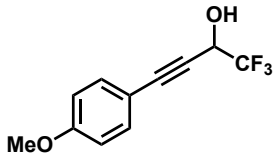
trifluoride diethyl etherate (12 mmol), and anhydrous THF (20 mL) were added. After an additional 2 h of stirring, the reaction was quenched with brine, extracted with ethyl acetate, and dried over Na_2SO_4. The resulting ketone was purified by flash chromatography (petroleum ether/EtOAc 9:1). The ketone was dissolved in methanol (10 mL). To the solution was added $NaBH_4$ (10 mmol) slowly and the reaction solution was stirred for 30 min at room temperature. The mixture was quenched by adding brine and extracted with ethyl acetate, dried over Na_2SO_4. Finally, purification by flash chromatography yielded the secondary propargylic alcohols.



1,1,1-Trifluoro-4-phenylbut-3-yn-2-ol **234** was prepared according to general procedure F using phenylacetylene (0.54 mL, 5.0 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 88 mg (44% yield) of yellow oil. The experimental data are in agreement with the literature.[116] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50–7.48 (m, 2H), 7.42–7.32 (m, 3H), 4.94–4.88 (m, 1H), 2.52 (d, *J* = 8.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 132.4, 129.9, 128.8, 123.2 (q, *J* = 281.9 Hz), 121.2, 88.4, 80.7, 63.3 (q, *J* = 36.5 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.2 (s, 3F).

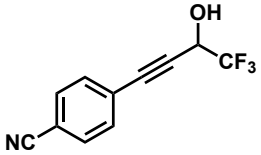


1,1,1-Trifluoro-4-(p-tolyl)but-3-yn-2-ol **329** was prepared according to general procedure F using 1-ethynyl-4-methylbenzene (0.63 mL, 5.0 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 98 mg (46% yield) of white solid. Mp: 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.95–4.89 (m, 1H), 2.47 (d, *J* = 6.7 Hz, 1H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 140.2, 132.3, 129.5, 123.1 (q, *J* = 281.7 Hz), 118.1, 88.6, 80.1, 63.3 (q, *J* = 36.4 Hz), 21.6. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.3 (s, 3F). HRMS ($APPI^+$-Orbitrap) *m/z*: for $C_{11}H_{10}OF_3$ $[M+H]^{+\cdot}$ Calcd 215.0678; found 215.0678 (–0.0 ppm).

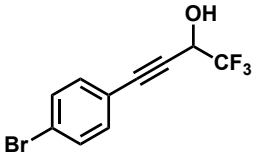


1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol **330** was prepared according to general procedure F using 1-ethynyl-4-methoxybenzene (0.65 mL, 5.0 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 85:15) gave 69 mg (30% yield) of yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44–7.39 (m, 2H), 6.89–6.83 (m, 2H), 4.89 (dq, *J* = 5.7, 8.2 Hz, 1H), 3.82 (s, 3H), 2.47 (d, *J* = 8.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 160.8, 133.9, 123.3 (q, *J* = 282.0 Hz), 114.4, 113.2, 88.4, 79.5, 63.3 (q, *J* = 36.7 Hz), 55.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –78.3 (s, 3F). HRMS ($APPI^+$): *m/z* for $C_{11}H_9O_2F_3$ ($[M]^+$): calculated 230.0555; found 230.0551 (–1.7 ppm).

[116] S-J. Ko. *Tetrahedron: Asymmetry* **2009**, 20, 1109



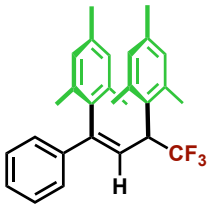
4-(4,4,4-Trifluoro-3-hydroxybut-1-yn-1-yl)benzonitrile **331** was prepared according to general procedure F using 1-ethynyl-4-isocyanobenzene (0.64 g, 5.0 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 56 mg (25% yield) of yellow solid. Mp: 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 4.98-4.91 (m, 1H), 2.59 (d, *J* = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 132.7, 132.3, 125.8, 122.7 (q, *J* = 282.0 Hz), 118.2, 113.1, 86.1, 84.6, 63.1 (q, *J* = 36.8 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.0 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M+H]^{+}$ Calcd for $C_{11}H_7ONF_3$ 226.0480; Found 226.0475 (–2.3 ppm).



4-(4-Bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol **332** was prepared according to general procedure F using 1-ethynyl-4-bromobenzene (0.60 mL, 5.0 mmol). Purification by flash column chromatography over silica (petroleum ether/EtOAc 9:1) gave 167 mg (60% yield) of yellow/dark yellow solid. Mp: 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.91–4.88 (m, 1H), 2.50 (d, *J* = 7.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 133.8, 132.2, 124.4, 123.1 (q, *J* = 282.4 Hz), 120.1, 87.2, 81.8, 62.3 (q, *J* = 36.6 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –80.2 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{10}H_5O^{79}BrF_3$ 276.9470; found 276.9473 (0.8 ppm).

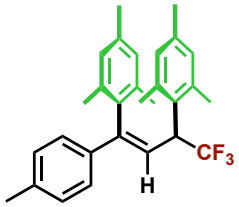
2.9.8. Characterization of alkenes

Characterization data for Friedel-Crafts reaction products of secondary propargylic alcohols

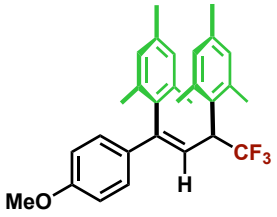


(Z)-2,2'-(4,4,4-Trifluoro-1-phenylbut-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) **303** was prepared according to general procedure E from 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (50 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 80 mg (75% yield) of white solid. Mp: 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27-7.21 (m, 5H), 6.95 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 6.65 (d, *J* = 5.1 Hz, 1H), 4.38-4.29 (m, 1H), 2.51 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.14 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.0, 139.2, 138.9, 137.6, 137.6, 137.3, 137.2, 135.3, 134.3, 130.9, 129.2, 128.7, 128.7, 128.6, 128.4, 127.9, 127.6 (q, *J* = 280.9 Hz) 125.9, 121.7, 45.8 (q, *J* = 27.8 Hz), 22.7 (q, *J* = 3.2 Hz), 21.2, 20.9, 19.9, 19.6, 18.4. ^{19}F

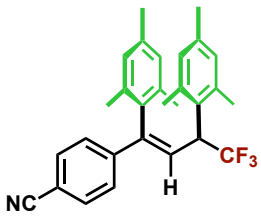
NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –68.4 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{29}F_3$ 422.2216; Found 422.2217 (0.4 ppm).



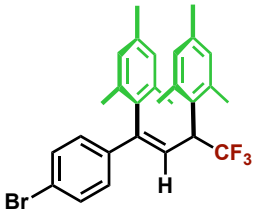
(Z)-2,2'-(4,4,4-Trifluoro-1-(p-tolyl)but-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) **307** was prepared according to general procedure E from 1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (53 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 84 mg (77% yield) of white solid. Mp: 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.95 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.76 (s, 1H), 6.65 (d, *J* = 4.5 Hz, 2H), 4.37–4.27 (m, 1H), 2.50 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.39 (s, 3H), 1.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.8, 139.2, 137.8, 137.6, 137.5, 137.1, 136.0, 135.3, 134.5, 130.9, 129.4 (2C), 129.1, 128.6, 128.4, 127.6 (q, *J* = 281.2 Hz), 125.8 (2C), 120.7, 45.8 (q, *J* = 27.8 Hz), 22.7 (q, *J* = 3.1 Hz), 21.3, 21.2, 20.9, 19.9, 19.6, 18.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –68.3 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{29}H_{31}F_3$ 436.2372; Found 436.2377 (1.1 ppm).



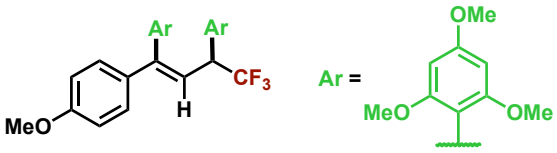
(Z)-2,2'-(4,4,4-Trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) **308** was prepared according to general procedure E from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether/EtOAc 98:2) gave 91 mg (81% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 6.9 Hz, 2H), 6.68 (d, *J* = 5.2 Hz, 2H), 4.40–4.26 (m, 1H), 3.81 (s, 3H), 2.53 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.42 (s, 3H), 1.17 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 142.4, 139.2, 137.6, 137.5, 137.1 (q, *J* = 2.6 Hz), 135.2, 134.6, 131.5, 130.9, 129.1, 128.6, 128.4, 127.7 (q, *J* = 281.1 Hz), 127.1 (2C), 119.6, 114.0 (2C), 55.4, 45.8 (q, *J* = 27.7 Hz), 21.2, 20.9, 19.9, 19.6, 18.3.^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –67.4 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{29}H_{31}OF_3$ 452.2322; Found 452.2323 (0.3 ppm).



(Z)-4-(4,4,4-Trifluoro-1,3-dimesitylbut-1-en-1-yl)benzonitrile **309** was prepared according to general procedure E from 4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)benzonitrile (56 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (88 h, 100 °C). Purification by flash column chromatography over silica (petroleum ether/EtOAc 98:2) gave 25 mg (22% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.98 (s, 1H), 6.77 (s, 1H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.40–4.30 (m, 1H), 2.48 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H), 1.40 (s, 3H), 1.10 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 143.3, 141.8, 139.3, 138.0, 137.6, 137.5, 137.4, 135.2, 133.0, 132.6, 131.0, 129.3, 128.9, 128.7, 128.0, 127.8 (q, *J* = 280.7 Hz), 126.4, 125.4, 119.0, 111.3, 46.0 (q, *J* = 28.0 Hz), 22.7 (q, *J* = 3.8 Hz), 21.2, 20.9, 19.8, 19.6, 18.3. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –67.3 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{29}H_{28}NF_3$ 447.2168; Found 447.2172 (0.8 ppm).

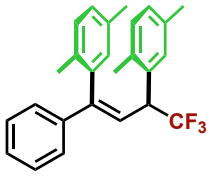


(Z)-2,2'-(1-(4-Bromophenyl)-4,4,4-trifluorobut-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) **310** was prepared according to general procedure E from 4-(4-bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol (70 mg, 0.25 mmol) and mesitylene (105 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 77 mg (61% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.96 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.77 (s, 1H), 6.67 (d, *J* = 6.1 Hz, 2H), 4.37–4.27 (m, 1H), 2.48 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 1.40 (s, 3H), 1.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 142.3, 139.4, 138.0, 137.8, 137.7, 137.5, 135.4, 134.5, 133.9, 132.0, 131.1, 129.4, 128.9, 128.7, 123.0 (q, *J* = 281.2 Hz), 127.7, 126.0, 123.1, 122.2, 46.1 (q, *J* = 27.8 Hz), 22.9, 21.5, 21.0, 20.1, 19.8, 18.5. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –67.3 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{28}H_{28}{}^{79}BrF_3$ 500.1321; Found 500.1331 (1.9 ppm).

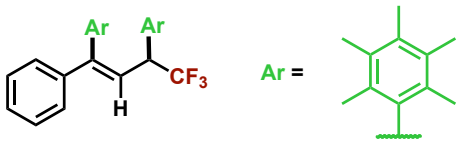


(Z)-2,2'-(4,4,4-Trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,3,5-trimethoxybenzene) **311** was prepared according to general procedure E from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (116 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether/EtOAc 8:2) gave 100 mg (73% yield) of white solid. Mp: 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (d, *J* = 8.9 Hz, 2H), 6.79 (dd, *J* = 21.3, 8.5 Hz, 3H), 6.20 (d, *J* = 2.1 Hz, 1H), 6.08 (s, 1H), 5.90 (s, 1H), 5.87 (d, *J* = 2.1 Hz, 1H), 4.60–4.49 (m, 1H), 3.82 (s, 6H), 3.78 (s, 3H), 3.76 (s, 6H), 3.43 (s, 3H), 3.07 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 161.1, 160.8, 159.2, 159.0, 158.3, 135.5, 133.9, 127.8 (q, *J* = 280.9 Hz), 127.3, 123.2, 113.7, 109.5, 105.9, 91.6, 90.5, 90.4, 90.2, 56.4, 56.2, 55.7, 55.6 (2C), 55.5, 55.2, 30.2 (q, *J* = 27.8 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.):

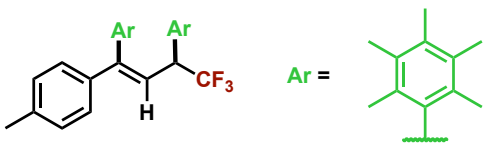
δ (ppm) –68.2 (s, 3F). HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{32}O_7F_3$ 549.2095; Found 549.2114 (3.6 ppm).



(Z)-2,2'-(4,4,4-Trifluoro-1-phenylbut-1-ene-1,3-diyl)bis(1,4-dimethylbenzene) **312** was prepared according to general procedure E from 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (50 µL, 0.25 mmol) and *p*-xylene (92 µL, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 48 mg (49% yield) of colorless oil which was isolated as a 6:4 mixture of stereoisomers as determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.69 (d, *J* = 9.7 Hz, 1H, major), 6.68 (d, *J* = 9.7 Hz, 1H, minor), 6,36 (s, 1H, minor), 4.39–4.22 (m, 1H, minor), 4.15–4.01 (m, 1H, major), 2.41 (s, 3H, minor), 2.34 (s, 6H, major), 2.16 (s, 3H, major), 2.06 (s, 3H, major), 1.78 (s, 3H, minor), 1.68 (s, 3H, minor), 1.45 (s, 3H, minor). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.1, 145.8, 140.0, 139.8, 138.0, 137.8, 135.7, 135.7, 135.3, 134.5, 134.0, 133.8, 133.7, 133.6, 133.3, 130.5, 130.4, 130.4, 130.3, 130.2, 129.7, 129.2, 128.8, 128.7, 128.6, 128.5, 128.0, 126.7, 126.6, 45.2 (q, *J* = 27.4 Hz), 44.8 (q, *J* = 27.4 Hz), 21.3, 21.2, 20.9, 19.1, 18.5, 18.5. (mixture of two rotamers). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –69.2 (s, 2.2F - minor), –69.5 (s, 3F - major). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{26}H_{25}F_3$ 394.1908; Found 394.1902 (–1.7 ppm).

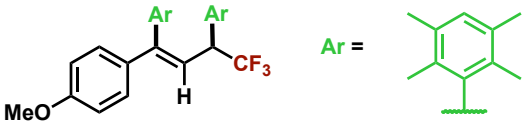


(Z)-6,6'-(4,4,4-Trifluoro-1-phenylbut-1-ene-1,3-diyl)bis(1,2,3,4,5-pentamet-hylbenzene) **313** was prepared according to general procedure E from 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (50 µL, 0.25 mmol) and pentamethylbenzene (111 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 114 mg (95% yield) of white solid. Mp: 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31–7.24 (m, 5H), 6.94 (d, *J* = 7.4 Hz, 1H), 4.53–4.43 (m, 1H), 2.41 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.29 (s, 3H), 0.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 144.4, 140.0, 135.1, 134.8, 134.4, 134.0, 133.7, 133.4, 133.2, 132.9, 132.7, 132.4, 130.3, 129.7, 128.8, 127.8, 127.8 (q, *J* = 280.5 Hz), 126.2, 122.8, 46.2 (q, *J* = 27.9 Hz), 19.9, 19.8, 17.5, 17.4, 17.3, 17.1, 16.9, 16.8, 16.2, 15.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –66.3 (s, 3F). HRMS (APPI$^+$-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{38}F_3$ 479.2920; Found 479.2923 (0.6 ppm).



(Z)-6,6'-(4,4,4-Trifluoro-1-(p-tolyl)but-1-ene-1,3-diyl)bis(1,2,3,4,5-pentamethylbenzene) **314** was prepared according to general procedure E from 1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (53 mg, 0.25 mmol) and pentamethylbenzene (111 mg, 0.75 mmol), with 2.2 µL (0.025 mmol)

of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether) gave 108 mg (88% yield) of white solid. Mp: 206–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 7.4 Hz, 1H), 4.52–4.41 (m, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.29 (s, 3H), 0.84 (s, 3H), 0.09 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 144.2, 137.7, 137.2, 135.1, 134.9, 134.4, 133.9, 133.7, 133.4, 133.2, 132.8, 132.7, 132.0, 130.3, 129.8, 129.5, 127.8 (q, *J* = 281.1 Hz), 126.1, 121.8, 46.2 (q, *J* = 27.8 Hz), 21.4, 19.9, 19.8, 17.5, 17.4, 17.2, 17.0, 16.9, 16.8, 16.2, 15.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –66.3 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{33}H_{39}F_3$ 492.2998; Found 492.3005 (1.2 ppm).



(Z)-3,3'-(4,4,4-Trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,2,4,5tetramethyl benzene) **315** was prepared according to general procedure E from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and durene (102 mg, 0.75 mmol), with 2.2 µL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (petroleum ether/EtOAc 98:2) gave 65 mg (54% yield) of white solid. Mp: 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 1H), 6.83 (d, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.52–4.35 (m, 1H), 3.78 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 1.88 (s, 3H), 1.22 (s, 3H), 0.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 159.6, 143.4, 137.7, 135.7, 134.8, 134.4, 134.1, 133.9, 133.8, 133.4, 133.3, 131.9, 131.2, 130.6, 130.4, 127.5 (q, *J* = 281.1 Hz), 127.2, 119.9, 110.2, 55.4, 45.9 (q, *J* = 27.8 Hz), 21.4, 21.1, 20.5, 19.9, 19.7, 18.6, 16.1, 15.4, 14.9. ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –66.3 (s, 3F). HRMS (APPI^{+}-Orbitrap) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{31}H_{35}OF_3$ 480.2635; Found 480.2636 (0.4 ppm).

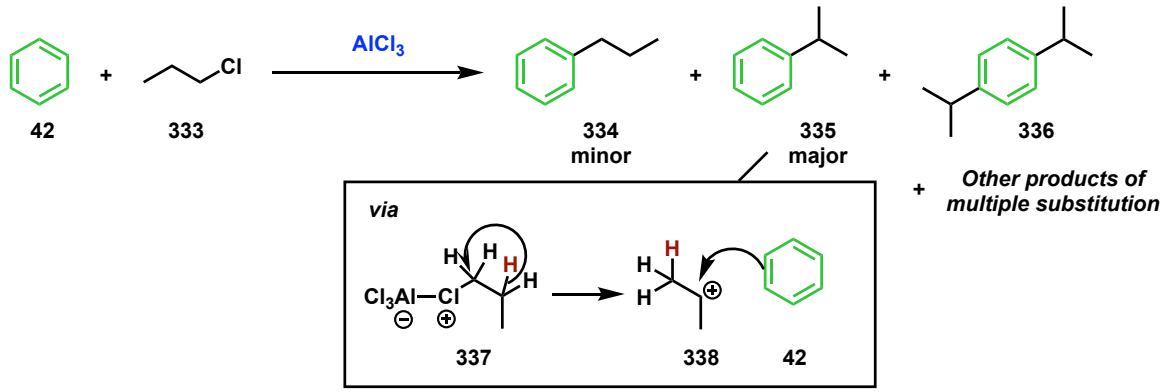
Part 3: Friedel-Crafts reaction of primary aliphatic alcohols in HFIP

3. Friedel-Crafts reaction of primary aliphatic alcohols in HFIP

3.1. Background

3.1.1. State of the art on alkylation of arenes

The first reaction that comes to mind when thinking about the alkylation of arenes is the Friedel-Crafts alkylation between an aryl nucleophile and an alkyl halide, alkyl triflate, or alkyl mesylate. These activated electrophilic species are usually synthesized from the corresponding alcohols and, thus, require an additional synthetic step which necessarily produces a stoichiometric amount of waste. All these factors make the whole process poorly atom- and step-economic. In addition, the Friedel-Crafts alkylation with linear alky halides generally leads to mixtures of branched and linear products (Scheme 75). Therefore, while this reaction is well described in undergraduate textbooks, efficient preparations of linear products remain scarce.[117] In this transformation, the formation of branched products results from a [1,2]-H shift, which generates a secondary carbocation rather than a primary one, which is too unstable to form.



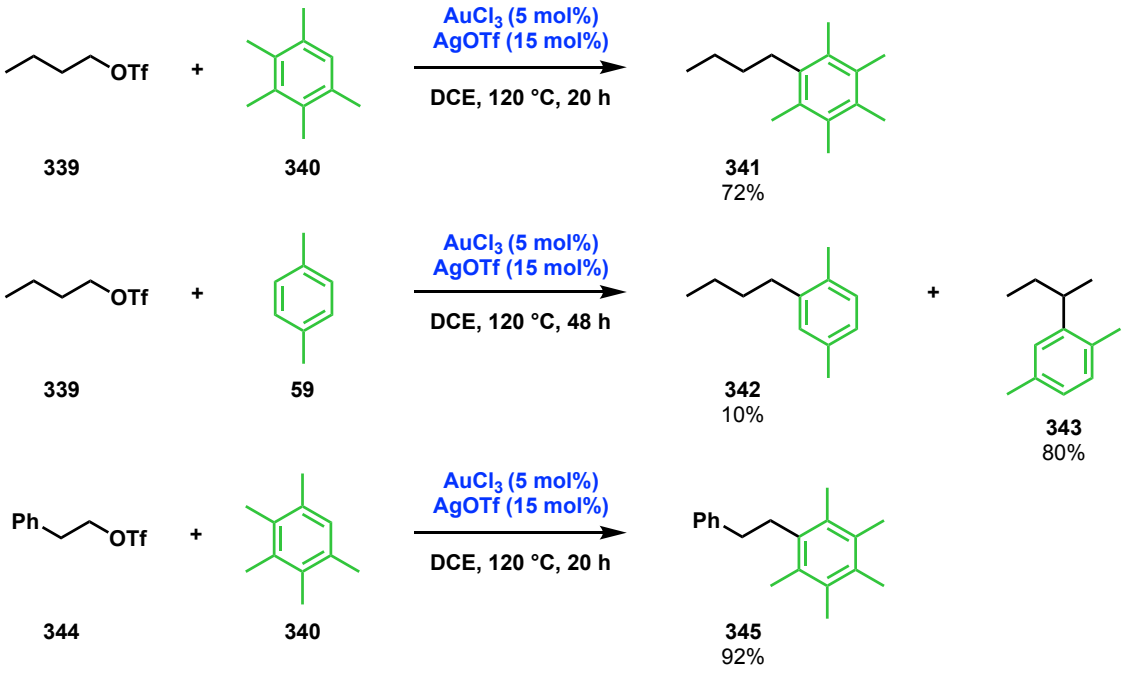
Scheme 75: Example of a Friedel-Crafts reaction with a primary alkyl halide

Regarding the substitution of triflate esters and mesylate esters, the group of He developed a gold(III)-catalyzed functionalization of aromatic C-H bonds (Scheme 76).[118] Good yield and selectivity were obtained with the sterically hindered pentamethylbenzene (Scheme 76, eq. 1). On the other hand, lower selectivity was observed with the less sterically hindered *p*-xylene, leading to the branched product as a major product (Scheme 76, eq. 2). The authors noticed the formation of 5 mol% of aryl chloride, resulting from the hydrolysis of an aryl-gold(III) complex upon treatment with brine. Therefore, they suggested that the role of the gold catalyst might be more complex than simply acting as a Lewis acid. Nevertheless, the authors did not consider the possible formation of triflic acid and hydrochloric acid following the hydrolysis of either the gold or silver catalyst. Phenylethyl mesylate also led to the corresponding product in an excellent yield (92%) with a complete selectivity in favor of the

[117] Clayden-Organic Chemistry-2nd Edition-p493

[118] Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 13596.

linear product (Scheme 76, eq. 3). However, we suspect a different mechanism in that case, which we will discuss later on.

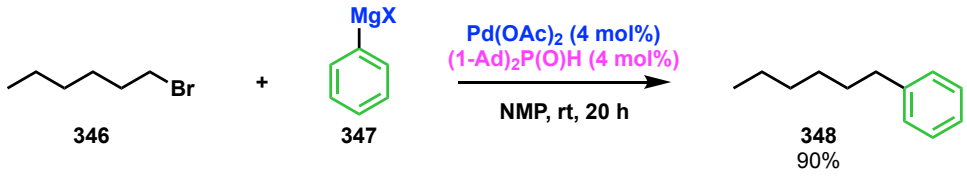


Scheme 76: Functionalization of arenes with primary sulfonate esters

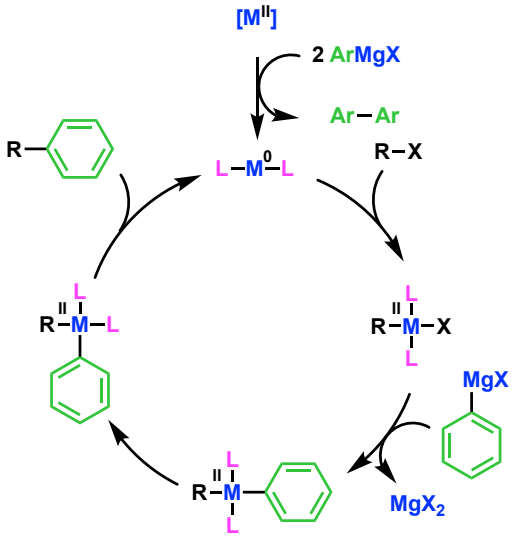
Another common method for the alkylation of arenes is the Kumada-Corriu cross-coupling reaction (Scheme 77).[119] This reaction involves an aryl Grignard and an alkyl halide. Cross-coupling reactions with alkyl halides have two significant barriers to overcome: the oxidative addition with relatively-electron rich alkyl electrophiles (compared to standard aryl and vinyl electrophiles) and the possibility of β-hydride elimination, which would lead to the formation of undesired byproducts.[120] The general mechanism starts by the oxidative addition of the metal into the carbon-halide bond, followed by a *trans*-metalation with the aryl Grignard. A subsequent *trans-cis* isomerization and a reductive elimination deliver the corresponding cross-coupling product, while regenerating the metal catalyst.

[119] L. Ackermann, A. R. Kapdi, C. Schulzke, *Org. Lett.* **2010**, *12*, 2298.

[120] (a) P. Ren, O. Vechorkin, K. von Allmen, R. Scopelliti, X. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 7084; (b) A. Rudolph, M. Lautens, Angew. *Chem. Int. Ed.* **2009**, *48*, 2656; (c) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545.



Kumada-Corriu general reaction

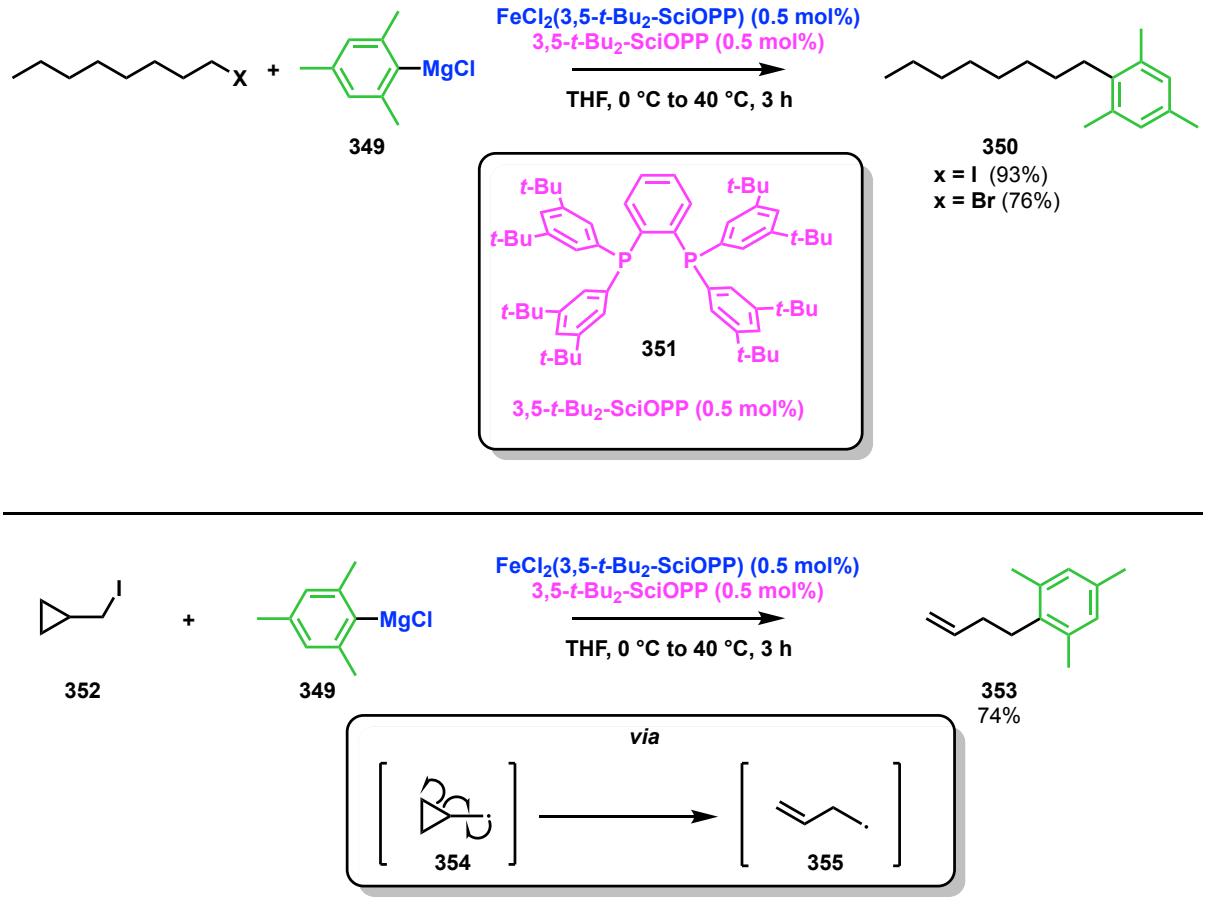


Scheme 77: Kumada-Corriu cross-coupling reaction

More recently, several iron-catalyzed Kumada-Corriu reactions have been described (Scheme 78).[121] Among them, the group of Nakamura reported the use of a bulky bidentate phosphine ligand, 3,5-(*t*-Bu)$_2$-SciOPP, for an efficient reaction (Scheme 78, eq. 1).[122] Previous methods required a large excess of ligand, such as TMEDA (tetramethylethylenediamine). The authors designed this *ortho*-phenylene-bisphosphine ligand with a peripheral steric bulk around the iron center such that the iron complex remains in a tetrahedral shape, which was believed to be the active form of the catalyst. In this way, it was possible to reduce the catalyst loading from 3 mol% to 0.5 mol%. Regarding the mechanism, the authors mentioned the plausible involvement of a radical intermediate as the reaction with iodomethylcyclopropane afforded the corresponding olefin under the standard conditions (Scheme 78, eq. 2), which might result from a radical ring-opening process.

[121] (a) R. B. Bedford, P. B. Brenner, E. Carter, P. M. Cogswell, M. F. Haddow, J. N. Harvey, D. M. Murphy, J. Nunn, C. H. Woodall, *Angew. Chem. Int. Ed.* **2014**, *53*, 1804; (b) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; (c) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; (d) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104.

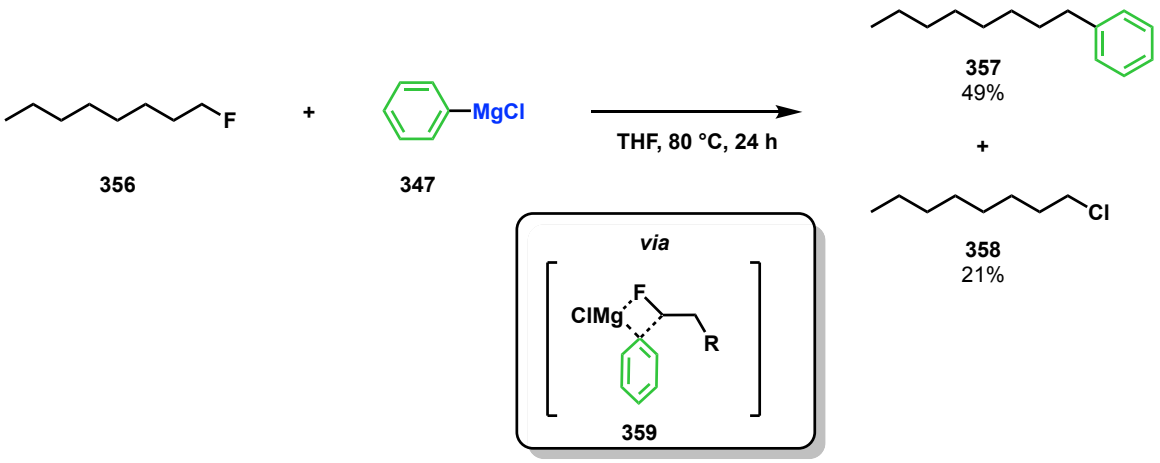
[122] T. Hatakeyama, Y.-i. Fujiwara, Y. Okada, T. Itoh, T. Hashimoto, S. Kawamura, K. Ogata, H. Takaya, M. Nakamura, *Chem. Lett.* **2011**, *40*, 1030.



Scheme 78: Iron-catalyzed Kumada-Corriu cross-coupling

Despite the strength of the carbon-fluoride bond, the group of Koga succeeded in preparing linear alkyl arenes in moderate yields from alkyl fluorides and an aryl Grignard (Scheme 79).[123] To probe the mechanism, the authors investigated whether the linear alkylarene **357** was produced from the alkyl chloride, which was formed in-situ. Although the reaction was possible with the alkyl chloride and the aryl Grignard, it was much slower, delivering the product in 7% yield. Hence, the authors ruled out the cross-coupling from the alkyl chloride as the major reaction pathway. The authors attributed this difference of reactivity to the Lewis acidic affinity of the magnesium for the fluoride of the fluoroalkanes. A first order radical mechanism was ruled out as the yield increased as the amount of reagent or reactant was increased (no S_N1 involved) and no *n*-hexadecane and *n*-octane were observed (no primary alkyl radical involved). Thus, the authors proposed a concerted mechanism. However, the addition of a radical scavenger, TEMPO, had a detrimental effect on the reaction, suggesting that a single electron transfer was involved in the reaction mechanism.

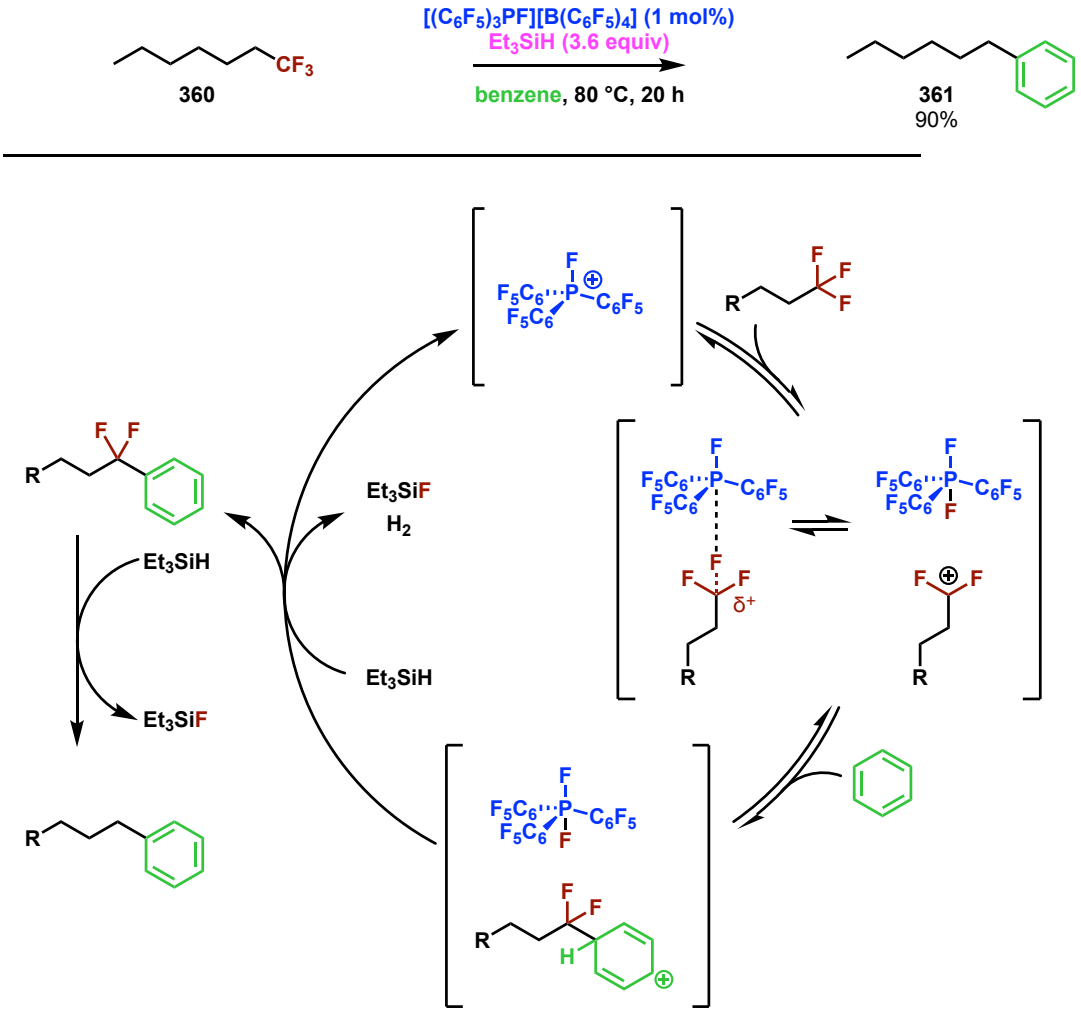
[123] K. Matsubara, T. Ishibashi, Y. Koga, *Org. Lett*. **2009**, *11*, 1765.



Scheme 79:Cross-coupling of an alkyl fluoride with an aryl Grignard

The group of Stephan has also developed a method for accessing linear alkyl arenes from the alkylation of benzene with alkanes bearing trifluoromethyl group and subsequent hydrodefluorination (Scheme 80).[124] Regarding the mechanism, the reaction begins with the activation of the trifluoromethyl group by a fluorophosphonium cation to generate a difluoro carbocation, which undergoes a subsequent electrophilic aromatic substitution. Hydride reduction of the catalyst regenerates the catalyst, while hydrodefluorination at the benzylic position affords the linear alkyl-arene product. The proposed mechanism was further confirmed as mono-fluorinated alkyl fluoride provided a mixture of linear and branched products via a hydride migration from the carbocation intermediate.

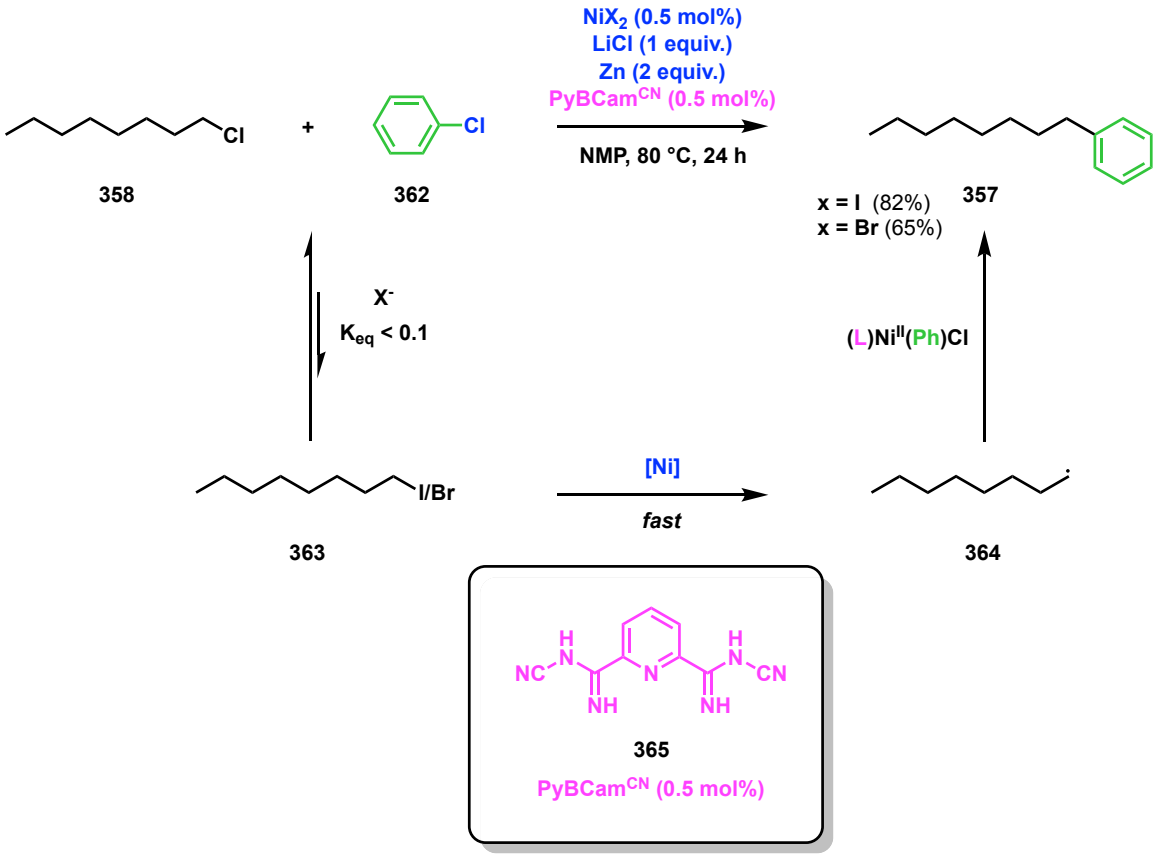
[124] (a) J. Zhu, M. Pérez, C. B. Caputo, D. W. Stephan, *Angew. Chem. Int. Ed.* **2016**, *55*, 1417; (b) C. B. Caputo, L. J. Hounjet, R. Dobrovetsky, D. W. Stephan, *Science,* **2013**, *341*, 1374.



Scheme 80: Catalytic benzylation and alkylation with subsequent hydrofluorination

For its part, the group of Weix reported the first selective nickel-catalyzed cross-electrophile coupling of aryl chlorides with primary alkyl chlorides (Scheme 81).[125] The main challenge with the activation of C-Cl bonds in cross-coupling reactions is the need for a reactivity comparable with C-Br or C-I versions of the cross-coupling reaction, without compromising the selectivity. Overcoming this dual reactivity-selectivity issue requires a catalyst that selectively reacts with the aryl chloride over the alkyl chloride and, yet, could slowly generate an alkyl radical from the alkyl chloride precursor. The authors circumvented this challenge by using salt additives in order to maintain a very low, steady-state concentration of an alkyl bromide or iodide and a uniquely selective pyridine-2,6-bis(*N*-cyanocarboxamide)-ligated nickel catalyst. The overall mechanism is still under investigation; nevertheless, the authors underlined that: (1) LiCl was essential for an efficient reduction of the nickel catalyst over the zinc surface, the role of LiCl being to prevent the formation of $ZnCl_2$ that is known for its inhibitory effect on reduction of nickel catalysts and, (2) halide exchange played a key role by increasing the reactivity of the alkyl chloride.

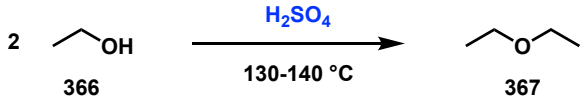
[125] S. Kim, M. J. Goldfogel, M. M. Gilbert, D. J. Weix, *J. Am. Chem. Soc.* **2020**, *142*, 9902.



Scheme 81: Nickel-catalyzed cross-coupling of aryl chlorides with primary alkyl chlorides

3.1.2. State of the art on direct alcohol substitution

Owing to the stability of the carbon-oxygen bond in aliphatic alcohols, only a few examples of direct primary alcohol substitution have been reported in the literature. A common example of this type of reaction is the synthesis of diethyl ether from the dehydration of ethanol. The formation of diethyl ether from ethanol with sulfuric acid occurs at 130-140 °C and has been known for more than 150 years (Scheme 82).[126] More recent industrial processes use catalytic amounts of metal salts such as Cs/Ge-Ɣ-Al_2O_3, Sn-Li-mordenite and Pt-Ɣ-Al_2O_3 and require high temperatures (250-400 °C) and pressures (17-34 bar).[127]

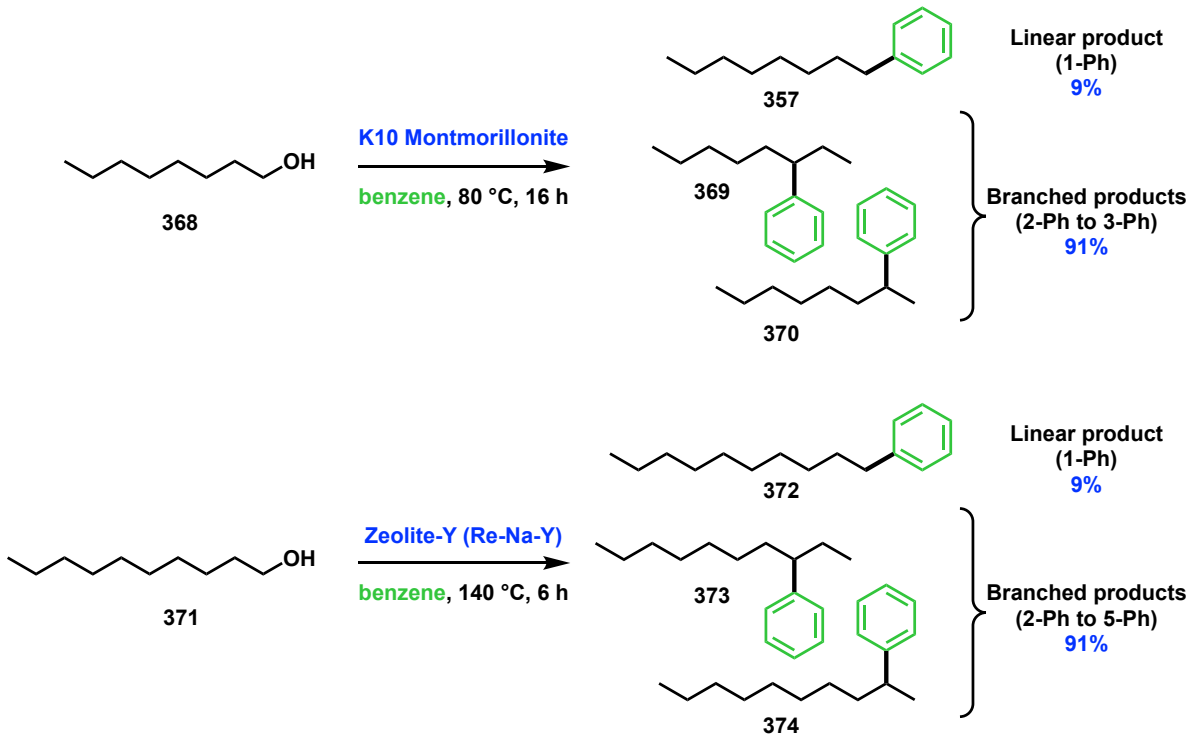


Scheme 82: Diethyl ether synthesis from ethanol

To the best of our knowledge, only two articles were published regarding the Friedel-Crafts alkylation of primary aliphatic alcohols. They both feature heterogeneous catalysis, using K10-montmorrillonite[128] and zeolite-Y[129] with benzene as the nucleophile and solvent (Scheme 83).

[126] A. W. Williamson, *Phil. Mag.* S. **1850**, *37*, 350.
[127] C. Zhang, V. J. Johnston, Patent No. US 2014/0275636 A1.
[128] O. Sieskind, P. Albrecht, *Tetrahedron Lett.* **1993**, *34,* 1197.
[129] A. R. A. S. Deshmukh, V. K. Gumaste, B. M. Bhawal, *Catal. Lett.* **2000**, *64*, 247.

In both cases, the direct alcohol substitution reaction yielding a linear product was in competition with elimination reactions, which led to the formation of branched products upon addition of benzene to the newly formed olefins. Aware of the current limitations of Friedel-Crafts reactions, we wondered whether the remarkable properties HFIP could enable Friedel-Crafts alkylations of primary aliphatic alcohols in order to exclusively provide the linear product.



Scheme 83: State of the art on direct alcohol substitution vs this work

3.2. Friedel-Crafts alkylation of primary aliphatic alcohols

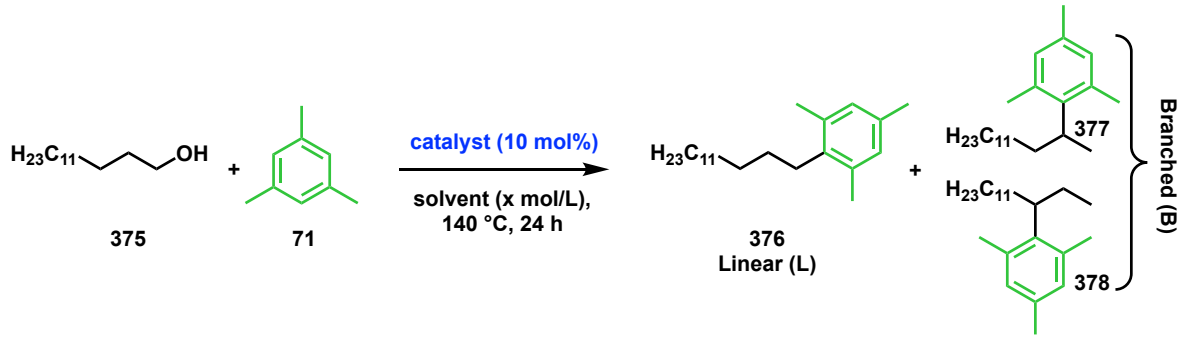
3.2.1. Reaction discovery and optimization

We began our investigation with the HFIP/TfOH system, which has proven its effectiveness in the prior chapter. 1-Tetradecanol was used as a model substrate because of its high boiling point, while mesitylene was employed as a nucleophile. The ratios of branched and linear products were estimated by the relative integration of the secondary aromatic carbons in ^{13}C

DEPT NMR. This method is unusual but given that only one signal was observed for each branched product and that all these signals came from two secondary aromatic carbons, the relaxation time should be approximately similar. It was not possible to use ^{1}H NMR to quantify the ratio between the branched and the linear products as the characteristic signals were overlapping. In this reaction, we noticed that the concentration was critical to the process. At 140 °C, a 1 M concentration of alcohol led to a mixture of linear and branched products (Table 6, entry 1), while lowering the concentration to 0.25 M led only to the linear product (Table 6, entry 2). We then screened other Lewis and Brønsted acids. Neither $FeCl_3$, which was an efficient catalyst for tertiary propargylic alcohols, nor the weak Brønsted acid TFA furnished the linear product or branched products (Table 6, entries 3 and 5). $Bi(OTf)_3$ provided a similar selectivity as triflic acid, albeit in a lower yield (Table 6, entry 4). We assumed that, under the reaction conditions, triflic acid might be easily formed *in-situ* via hydrolysis of $Bi(OTf)_3$. In these circumstances, we limited our studies to triflic acid.

The influence of the solvent was then studied. When the reaction was conducted in isopropanol, no reaction was observed (Table 6, entry 6). The use of other fluorinated solvents such as trifluoroethanol and hexafluoro-2-methyl-2-propanol was also detrimental to both yield and selectivity (Table 6, entries 7 and 8). Other solvents such as chloroform and nitromethane, the latter known for its H-bonding properties, did not improve the reactivity either (Table 6, entries 10 and 11).[130] When the nucleophile was used as a solvent, the target product was obtained in moderate yield and selectivity (Table 6, entry 9). Initial attempts to conduct the reaction at a lower temperature using the optimal conditions (HFIP/TfOH at 0.25 M) furnished a mixture of branched and linear product.

[130] M. Dryzhakov, M. Hellal, E. Wolf, F. C. Falk, J. Moran, *J. Am. Chem. Soc.* **2015***, 137,* 9555.



Entry	Catalyst	Solvent	[mol/L]	Ratio L/B[b]	Yield[c]
1	TfOH	HFIP	1	58:42	56%
2	TfOH	HFIP	0.25	>99:1	56%
3	$FeCl_3$	HFIP	0.25	-	<1%
4	$Bi(OTf)_3$	HFIP	0.25	>99:1	47%
5	TFA	HFIP	0.25	-	<1%
6	TfOH	*i*-PrOH	0.25	-	<1%
7	TfOH	$(CF_3)CH_3OH$	0.25	47:53	43%
8	TfOH	CH_3CH_2OH	0.25	42:58	24%
9	TfOH	Mesitylene	0.25	71:29	33%
10	TfOH	Chloroform	0.25	87:13	<5%
11	TfOH	Nitromethane	0.25	41:59	<5%

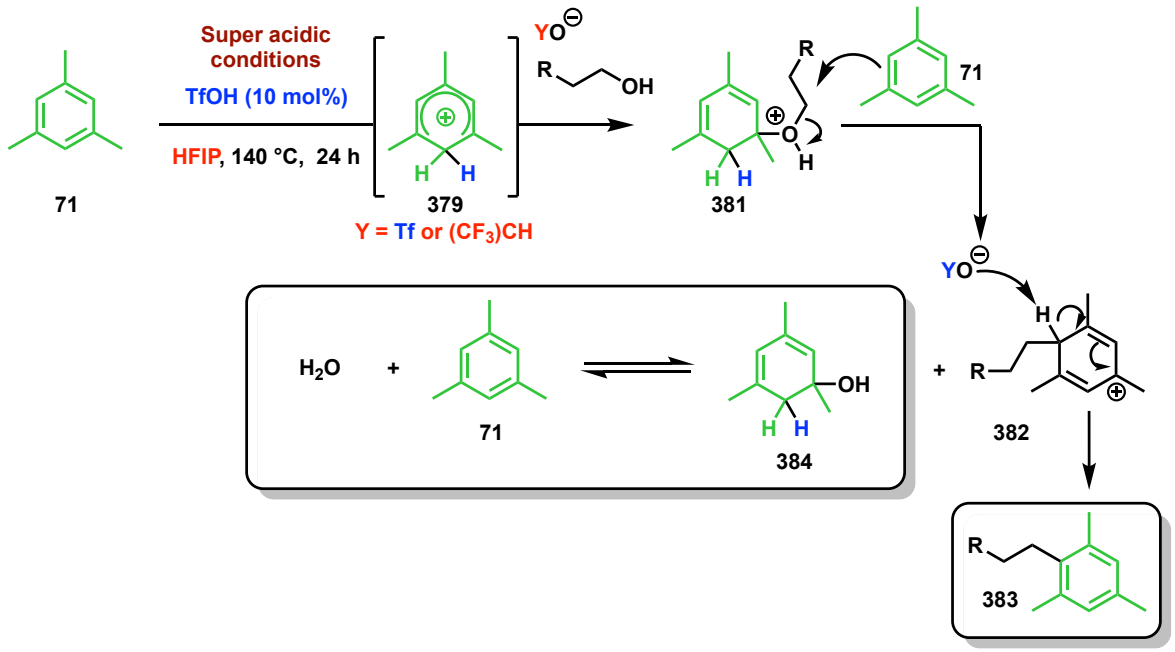
Table 6: Optimization studies for the alkylation of 1-tetradecanol with mesitylene

[a] All reactions were conducted in the presence of 5 equivalents of mesitylene in a sealed Pyrex® high pressure reaction tube. [b] Ratio estimated by ^{13}C DEPT NMR from the isolated mixture. [c] Isolated yields after flash column chromatography.

3.2.3. Mechanistic proposal for the Friedel-Crafts alkylation of aliphatic alcohols

Primary aliphatic alcohols do not undergo nucleophilic substitution *via* an S_N1 pathway because of the extreme instability of primary carbocations. In addition to the difficulty of the carbocation formation, the C-O bond energy is more than 200 kJ/mol higher than that of the C-F bond, the least likely leaving group among the halogens. As the formation of the desired product was observed when the reaction was conducted in mesitylene, our first assumption was that the aryl nucleophile acts as an activating group and pre-activates the alcohol into a phenol-ether moiety (Scheme 84). We hypothesized that this phenol-ether moiety would be

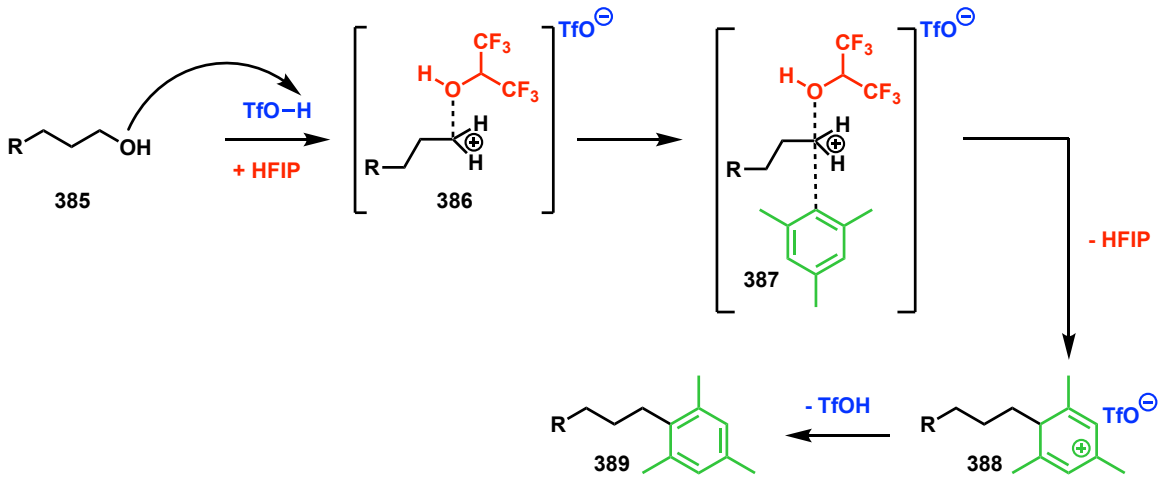
a better leaving group than the starting primary alcohol. Nevertheless, we did not observe by ^{1}H NMR or GC-MS the formation of the enol product **384** which should be formed as a byproduct of the reaction. As the enol ether byproduct could easily re-aromatize into mesitylene under acidic conditions, further computational studies would be required to rule out this mechanism.



Scheme 84: A plausible mechanism for the Friedel-Crafts alkylation of aliphatic alcohols

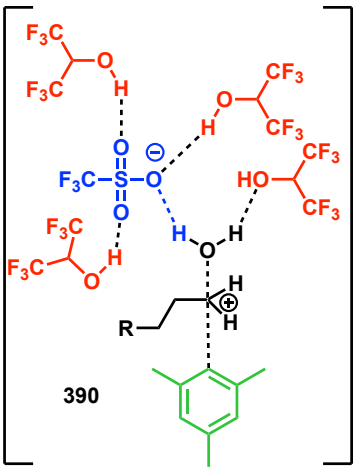
Other mechanisms have been considered using DFT calculations (carried out by Prof. Christopher Rowley):

(1) Under standard conditions, the beginnings of the formation of a primary aliphatic carbocation would presumably be accompanied by a nearly synchronous 1,2-proton shift to form a secondary carbocation, which would yield the standard branched product for a typical dissociative Friedel-Crafts mechanism. It was found by DFT that the primary carbocation could be stabilized by coordination of an explicit HFIP molecule (Scheme 85). This complex can react with the arene through a mechanism where the arene starts to form a bond from the opposite face, displacing the HFIP molecule and forming the Wheland intermediate. Modeling this reaction for butanol and mesitylene as substrates, it was found that the Gibbs energy of activation of this step is 50.7 kcal/mol, largely because the carbocation-HFIP complex is unstable relative to the alcohol, elevating the reaction barrier.



Scheme 85: Substitution mechanism for primary aliphatic alcohols involving carbocation stabilization by a molecule of HFIP

(2) The ability of HFIP to facilitate proton transfer reactions through hydrogen bonding interactions presents an alternative mechanism, where proton transfer to the hydroxyl group and the formation of the bond with the arene occur simultaneously (Scheme 86). In this mechanistic model, a molecule of triflic acid, stabilized by hydrogen bonds from explicit HFIP molecules, transfers a proton to the hydroxyl group of butanol while mesitylene attacks from the opposite face of the alcohol centre. The proton transfer occurs early in this mechanism, such that the protonated hydroxyl group has begun to dissociate from the alcohol to form a water molecule in the transition state. The Gibbs energy of activation energy for this mechanism was calculated to be 20.6 kcal/mol.



Scheme 86: Concerted mechanism

(3) An alternative mechanism where a protonated cluster of HFIP transfers the proton was also considered. A similar transition state structure was identified, where a proton is transferred to the hydroxyl group of the alcohol from a protonated cluster of 4 HFIP molecules. The transition state geometry is otherwise similar to that of the concerted mechanism where triflic acid is the proton donor. The calculated activation energy is higher for this mechanism (48.6 kcal/mol), although the mixed continuum/explicit solvent model used to represent the HFIP may be underestimating the significance of HFIP-mediated proton transfer.

3.2.4 Stability of branched and linear products

To test the stability of linear and branched products under the standard reaction conditions, three control experiments were carried out with (1) the linear product, (2) the mixture of branched products and (3) the mixture of linear and branched products (Figure 7). We observed that only the linear product remained stable after 8 hours. From the above information, we deduced that, under the standard conditions, the arylation was reversible in the case of branched products, leading to the formation of oligomers over time, and irreversible in the case of the linear product (Scheme 87). Indeed, the retro-hydroarylation of branched products leads to a secondary carbocation, which is much more stable than the formation of a primary carbocation resulting from the retro-hydroarylation of a linear product. Thus, while only the linear product was isolated under the optimized reaction conditions, we cannot rule out that some branched products were not formed during the course of the reaction.

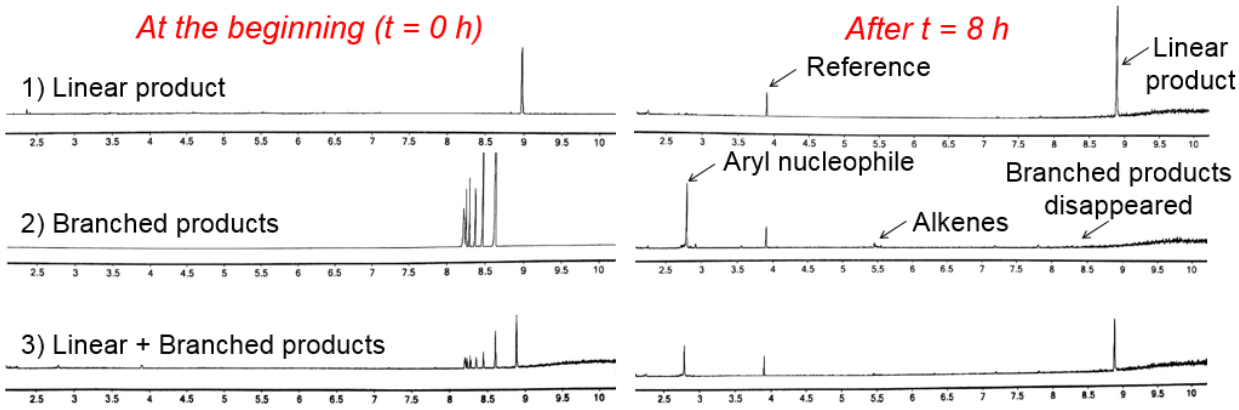
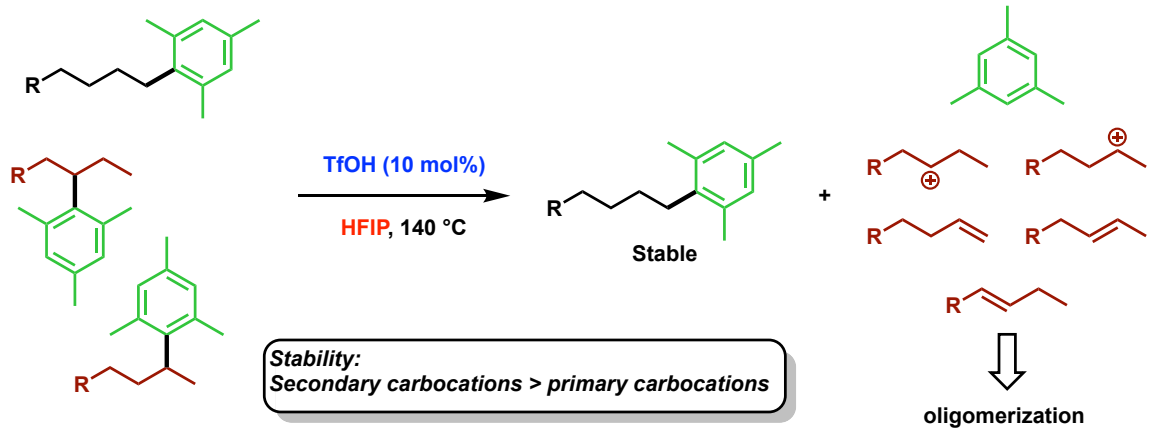


Figure 7: GC-experiment, stability of linear and branched products under standard reaction conditions

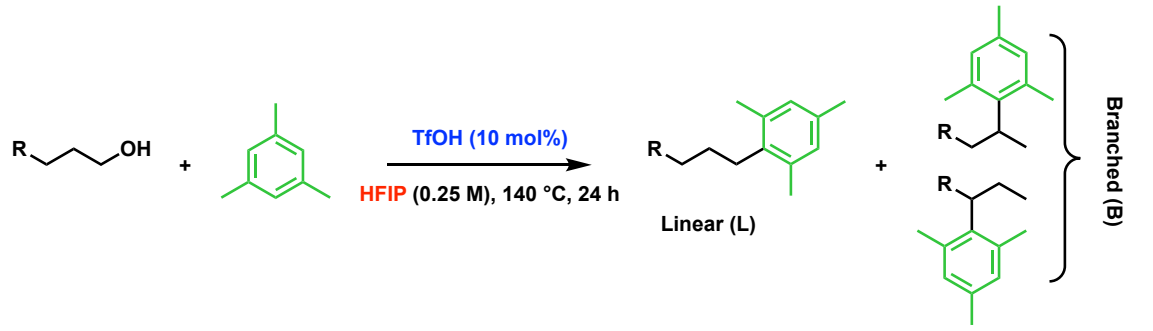


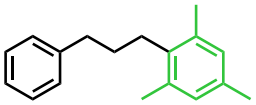
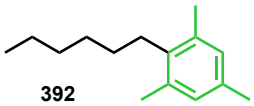
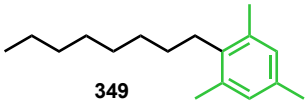
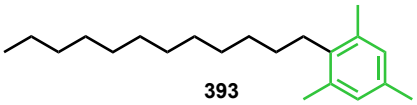
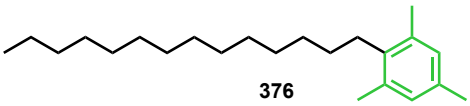
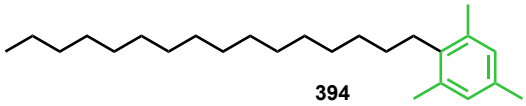
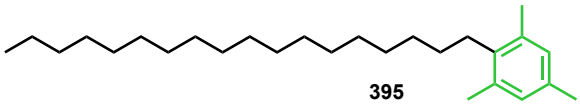
Scheme 87: Stability of branched and linear products

3.2.5. Scope of arylated primary aliphatic alcohols

We then explored the scope of the transformation with various primary aliphatic alcohols under the optimized reaction conditions (Scheme 88). As above, only the formation of the linear product was obtained. The longer the aliphatic chain, the better was the yield. For all

reactions, complete conversion of the starting material was observed. During the reaction, the reaction mixture took on a yellow-brown color and a broad signal was observed by ^{1}H NMR in the aliphatic region suggesting the formation of oligomers. We assumed that dehydration (elimination reaction) of the starting primary alcohol and oligomerization competed with the direct substitution of the alcohol by the aryl nucleophile. It would be interesting to investigate further how to inhibit those side reactions to obtain better yields.

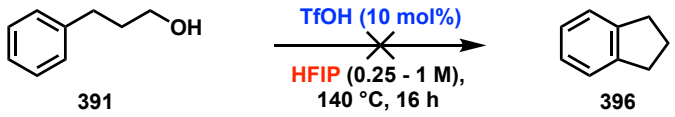


	Ratio L/B	Yield[b]
 391	>99 : 1	21%[c] (44%)[d]
 392	>99 : 1	32%
 349	>99 : 1	47%
 393	>99 : 1	42%
 376	>99 : 1	56%
 394	>99 : 1	79%
 395	>99 : 1	79%

Scheme 88: Scope of primary aliphatic alcohols

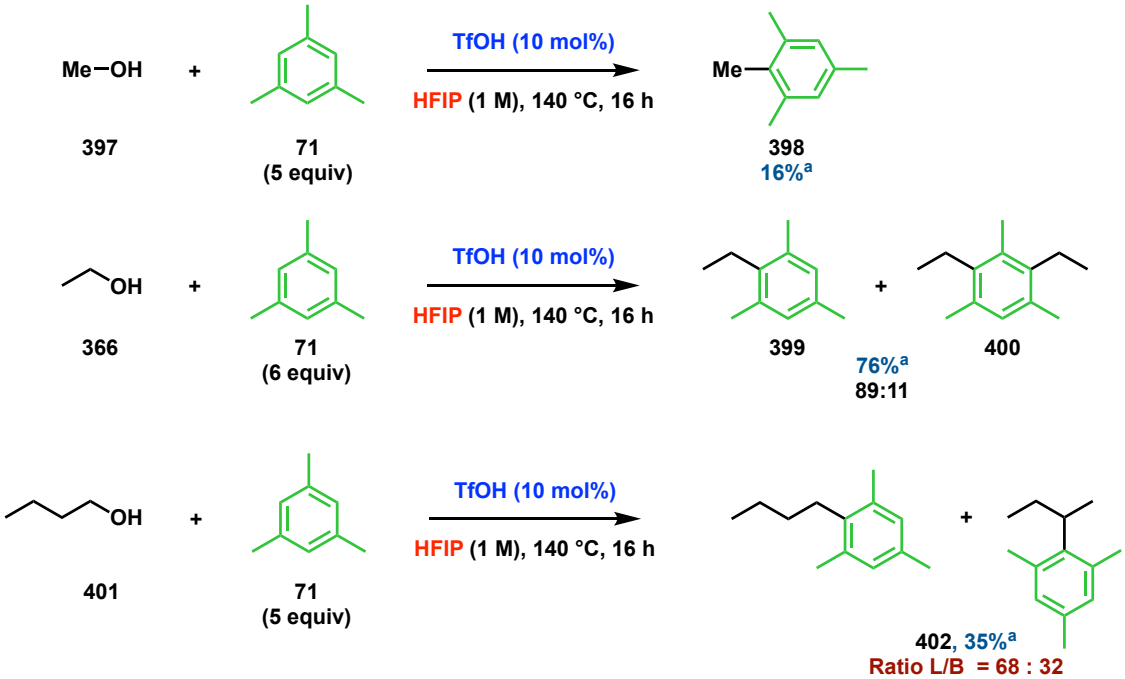
[a]All reactions were conducted in the presence of 5 equivalents of mesitylene in a sealed Pyrex® high pressure reaction tube. [b] Isolated yield after flash column chromatography. [c] Concentration = 1 M. [d] Concentration = 0.25 M.

Regarding the reactivity of 3-phenylpropan-1-ol **391**, we hypothesized that the moderate yield was due to a competitive intramolecular cyclization. Thus, 3-phenylpropan-1-ol **391** was subjected to the standard reaction conditions in the absence of nucleophile (Scheme 89). However, the corresponding indane product was neither observed by NMR nor by GC-MS. Therefore, this moderate yield might be explained by an enhanced acidity of the hydrogens connected to the C-2 carbon due to the electron rich π system of the aromatic ring, which might trigger elimination reactions.



Scheme 89: Control experiment with 3-phenylpropan-1-ol

Primary alcohols with a short aliphatic chain displayed a different behavior than those with a long aliphatic chain (Scheme 90). As an example, a low yield was obtained with methanol. This might be due to a higher proportion of the alcohol residing in the gas phase with respect to the liquid phase inside the high-pressure reaction tube. Ethanol furnished relatively high yields; nevertheless, because of its limited steric hindrance, a mixture of *bis*-alkylated and *mono*-alkylated products was obtained. On the other hand, a lower selectivity was obtained with butanol with a 68:32 linear/branched ratio.



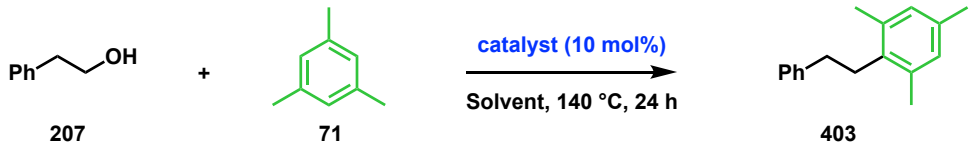
Scheme 90: Substitution of primary alcohols with short alkyl chains

[a] ^{1}H NMR yield with hexamethyldisiloxane as external standard.

3.3. Friedel-Crafts alkylation of phenyl ethanol derivatives

3.3.1. Optimization of Friedel-Crafts reaction on phenyl ethanol

An interesting feature of this transformation was the excellent efficiency of the combination TfOH/HFIP for the activation of phenyl ethanol substrates (Table 7). At a 1 M concentration, phenyl ethanol led to the arylated product **403** in 98% yield. Regarding the screening of other catalysts and solvents, the same trends as with 1-tetradecanol were observed in terms of reactivity.



207 71 403

Entry	Catalyst	Solvent (1 M)	Yield[b]
1	TfOH	HFIP	98%
2	$FeCl_3$	HFIP	>1%
3	$BiOTf_3$	HFIP	75%
4	TFA	HFIP	>1%
5	TfOH	*i*-PrOH	>1%
6	TfOH	$(CF_3)_2CCH_3OH$	88%
7	TfOH	CH_3CH_2OH	29%
8	TfOH	Mesitylene	46%
9	TfOH	Chloroform	60%
10	TfOH	Nitromethane	18%

Table 7: Optimization studies for the alkylation of phenyl ethanol with mesitylene

[a]All reactions were conducted in the presence of 5 equivalents of mesitylene in a sealed Pyrex® high pressure reaction tube. [b] Isolated yield after flash column chromatography.

3.3.2. Mechanistic proposal for the Friedel-Crafts alkylation of phenyl ethanol

The difference of reactivity, notably in terms of yields, between primary aliphatic alcohols bearing a long alkyl chain and phenyl ethanol might be explained by the formation of a well-

established phenonium ion.[131] Back bonding effect from the LUMO of the phenyl cation moiety to the HOMO of the ethylene fragment is responsible for the orthogonal nature of the *ipso*-carbon (Figure 8). These orbital interactions make the phenonium ion more stable than a hypothetic primary carbocation. Once the phenonium ion is formed, a subsequent nucleophilic addition of mesitylene will generate a Wheland intermediate (Scheme 91). Finally, re-aromatization of this species will lead to the corresponding linear adduct.

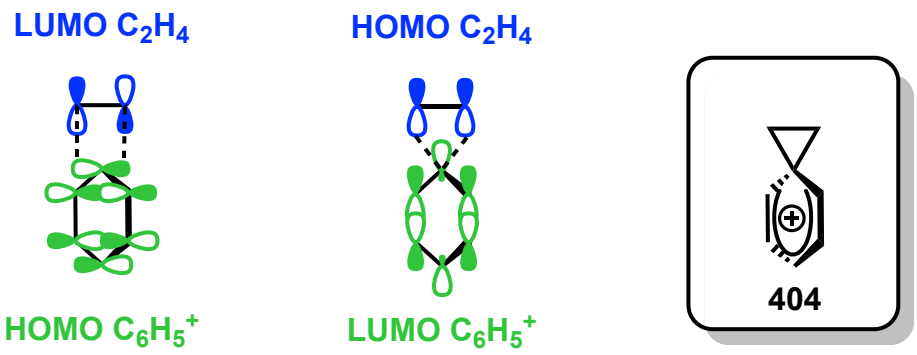
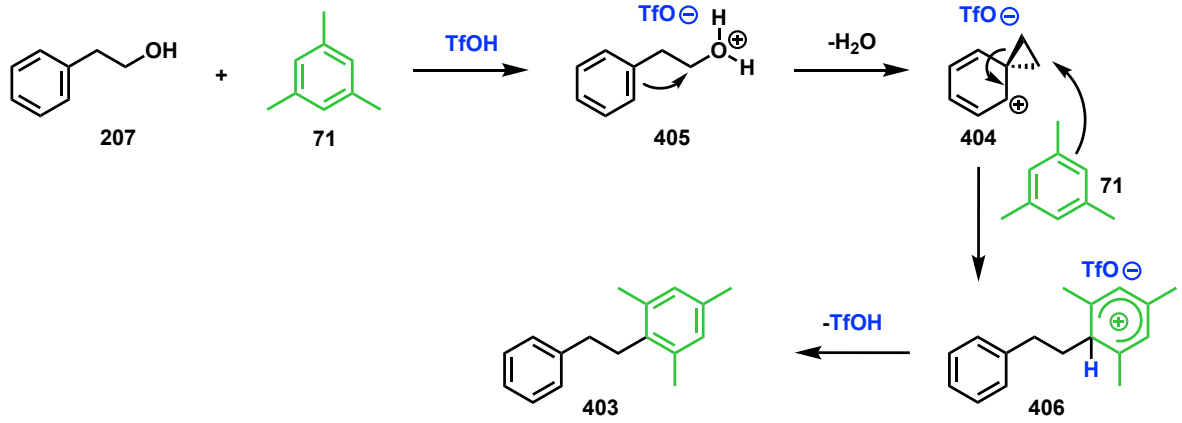
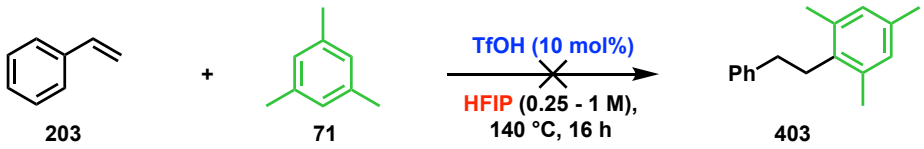


Figure 8: The orthogonal ipso-carbon in the phenonium ion



Scheme 91: Proposed mechanism for Friedel-Crafts alkylation with phenyl ethanol

When phenyl ethanol was used as a substrate, an alternative reaction pathway might be that the branched product underwent a retro-arylation leading to styrene **203**, which subsequently undergoes an anti-Markovnikov hydroarylation to give a linear product. To definitively rule out this unlikely pathway, styrene was subjected to the standard reaction conditions (Scheme 92).

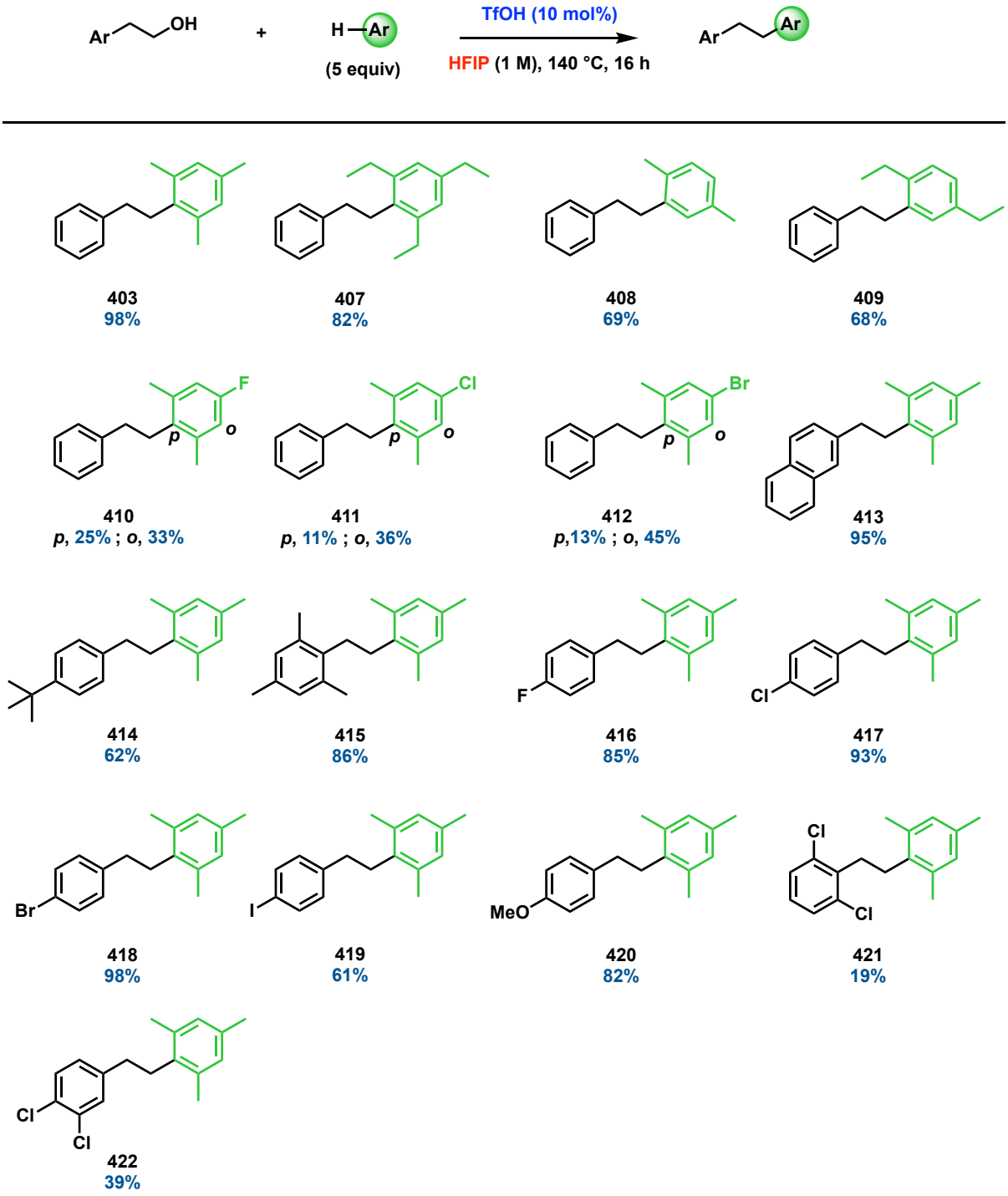


Scheme 92: Control experiment with styrene

[131] E. del Río, M. I. Menéndez, R. López, T. L. Sordo, *J. Phys. Chem.* **2000,** *104,* 5568.

3.3.3. Scope of arylated phenyl ethanol derivatives

Encouraged by this initial result, the scope of arenes and phenyl ethanol derivatives was explored (Scheme 93). The bulkier 1,3,5-triethylbenzene **407** was also well tolerated for this reaction. Other less nucleophilic arenes such as *p*-xylene **408** and 1,4-diethylbenzene **409** delivered the products in good yields. Not surprisingly, halogenated nucleophiles such as 3,5-dimethyl-1-fluorobenzene **410**, 3,5-dimethyl-1-chlorobenzene **411** and 3,5-dimethyl-1-bromobenzene **412** furnished two regioisomers in moderate yields. Replacing the phenyl group by a naphthalene group **413** had no impact on the reactivity, providing the corresponding linear adduct in 95% yield. The reaction proved to be compatible with the introduction of electron-donating and moderately electron-withdrawing groups at the *para*-position (yields up to 98%). On the other hand, a significant decrease of the reactivity was observed with *bis*-halogenated aryl substituents as dechlorination was observed during the course of the reaction.

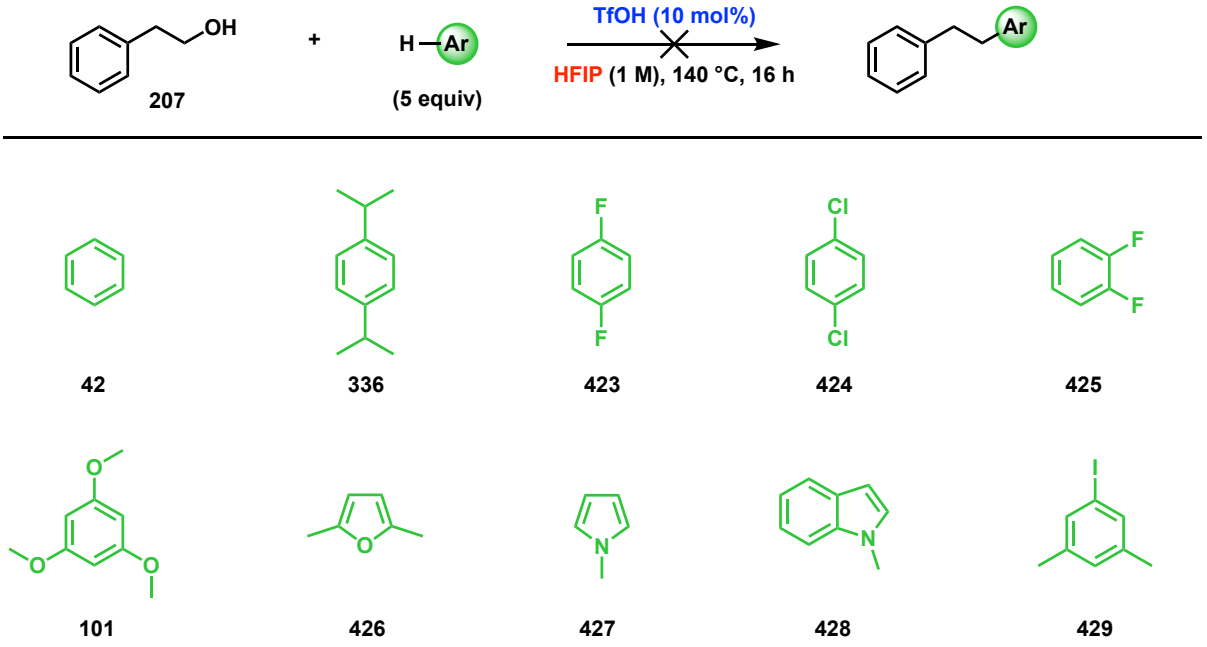


Scheme 93: Scope of phenyl ethanol derivatives and arene nucleophiles

[a]All reactions were conducted in the presence of 5 equivalents of mesitylene in a sealed Pyrex® high pressure reaction tube and all isolated yields were obtained after flash column chromatography.

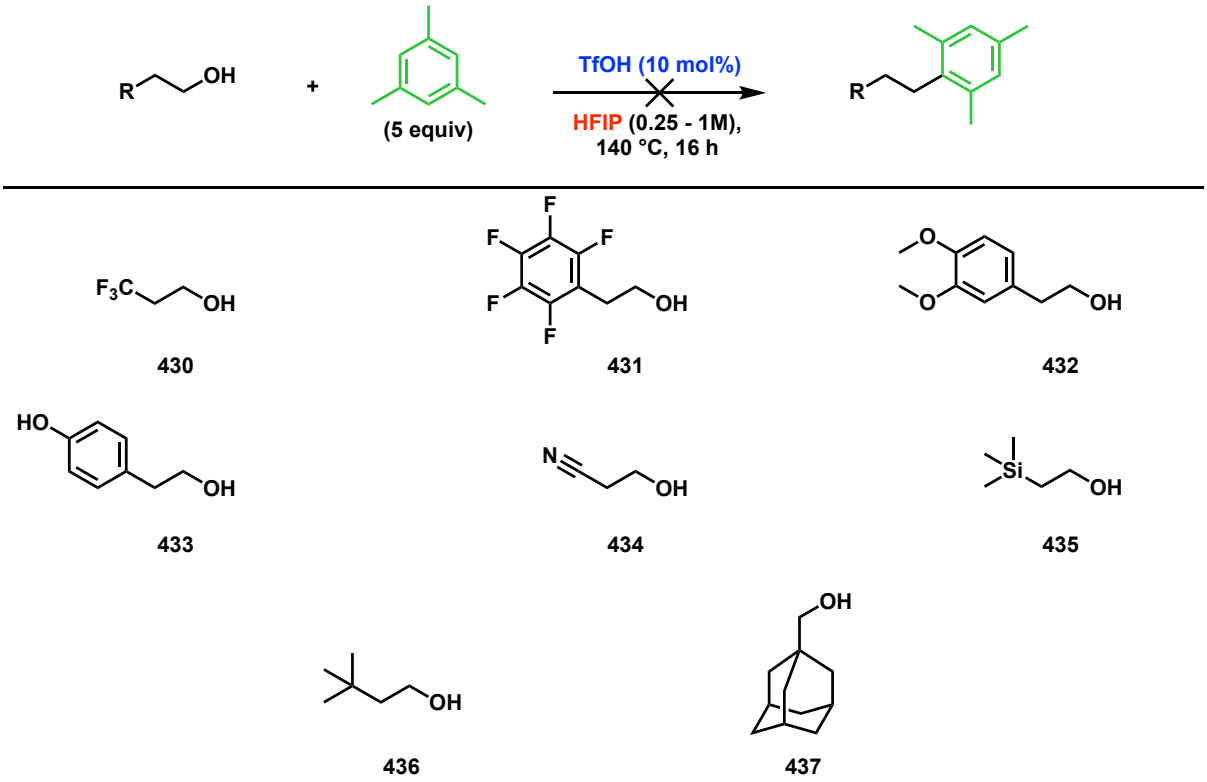
Unfortunately, several nucleophiles were not compatible with this transformation (Scheme 94), either because they are not nucleophilic enough (benzene, 1,4-difluorobenzene, 1,4-dichlorobenzene and 1,2-difluorobenzene), too sterically hindered (1,4-diisopropylbenzene) or unstable under the highly acidic reaction conditions (2,5-dimethylfurane, *N*-methylpyrrole and *N*-methylindole). In the case of 1,3,5-trimethoxybenzene, we suspect that, since this compound can be easily protonated (cf introduction on hydroarylation of cyclopropanes), the

retro-Friedel-Crafts reaction could easily take place to re-generate the alcohol substrate. In the case of 3,5-dimethyl-1-iodobenzene, this compound underwent a dehalogenation under the reaction conditions as the reaction turned deep purple and iodide crystals were observed in the reaction media.



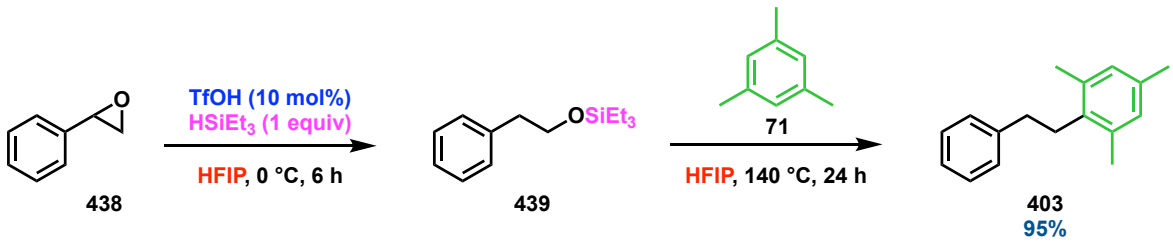
Scheme 94: Unsuccessful Friedel-Crafts alkylations

Other phenyl ethanol derivatives and substituted aliphatic alcohols were screened (Scheme 95). 3-Trifluoropropan-1-ol **430** did not lead to the expected product due to the depolarization of the C-OH bond owing to the proximity of an electron withdrawing group. Not surprisingly, pentafluoro-substituted phenyl ethanol **431-432** did not lead to the corresponding product as the nucleophilicity of the aromatic ring was lowered due to the presence of several electron withdrawing groups, thus reducing the propensity of this alcohol to form a stabilized phenonium ion to enable the reaction. Starting arylethanol derivatives substituted with methoxy and hydroxy group did not afford the corresponding product, likely because of their basicity and ability to interact with HFIP networks. Alcohols bearing either a nitrile and silyl moiety did not provide the target products as they readily transformed into the corresponding alkenes and oligomerize. In the case of adamantane derivative **437**, a complex mixture of products was obtained.



Scheme 95: Unsuccessful Friedel-Crafts alkylations

Our studies on the dehydrative Friedel-Crafts reactions of phenyl ethanol derivatives inspired us to develop an alternative way to access diaryl compounds, starting from the epoxide (Scheme 96). This one-pot reaction was achieved in two steps: (1) reduction of the epoxide using triethylsilane and, then, (2) a Friedel-Crafts alkylation of the silyl ether with mesitylene. Gratifyingly, the target compound was obtained in high yield (95%).



Scheme 96: Epoxide ring-opening and subsequent Friedel-Crafts alkylation

3.4. Summary

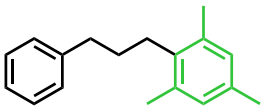
In summary, we described a simple and highly selective method for the Friedel-Crafts alkylation of primary aliphatic alcohols, using a combination of TfOH and HFIP. Preliminary DFT calculations support a S_N2 mechanism. The combination of TfOH with HFIP was particularly effective for the substitution of phenylethanol derivatives, paving the way for more extensive access to diarylalkanes. The difference in reactivity between simple aliphatic alcohols and phenyl ethanol derivatives was attributed to the formation of a stable cyclopropenium ion in the latter case. To date, this report is the first example of a reliable Brønsted acid-catalyzed Friedel-Crafts alkylation of primary aliphatic alcohols, only leading to

linear products. This selectivity has been attributed to a lack of stability of the branched products under the reaction conditions, rendering our method well-suited to isolate the linear products when compared to methods that furnish a mixture of linear and branched products.

3.5. Experimental data

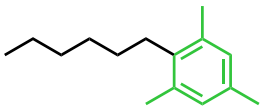
All Friedel-Crafts reactions were performed in 15 mL ACE pressure reaction tubes under an atmosphere of air. Elevated temperatures were achieved by way of a silicon oil bath and heating plates equipped with a thermocouple. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 µm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel 60 F254 (Merck), cut to size. ^{1}H NMR spectra were recorded on a Bruker UltraShield Plus 400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard (residual $CHCl_3$ at 7.26 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker UltraShield Plus 400 (100 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F NMR spectra were recorded on a Bruker UltraShield Plus 400 (376.5 MHz) spectrometer at ambient temperature and are reported in ppm. Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, qd = quartet of doublets, dt = doublet of triplets, dm = doublet of multiplets, td = triplet of doublets, quintd = quintet of doublets), coupling constants (in Hz) and integration. High resolution mass spectrometry (HRMS) analysis was performed on the instrument GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer). **Materials:** All commercial materials were purchased from Sigma-Aldrich and FluoroChem, and were used as received, without further purification.

General Procedure: A 15 mL ACE pressure reaction tube equipped with a stir bar was charged with the requisite alcohol (10 mmol), nucleophile (5 equiv) and HFIP. TfOH (10 mol%) was then added, the tube capped and heated at 140 ^{o}C for 24 h. After cooling to room temperature, the reaction mixture was evaporated then purified by chromatography column using (40-63 µm) silica gel and ethyl acetate/petroleum ether eluent system. The author states that the reproduction of these reactions may require small modifications depending on the thickness of the tube and the stability of the heating system.

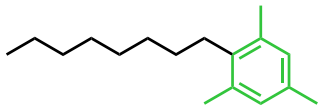


1,3,5-Trimethyl-2-(3-phenylpropyl)benzene 391 was prepared according to *General Procedure* from 3-phenyl-1-propanol (264 µL, 1.94 mmol) and mesitylene (1.35 mL, 9.71 mmol, 5 equiv) with 17.2 µL (0.194 mmol) of TfOH, in 1.94 mL of HFIP. The reaction mixture was stirred at 140 °C during 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 101 mg (21% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33–7.29 (m, 2H), 7.24–7.19 (m, 3H), 6.83 (s, 2H), 2.76 (t, *J* = 7.6 Hz, 2H),

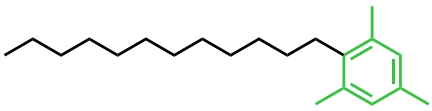
2.63–2.59 (m, 2H), 2.26 (s, 3H), 2.24 (s, 6H), 1.84–1.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.4, 136.3, 136.0, 135.0, 129.0, 128.5, 128.4, 125.9, 36.5, 30.8, 29.1, 20.9, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{18}H_{22}$ [$M^{+\cdot}$]: calculated 238.17160; found 238.17170 (0.2 ppm).



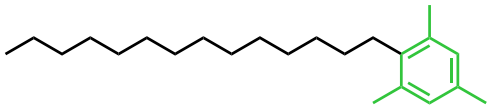
2-Hexyl-1,3,5-trimethylbenzene 392 was prepared according to *General Procedure* from hexan-1-ol (63.9 µL, 0.509 mmol) and mesitylene (0.35 mL, 2.5 mmol, 5 equiv) with 4.5 µL (0.051 mmol) of TfOH in 2.04 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 33.6 mg (32 % yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.85 (s, 2H), 2.63–2.54 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H), 1.50–1.41 (m, 4H), 1.39–1.32 (m, 4H), 0.97–0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9, 136.0, 134.8, 128.9, 31.9, 30.1, 29.6, 29.5, 22.8, 20.9, 19.8, 14.3. HRMS (APPI-Orbitrap): *m/z* for $C_{15}H_{24}$ [$M^{+\cdot}$]: calculated 204.1873; found 204.1866 (-3.1 ppm).



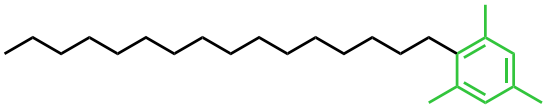
1,3,5-Trimethyl-2-octylbenzene 349 was prepared according to *General Procedure* from octan-1-ol (121 µL, 0.768 mmol) and mesitylene (0.53 mL, 3.8 mmol, 5 equiv) with 6.8 µL (0.076 mmol) of TfOH, in 3.1 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 84.4 mg (47% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.84 (s, 2H), 2.60–2.54 (m, 2H), 2.29 (s, 6H), 2.26 (s, 3H), 1.37–1.26 (m, 11H), 0.96–0.87 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9, 136.0, 134.8, 128.9, 32.1, 30.4, 29.6 (2C), 29.5 (2C), 22.8, 20.9, 19.8, 14.3. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{28}$ [$M^{+\cdot}$]: calculated 232.2186; found 232.2176 (-4.2 ppm).



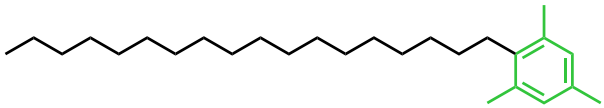
2-Dodecyl-1,3,5-trimethylbenzene 393 was prepared according to *General Procedure* from dodecan-1-ol (103 mg, 0.554 mmol) and mesitylene (0.39 mL, 2.8 mmol, 5 equiv) with 4.9 µL (0.055 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 67.3 mg (42% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (s, 2H), 2.60–2.48 (m, 2H), 2.28 (s, 6H), 2.25 (s, 3H), 1.27 (s, 19H), 0.91–0.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.7, 135.8, 134.7, 128.8, 32.0, 30.3, 29.7 (4C), 29.5 (2C), 29.4 (2C), 22.7, 20.8, 19.7, 14.1. HRMS (APPI-Orbitrap): *m/z* for $C_{21}H_{36}$ [$M^{+\cdot}$]: calculated 288.2812; found 238.2800 (-4.0 ppm).



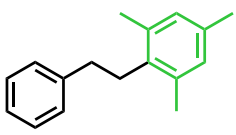
1,3,5-Trimethyl-2-tetradecylbenzene 376 was prepared according to *General Procedure* from tetradecan-1-ol (160 mg, 0.746 mmol) and mesitylene (0.52 mL, 3.7 mmol, 5 equiv) with 6.6 µL (0.075 mmol) of TfOH in 3.0 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 133.4 mg (56% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (s, 2H), 2.59–2.53 (m, 2H), 2.29 (s, 6H), 2.25 (s, 3H), 1.27 (s, 27H), 0.93–0.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9, 136.0, 134.8, 128.9, 32.1, 30.4, 29.9–29.8, 29.7, 29.6, 29.5 (2C), 22.9, 20.9, 19.9, 14.3. (6 carbons hidden)



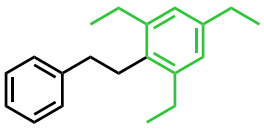
2-Hexadecyl-1,3,5-trimethylbenzene 394 was prepared according to *General Procedure* from hexadecan-1-ol (138 mg, 0.569 mmol) and mesitylene (0.40 mL, 2.8 mmol, 5 equiv) with 5.0 µL (0.057 mmol) of TfOH in 2.3 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 154.0 mg (79% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (s, 2H), 2.59–2.53 (m, 2H), 2.29 (s, 6H), 2.25 (s, 3H), 1.27 (s, 27H), 0.92–0.87 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9, 136.0, 134.8, 128.9, 32.1, 30.4, 29.9–29.8, 29.7, 29.6, 29.5 (2C), 22.9, 20.9, 19.9, 14.3. (8 carbons hidden)



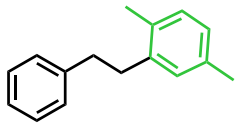
1,3,5-Trimethyl-2-octadecylbenzene 395 was prepared according to *General Procedure* from octadecan-1-ol (173 mg, 0.640 mmol) and mesitylene (0.45 mL, 3.2 mmol, 5 equiv) with 5.7 µL (0.064 mmol) of TfOH in 2.6 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether) gave 188.0 mg (79% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.84 (s, 2H), 2.60–2.53 (m, 2H), 2.29 (s, 6H), 2.26 (s, 3H), 1.28 (s, 31H), 0.93–0.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.9, 136.0, 134.8, 128.9, 32.1, 30.4, 29.9–29.8 (m), 29.7, 29.6, 29.5 (2C), 22.9, 20.9, 19.9, 14.3. (10 carbons hidden)



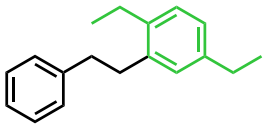
1,3,5-Trimethyl-2-phenethylbenzene 207 was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and mesitylene (1.54 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 488.1 mg (98% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41–7.37 (m, 2H), 7.33–7.27 (m, 3H), 6.94 (s, 2H), 2.96 (dd, *J* = 11.4, 5.4 Hz, 2H), 2.82 (dd, *J* = 10.8, 6.0 Hz, 2H), 2.40 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.4, 136.1, 135.6, 135.3, 129.1, 128.6, 128.4, 126.1, 35.7, 31.9, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{20}$ $[M^+]$: calculated 223.14826; found 223.4830 (0.6 ppm).



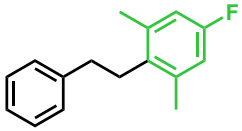
1,3,5-Triethyl-2-phenethylbenzene 407 was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and 1,3,5-triethylbenzene (2.08 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140°C during 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 482.3 mg (82% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37–7.33 (m, 2H), 7.3–7.29 (m, 2H), 7.26 (d, *J* = 4.7 Hz, 1H), 6.95 (s, 2H), 2.96–2.91 (m, 2H), 2.81–2.77 (m, 2H), 2.74 (q, *J* = 7.5 Hz, 4H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.3 –1.25 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 142.5, 142.3, 142.1, 134.4, 128.6, 128.3, 126.1, 126.0, 37.5, 30.7, 28.7, 26.1, 16.0, 15.7. HRMS (APPI-Orbitrap): *m/z* for $C_{20}H_{25}$ $[M-H]^+$: calculated 265.1962; found 265.1950 (-4.9 ppm).



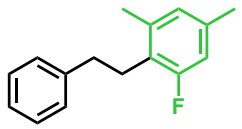
1,4-Dimethyl-2-phenethylbenzene 408 was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and *p*-xylene (1.36 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 318.7 mg (69% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34–7.29 (m, 2H), 7.24–7.22 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 6.97 – 6.94 (m, 1H), 2.86 (s, 4H), 2.31 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 142.3, 140.0, 135.5, 132.9, 130.2, 129.7, 128.5 (2C), 126.9, 126.1, 37.0, 35.7, 21.1, 18.9. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{17}$ $[M-H]^+$: calculated 209.1336; found 209.1327 (-4.3 ppm).



1,4-Diethyl-2-phenethylbenzene 409 was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and 1,4-diethylbenzene (1.72 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 358.9 mg (68% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.35–7.30 (m, 2H), 7.26–7.21 (m, 3H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.0 –7.01 (m, 2H), 2.95–2.87 (m, 4H), 2.70–2.59 (m, 4H), 1.26–1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 141.8, 139.3, 139.2, 128.9, 128.5 (3C), 126.1, 125.9, 37.9, 35.1, 28.6, 25.3, 15.8, 15.6. HRMS (APPI-Orbitrap): *m/z* for $C_{18}H_{21}$ $[M-H]^+$: calculated 237.1649; found 237.1639 (-4.1 ppm).

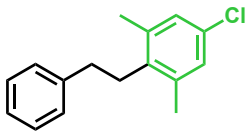


5-Fluoro-1,3-dimethyl-2-phenethylbenzene 410-*p* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and fluoro-*m*-xylene (1.39 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 124.4 mg (25% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34–7.30 (m, 2H), 7.24–7.20 (m, 3H), 6.74 (d, *J* = 9.5 Hz, 2H), 2.90–2.86 (m, 2H), 2.75–2.71 (m, 2H), 2.31 (s, 6H). ^{13}C NMR (ppm) (126 MHz, $CDCl_3$) δ 160.74 (d, *J* = 242.7 Hz), 142.0, 138.3 (d, *J* = 7.8 Hz), 134.1 (d, *J* = 3.0 Hz), 128.6, 128.4, 126.2, 114.6 (d, *J* = 20.3 Hz), 35.6 (d, *J* = 1.5 Hz), 31.5, 20.1 (d, *J* = 1.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) -118.6. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}F$ $[M-H]^+$: calculated 227.1236; found 227.1230 (-2.7 ppm).

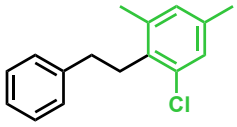


1-Fluoro-3,5-dimethyl-2-phenethylbenzene 410-*o* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and fluoro-*m*-xylene (1.39 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH, in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 164.6 mg (33% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.27 (m, 2H), 7.22 (dd, *J* = 3.2, 7.4 Hz, 3H), 6.75 (s, 1H), 6.72 (d, *J* = 10.5 Hz, 1H), 2.90–2.86 (m, 2H), 2.79 (dd, *J* = 5.9, 10.3 Hz, 2H), 2.29 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 161.5 (d, *J* = 243.0 Hz), 142.1, 138.2 (d, *J* = 5.1 Hz), 137.1 (d, *J*

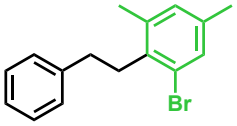
= 9.0 Hz), 128.6, 128.5, 126.5 (d, *J* = 2.5 Hz), 126.1, 124.1 (d, *J* = 15.6 Hz), 113.4 (d, *J* = 22.8 Hz), 36.1, 28.0 (d, *J* = 3.4 Hz), 21.1 (d, *J* = 1.8 Hz), 19.1 (d, *J* = 3.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, CF_3COOH-ext. st.) δ (ppm) -120.2. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}F$ $[M-H]^+$: calculated 227.1236; found 227.1231 (-2.4 ppm).



5-Chloro-1,3-dimethyl-2-phenethylbenzene 411-*p* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and chloro-*m*-xylene (1.49 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 62.1 mg (11% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.2–7.19 (m, 3H), 7.01 (s, 2H), 2.89–2.84 (m, 2H), 2.72 (dd, *J* = 6.5, 10.1 Hz, 2H), 2.29 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 141.9, 138.1, 137.0, 131.0, 128.6, 128.4, 128.0, 126.3, 35.3, 31.7, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}Cl^{35}$ $[M-H]^+$: calculated 243.0935; found 243.0935 (0.1 ppm).

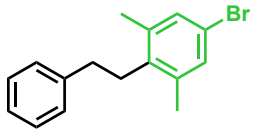


1-Chloro-3,5-dimethyl-2-phenethylbenzene 411-*o* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and chloro-*m*-xylene (1.49 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 194.0 mg (36% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38–7.33 (m, 2H), 7.32–7.23 (m, 3H), 7.12 (s, 1H), 6.91 (s, 1H), 3.08–3.02 (m, 2H), 2.84 (dt, *J* = 4.2, 8.3 Hz, 2H), 2.31 (s, 6H). ^{13}C NMR (ppm) (126 MHz, $CDCl_3$) δ 142.1, 138.0, 136.8, 134.7, 134.3, 129.8, 128.5 (2C), 127.8, 126.1, 35.1, 32.5, 20.8, 20.1. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}Cl^{35}$ $[M-H]^+$: calculated 243.0935; found 243.0935 (0.0 ppm).

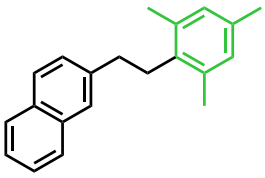


1-Bromo-3,5-dimethyl-2-phenethylbenzene 412-*o* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and bromo-*m*-xylene (1.50 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH, in 2.2 mL of HFIP. The reaction mixture

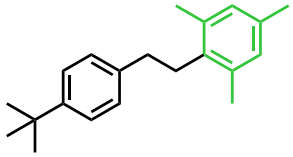
was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 288.0 mg (45% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34–7.27 (m, 5H), 7.25–7.20 (m, 1H), 6.92 (s, 1H), 3.05–3.01 (m, 2H), 2.82–2.78 (m, 2H), 2.31 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 142.0, 138.0, 137.3, 136.3, 131.2, 130.6, 128.6, 128.5, 126.2, 125.3, 35.3, 35.1, 20.7, 20.5. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}Br^{79}$ $[M-H]^+$: calculated 287.0430; found 287.0431 (0.4 ppm).



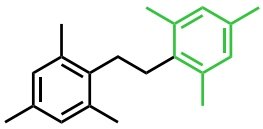
5-Bromo-1,3-dimethyl-2-phenethylbenzene 411-*p* was prepared according to *General Procedure* from 2-phenyl-1-ethanol (265 µL, 2.21 mmol) and (1.50 mL, 11.1 mmol, 5 equiv) with 19.6 µL (0.221 mmol) of TfOH, in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 0,0816 mg (13 % yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.33–7.29 (m, 2H), 7.24–7.19 (m, 3H), 7.17 (s, 2H), 2.86 (dd, *J* = 10.1, 6.5 Hz, 2H), 2.72 (dd, *J* = 6.4, 10.2 Hz, 2H), 2.29 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 141.8, 138.5, 137.6, 130.9, 128.6, 128.4, 126.3, 119.3, 35.2, 31.8, 19.7. HRMS (APPI-Orbitrap): *m/z* for $C_{16}H_{16}Br^{79}$ $[M-H]^+$: calculated 287.0430; found 287.0431 (0.4 ppm).



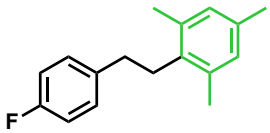
1-(2,4,6-Trimethylphenethyl)naphthalene 413 was prepared according to *General Procedure* from 2-(1-naphthyl)ethanol (4267 mg, 2.478 mmol) and mesitylene (1.72 mL, 12.4 mmol, 5 equiv) with 24.8 µL (0.248 mmol) of TfOH in 2.5 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 643.3 mg (95% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.58–7.46 (m, 2H), 7.45–7.41 (m, 1H), 7.38 (d, *J* = 6.8 Hz, 1H), 6.90 (s, 2H), 3.21 (dd, *J* = 10.3, 6.5 Hz, 2H), 3.04 (dd, *J* = 10.3, 6.5 Hz, 2H), 2.37 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 138.6, 136.3, 135.8, 135.5, 134.0, 132.0, 129.2 (2C), 129.0, 126.8, 126.0, 125.8, 125.6, 123.7, 32.5, 30.9, 21.0, 20.0. HRMS (APPI-Orbitrap): *m/z* for $C_{21}H_{22}$ $[M^+]$: calculated 274.1716; found 274.1714 (-2.6 ppm).



2-(4-(*tert*-Butyl)phenethyl)-1,3,5-trimethylbenzene 414 was prepared according to *General Procedure* from 4-*tert*-butylphenethyl alcohol (431 mg, 2.42 mmol) and mesitylene (1.68 mL, 12.1 mmol, 5 equiv) with 21.4 µL (0.242 mmol) of TfOH in 2.4 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 420.7 mg (62% yield) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.88 (s, 2H), 2.91–2.87 (m, 2H), 2.74–2.69 (m, 2H), 2.35 (s, 6H), 2.28 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 149.0, 139.4, 136.1, 135.8, 135.3, 129.1, 128.0, 125.5, 35.1, 34.5, 31.9, 31.6, 21.0, 19.8. HRMS (CI): *m/z* for $C_{21}H_{27}$ $[M-H]^+$: calculated 279.2107; found 279.2105 (-1.9 ppm).

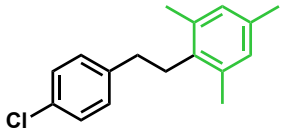


1,2-Dimesitylethane 415 was prepared according to *General Procedure* from 2-mesityl-1-ethanol (358 mg, 2.18 mmol) and mesitylene (1.52 mL, 10.9 mmol, 5 equiv) with 19.3 µL (0.218 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 120 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 501.2 mg (86% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.86 (s, 4H), 2.77 (s, 4H), 2.36 (s, 12H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 136.4, 135.8, 135.3, 129.2, 29.1, 20.9, 20.3. HRMS (APPI-Orbitrap): *m/z* for $C_{20}H_{25}$ $[M-H]^+$: calculated 265.1950; found 265.1949 (-2.4 ppm).

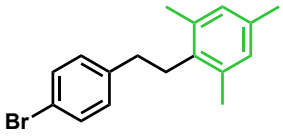


2-(4-Fluorophenethyl)-1,3,5-trimethylbenzene 416 was prepared according to *General Procedure* from 2-(4-fluorophenyl)-1-ethanol (268 µL, 2.14 mmol)and mesitylene (1.49 mL, 10.7 mmol, 5 equiv) with 18.9 µL (0.214 mmol) of TfOH in 2.14 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 438.8 mg (85% yield) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.10–7.06 (m, 2H), 6.93–6.87 (m, 2H), 6.87, (s, 2H), 2.77 (dd, *J* = 10.3, 6.4 Hz, 2H), 2.63 (dd, *J* = 10.4, 6.4 Hz, 2H), 2.21 (s, 6H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.5 (d, *J* = 243.5 Hz), 138.0 (d, *J* = 3.2 Hz), 136.1, 135.4, 135.3, 129.8 (d, *J* = 7.6 Hz), 129.1, 115.3 (d, *J* = 21.1 Hz), 34.8, 32.0, 21.0, 19.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) -117.6

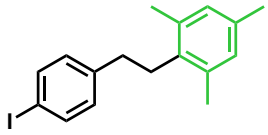
(s, 1F). HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{18}{}^{18}F$ $[M-H]^+$: calculated 241.1387; found 241.1386 (-2.7 ppm).



2-(4-Chlorophenethyl)-1,3,5-trimethylbenzene 417 was prepared according to *General Procedure* from 2-(4-chlorophenyl)-1-ethanol (303 µL, 2.24 mmol) and mesitylene (1.55 mL, 11.2 mmol, 5 equiv) with 19.8 µL (0.223 mmol) of TfOH in 2.23 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 535.5 mg (93% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30–7.27 (m, 2H), 7.17–7.13 (m, 2H), 6.87 (s, 2H), 2.86 (dd, *J* = 10.7, 5.8 Hz, 2H), 2.72 (dd, *J* = 10.7, 5.9 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.8, 136.1, 135.5, 135.1, 131.8, 129.8, 129.1, 128.6, 35.0, 31.7, 20.9, 19.8. HRMS (APPI-Orbitrap**)**: *m/z* for $C_{17}H_{18}{}^{35}Cl$ $[M-H]^+$: calculated 257.1092; found 257.1089 (0.9 ppm).

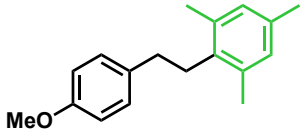


2-(4-Bromophenethyl)-1,3,5-trimethylbenzene 418 was prepared according to *General Procedure* from 2-(4-bromophenyl-1-ethanol (320 µL, 2.29 mmol) and mesitylene (1.59 mL, 11.4 mmol, 5 equiv) with 20.3 µL (0.229 mmol) of TfOH, in 2.3 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 677.9 mg (98% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.87 (s, 2H), 2.85 (dd, *J* = 10.4, 6.3 Hz, 2H), 2.70 (dd, *J* = 10.4, 6.3 Hz, 2H), 2.30 (s, 6H), 2.28 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.3, 136.1, 135.5, 135.1, 131.6, 130.2, 129.1, 119.8, 35.1, 31.7, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{18}{}^{81}Br$ $[M-H]^+$: calculated 301.0586; found 301.0584 (-0.6 ppm).

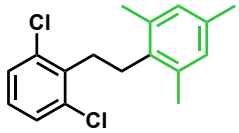


2-(4-Iodophenethyl)-1,3,5-trimethylbenzene 419 was prepared according to *General Procedure* from 2-(4-iodophenyl)-1-ethanol (500 mg, 2.02 mmol) and mesitylene (1.40 mL, 10.1 mmol, 5 equiv) with 17.8 µL (0.202 mmol) of TfOH in 2.0 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 433.2 mg (61% yield) of white solid. ^{1}H NMR (400

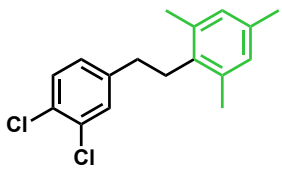
MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.86 (s, 2H), 2.84 (dd, *J* = 10.3, 6.4 Hz, 2H), 2.68 (dd, *J* = 10.4, 6.3 Hz, 2H), 2.29 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.0, 137.6, 136.1, 135.5, 135.1, 130.6, 129.1, 91.1, 35.2, 31.6, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{18}{}^{127}I$ $[M-H]^+$: calculated 349.0447; found 349.0444 (-0.9 ppm).



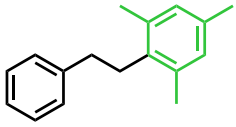
2-(4-Methoxyphenethyl)-1,3,5-trimethylbenzene 420 was prepared according to *General Procedure* from 2-(4-iodophenyl)-1-ethanol (349 mg, 2.29 mmol) and mesitylene (1.60 mL, 11.5 mmol, 5 equiv) with 20.3 µL (0.229 mmol) of TfOH, in 2.3 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 478.3 mg (82% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.17 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.88 (s, 2H), 3.82 (s, 3H), 2.86 (dd, *J* = 10.4, 6.5 Hz, 2H), 2.70 (dd, *J* = 10.4, 6.5 Hz, 2H), 2.33 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$**)** (ppm) δ 158.0, 136.1, 135.6, 135.3, 134.6, 129.3, 129.1, 114.0, 55.4, 34.7, 32.2, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{18}H_{21}O$ $[M-H]^+$: calculated 253.1586; found 253.1585 (-2.9 ppm).



2-(2,6-Dichlorophenethyl)-1,3,5-trimethylbenzene 421 was prepared according to *General Procedure* from 2,6-dichlorophenethyl alcohol (437 mg, 2.29 mmol) and mesitylene (1.60 mL, 11.4 mmol, 5 equiv) with 20.2 µL (0.228 mmol) of TfOH in 2.3 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 130.7 mg (19% yield) of colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34 (d, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.92 (s, 2H), 3.12–3.08 (m, 2H), 2.92–2.87 (m, 2H), 2.49 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.9, 136.8, 135.6 (2C), 134.8, 129.1, 128.4, 127.8, 31.3, 28.2, 21.0, 20.1. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{17}{}^{35}Cl_2$ $[M-H]^+$: calculated 291.0701; found 291.0701 (-1.9 ppm).



2-(3,4-Dichlorophenethyl)-1,3,5-trimethylbenzene 422 was prepared according to *General Procedure* from 3,4-dichlorophenethyl alcohol (318 µL, 2.20 mmol) and mesitylene (1.53 mL, 11.0 mmol, 5 equiv) with 19.5 µL (0.229 mmol) of TfOH in 2.2 mL of HFIP. The reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 219.8 mg (39% yield) of white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 1H), 7.06 (dd, *J* = 8.2 Hz, 1H), 6.89 (s, 2H), 2.87 (dd, *J* = 6.5, 10.1 Hz, 2H), 2.73–2.69 (m, 2H), 2.32 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.5, 136.0, 135.6, 134.7, 132.4, 130.4, 130.3, 130.0, 129.2, 127.9, 34.7, 31.4, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{17}{}^{35}Cl_2$ [M-H$^{\cdot}$]: calculated 291.0701; found 291.0698 (-3.2 ppm).



1,3,5-Trimethyl-2-phenethylbenzene 207 was prepared from styrene oxide (256 µL, 2.25 mmol) and triethylsilane (359 µL, 2.25 mmol, 1 equiv) with 19.9 µL (0.225 mmol) of TfOH in 2.25 mL of HFIP. The reaction mixture was stirred at 0 °C for 6 h then, mesitylene (1.56 mL, 11.2 mmol, 5 equiv) was added and the reaction mixture was stirred at 140 °C for 24 h. Purification by flash column chromatography over silica (petroleum ether/EtOAc 10:0 to 9:1) gave 488.1 mg (95% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41–7.37 (m, 2H), 7.33–7.27 (m, 3H), 6.94 (s, 2H), 2.96 (dd, *J* = 11.4, 5.4 Hz, 2H), 2.82 (dd, *J* = 10.8, 6.0 Hz, 2H), 2.40 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.4, 136.1, 135.6, 135.3, 129.1, 128.6, 128.4, 126.1, 35.7, 31.9, 21.0, 19.8. HRMS (APPI-Orbitrap): *m/z* for $C_{17}H_{20}$ [M$^{+\cdot}$]: calculated 223.14826; found 223.4830 (0.6 ppm).

4. General conclusion and perspectives

This doctoral thesis was devoted to the exploration and the application of Brønsted and Lewis acid catalysis in combination with HFIP for the activation of alcohols, particularly propargylic and primary alcohols. Over the last few years, our research group obtained some valuable results by employing the TfOH/HFIP system and $FeCl_3$/HFIP system. In a second part, we have described a straightforward method to access triaryl CF_3-bearing allenes, indenes, chromenes and alkene directly from α-CF_3 propargylic alcohols. Mechanistic experiments suggest the initial formation of a CF_3-allene that could then be diverted into the given allene, chromene, or alkene depending on the substitution of the starting propargylic alcohol.

This work led to an article:

F. Noël, V. D. Vuković, J. Yi, E. Richmond, P. Kravljanac, J. Moran. *J. Org. Chem.* **2019**, *84*, 15926.

In a third part, we have described a simple and highly selective method for the dehydroarylation (Friedel-Crafts reaction) of primary aliphatic alcohols. Computational studies were consistent with an S_N^2 mechanism. The developed method was especially effective for the substitution of phenylethanol derivatives. The difference of reactivity between simple aliphatic alcohols and phenylethanol derivatives was attributed to the latter's ability to form stable phenonium ion intermediates. To date, this report is the first example of a Brønsted acid catalyzed Friedel-Crafts reaction on primary aliphatic alcohols leading to the exclusive formation of the linear product.

Nevertheless, the work on the Friedel-Crafts reactions of primary aliphatic alcohols will not be published alone but will be part of a bigger project. As these discoveries paved the way for the one pot synthesis of diaryl and triaryl alkanes from cyclopropanes. At the current time, another PhD student, Shaofei Zhang, is actively working on this part. However, publication of this work would require 1) additional computational experiments to determine the energy of formation of the cyclopropenium intermediate. 2) additional experimental and computational research to better understand the selectivity in the case of the substitution of regular aliphatic propargylic alcohols. All of the above-mentioned work is ongoing at the time of the writing of this thesis.