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Synergistic Effect of Acids and HFIP on Friedel-Crafts Reactions of Alcohols and Cyclopropanes

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Посвећено онима којима сам највише недостајао док сам био у лабораторији:

Мајци, брату, Брани и Тијани.

LIST OF ABBREVIATIONS

Ac	acetyl
ACS	American Chemical Society
APCI	atmospheric pressure chemical ionization
APPI	atmospheric pressure photoionization
Ar	- within chemical structures means: aryl
	- followed by "(g)" means: argon
B	in chapter 4 means: branched
Bn	benzyl
CAS	CAS registry number, Chemical Abstracts Service
cat.	catalyst, catalytic amount
CI	chemical ionization
CSA	camphorsulfonic acid
DA	donor-acceptor
DCE	1,2-dichloroethane
DCM	dichloromethane
DDT	dichlorodiphenyltrichloroethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DFT	density function theory
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DOSY	diffusion-ordered spectroscopy
equiv	equivalent
ext. std. or **ext. st.**	external standard
E1	monomolecular elimination
E2	bimolecular elimination
EI	electron impact
ESI	electron spray ionization
Et	ethyl

GC	gas chromatography
GC/MS	gas chromatography coupled with mass spectrometry
Het	heterocycle, heterocyclic
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol, hexafluoroisopropanol
HFIP-ME or **HFIPME**	hexafluoroisopropyl methyl ether
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
int. std. or **int. st.**	internal standard
iPr	isopropyl
IR	infrared
KIE	kinetic isotope effect
KSIE	kinetic solvent isotope effect
L	in Chapter 4 means: linear
LFER	linear free-energy relation
LG	leaving group
M	after numbers means: molar
Me	methyl
Mp or **mp**	melting point
Ms	mesyl, methanesulfonyl
NMR	nuclear magnetic spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
nBu	*n*-butyl
Nu or **NuH**	nucleophile
***p*-TSA**	*p*-toluenesulfonic acid
Ph	phenyl
phen	phenanthroline
PMP	*p*-methoxyphenyl
Rep.	repetition
$\mathbf{R_f}$	retention factor
rt	room temperature
$\mathbf{R_t}$	retention time

SAXS	small angle X-ray scattering
S_N1	monomolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
St. dev.	standard deviation
St. ser.	standard series
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEFDDOL	α,α,α',α'-tetrakis(perfluoroaryl/alkyl)-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol
terpy	terpyridine
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
Tf	trifluoromethanesulfonyl
TfOH	triflic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
$\Delta H^{\neq}$	enthalpy of activation
$\Delta S^{\neq}$	entropy of activation
$\Delta G^{\neq}$	activation free Gibbs energy

RÉSUMÉ

1. Introduction

La fonctionnalisation directe de manière catalytique des composés chimiques pour la formation des liaisons C-C est devenue l'un des plus grands centres d'intérêt en chimie organique au cours des dernières décennies. Un intérêt particulier est porté sur les réactions de Friedel-Crafts des substrats non-préfonctionnalisés pour le développement de nouveaux produits pharmaceutiques actifs. Bien qu'un grand nombre d'acides de Brønsted et de Lewis, ainsi que des métaux de transition, ont été décrit comme catalyseurs des réactions de Friedel-Crafts des différents classes d'alcools, la fonctionnalisation directe (à l'aide des catalyseurs) des alcools benzyliques fortement désactivés et des alcools aliphatiques primaires et secondaires représente toujours un important défi dans ce domaine.

Dans cette optique, le but de cette thèse est de développer de nouvelles méthodes pour la fonctionnalisation directe des alcools en utilisant 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) comme solvant, et les acides de Brønsted ou de Lewis comme catalyseurs. Le solvant HFIP est connu pour ces propriétés uniques, surtout pour former un réseau de liaisons hydrogène et de micro-agrégats qui stabilisent les carbocations peu stables. Pour cette raison, nous avons choisi d'étudier l'influence de ce solvant pour des réactions de Friedel-Crafts des alcools benzyliques, propargyliques et aliphatiques (parties 2. 1., 2. 2. et 2. 3. de ce résumé). Les résultats initiaux nous ont permis d'élargir le scope de transformations que notre système est capable de catalyser, et nous avons donc poursuivi avec l'étude des réactions de déshydroarylation des cyclopropanes substitués (partie 2. 4. de ce résumé).

2. Résultats et discussion

Comme il est décrit dans la partie précédente de ce rapport, les études qu'ont été menées au cours de cette thèse divergent en quatre axes principaux, et ils seront donc présentés séparément. Cependant, il faut bien noter que le point commun de ces études est l'exploitation du système HFIP/acide pour la catalyse des réactions de Friedel-Crafts des différentes classes des substrats.

2. 1. Les réactions de Friedel-Crafts des alcools benzyliques dans HFIP

Une méthode pour la fonctionnalisation directe catalytique des alcools benzyliques fortement désactivés avec des nucléophiles aromatiques a été développée. Les réactions ont lieu dans HFIP comme solvant et l'acide triflique est utilisé comme catalyseur. Nous avons montré que ce système est très efficace pour la catalyse des réactions de Friedel-Crafts. Un large scope d'alcools benzyliques primaires (portant des groupements cyano, nitro et fluoro), ainsi que d'alcools benzyliques secondaires portant un groupement trifluorométhyle en position alpha par rapport à la fonction hydroxyle (Figure 1) a été développé. Une vingtaine de nouveaux produits ont été obtenus de cette manière, avec des rendements de 50 à 95%, avec le naphthalène, benzène, fluorobenzène et des xylènes comme nucléophiles. Afin de mieux comprendre et identifier l'espèce active catalytique, des nombreuses expériences cinétiques ont été réalisées (dont le suivi des réactions par RMN du ^{19}F, titrations RMN etc.). Celles-ci suggèrent l'existence d'agrégats représentant les espèces actives catalytiques, composées d'environ cinq molécules de HFIP et d'une molécule d'acide triflique dans la solution. Des expériences supplémentaires ont confirmé que le mécanisme qui a lieu dans ces réactions est bien de type S_N1, ce qui confirme l'apparition des carbocations au cours des réactions étudiées. Avec ces résultats, l'étude a été complétée et publiée (Vuk D. Vuković, Edward Richmond, Eléna Wolf, Joseph Moran, Catalytic Friedel-Crafts Reactions of Highly Electronically Deactivated Benzylic Alcohols, *Angewandte Chemie International Edition*, **2017**, 56, 3085-3089).

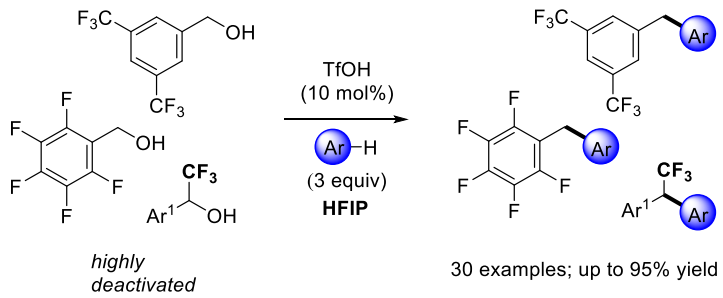


Figure 1. Les réactions de Friedel-Crafts des alcools benzyliques dans HFIP

2. 2. Les réactions de Friedel-Crafts des alcools propargyliques

Cette partie de l'étude a montré qu'un nombre très limité d'alcools propargyliques réagissent de manière analogue aux alcools primaires benzyliques en utilisant l'acide triflique comme catalyseur dans HFIP. Néanmoins, la majorité des alcools propargyliques dans ces conditions donne des mélanges de produits qui sont difficiles à interpréter.

Cependant, les alcools propargyliques secondaires portant un groupement trifluorométhyle en position alpha par rapport à la fonction hydroxyle réagissent de maniére très différente que celle des alcools benzyliques. En présence de chlorure de fer(III) en quantité catalytique dans HFIP comme solvant, ces alcools réagissent dans un premier temps avec des nucléophiles aromatiques (tels que mésitylène, xylènes, benzène) afin de former un diène cumulé (allène) à température ambiante, en 5-10 minutes. Dans un deuxième temps, après un temps réactionnel prolongé (quelques heures), la plupart des substrats se transforment en indènes à travers une cyclisation du type Nazarov. De cette manière, nous avons pu obtenir une trentaine de nouveaux allènes et indènes portant le groupement CF_3 avec des rendements entre 40 et 93% (Figure 2).

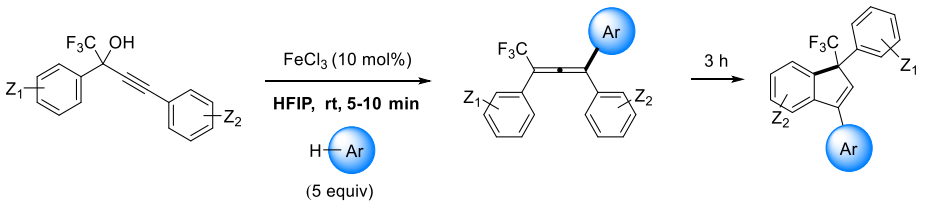


Figure 2. Formation d'allènes et d'indènes à partir d'alcools propargyliques

Néanmoins, les alcools propargyliques tertiaires portant un groupement trifluorométhyle en position alpha par rapport à la fonction hydroxyle montrent une réactivité différente que les alcools benzyliques et les alcools propargyliques secondaires. Dans HFIP, avec l'acide triflique comme catalyseur, en présence de nucléophiles aromatiques, ces substrats se transforment en chromènes portant le groupement CF_3. Huit nouveaux produits avec le motif chromène ont été obtenus avec des rendements entre 43 et 99%.

2. 3. Les réactions de Friedel-Crafts des alcools aliphatiques tertiaires, secondaires et primaires

Les alcools primaires aliphatiques représentent les substrats les plus difficiles à utiliser dans les réactions de Friedel-Crafts, à cause de la migration de carbocation qui se forme après le départ de groupe hydroxyle. Pourtant, avec l'acide triflique en quantité catalytique dans HFIP comme solvant, nous avons réussi à atténuer l'effet de migration des carbocations. Au lieu d'obtenir un mélange de produits branchés et du produit linéaire, nous avons isolé avec des rendements de 30-70% le produit linéaire seulement (Figure 3) à partir des alcools primaires aliphatiques linéaires (y compris les alcools avec une longueur de chaîne aliphatique de C6 à C16). Plusieurs études de mécanisme réactionnel ont été faites, dont le suivi du progrès de la réaction par chromatographie gazeuse, ainsi que l'analyse de l'influence de la concentration de HFIP sur le ratio des produits branchés et du produit linéaire obtenus lors de la réaction. Ces études ont ciblé une concentration de HFIP limite où l'effet de HFIP sur la sélection du produit linéaire apparaît. Nous avons ainsi optimisé le protocole pour les réactions de Friedel-Crafts des alcools secondaires dans HFIP. Les dernières expériences sont actuellement en cours.

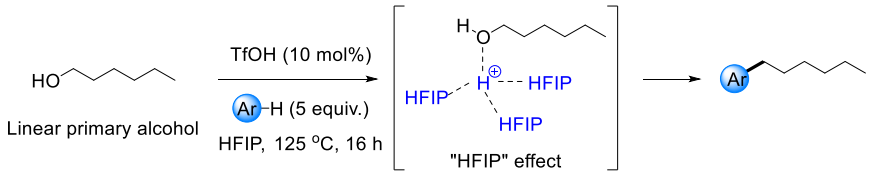


Figure 3. Les réactions de Friedel-Crafts des alcools aliphatiques primaires dans HFIP

2. 4. Déshydroarylation et ouverture des cyclopropanes substitués dans HFIP

Lors de l'étude des réactions de Friedel-Crafts des alcools aliphatiques dans HFIP, nous avons observé que les alcools portant un cycle à 3 ou un cycle à 4 ne subissent pas uniquement la substitution de la fonction hydroxyle avec le nucléophile, mais aussi l'ouverture du cycle de manière nucléophilique. Cela nous a permis d'ouvrir un nouvel axe de recherche sur l'étude du

comportement des cyclopropanes et cyclobutanes dans HFIP en présence de l'acide de Brønsted comme catalyseur.

2. 4. 1. Ouverture des cyclopropanes du type donneur-accepteur. En utilisant les conditions précédemment mentionnées, un vaste scope de cyclopropanes substitués de manière donneur-accepteur a été développé en utilisant des nucléophiles aromatiques (tels que mesitylène, 1,3,5-triméthoxybenzène, indole) et non-aromatiques (les azotures et les alcools primaires aliphatiques). Des rendements de 50 à 99% ont été obtenus, aboutissant à la formation d'une quarantaine de nouveaux produits chimiques (Figure 4). Cette étude a récemment été publiée (E. Richmond, V. D. Vuković, J. Moran, Nucleophilic Ring Opening of Donor-Acceptor Cyclopropanes Catalyzed by a Brønsted Acid in Hexafluoroisopropanol, *Organic Letters*, **2018**, 20, 574-577).

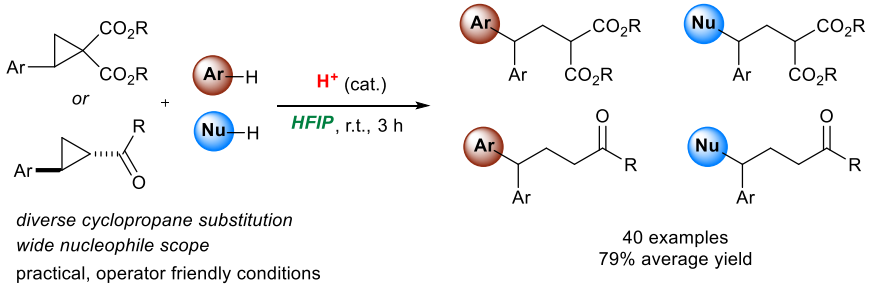


Figure 4. Ouverture des cyclopropanes du type donneur-accepteur dans HFIP

2. 4. 2. Ouverture des cyclopropanes monosubstitués (du type non-donneur-accepteur). Le protocole pour l'ouverture des cyclopropanes du type donneur-accepteur a été ensuite adapté pour l'ouverture nucléophilique des substrats plus difficiles, comme les cyclopropanes monosubstitués (Figure 5). Une trentaine d'exemples de nouveaux composés ont été synthétisés par une réaction d'ouverture de ces cyclopropanes du type « non-donneur-accepteur » avec des nucléophiles aromatiques portant des groupements méthoxy. Plusieurs études mécanistiques ont aussi été faites : l'étude de Hammett, l'analyse DFT, ainsi que le suivi des réactions par RMN et la comparaison de ses vitesses relatives. Ces résultats ont montré que le mécanisme réactionnel est plutôt de type S_N2, et qu'une charge positive existe dans l'état de transition. Les résultats obtenus lors de cette étude ont été également publiés récemment (E. Richmond, J. Yi, V. D. Vuković, F.

Sajadi, C. N. Rowley, J. Moran, Ring-opening Hydroarylation of Monosubstituted Cyclopropanes Enabled by Hexafluoro-isopropanol, *Chemical Science*, **2018**, 9, 6411-6416).

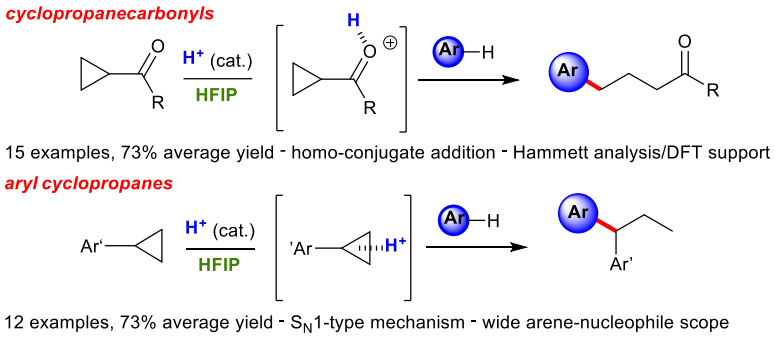


Figure 5. Ouverture des cyclopropanes du type non-donneur-accepteur dans HFIP

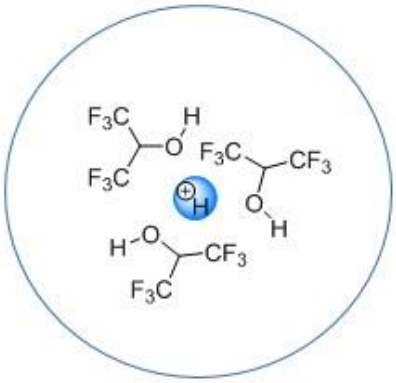
3. Conclusion générale

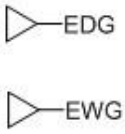
En cours de cette thèse, une nouvelle méthode de fonctionnalisation des alcools benzyliques fortement désactivés, alcools propargyliques triméthylfluorés et alcools aliphatiques primaires et secondaires a été développée. La méthode se base sur l'effet de stabilisation de carbocations très réactifs dans l'HFIP et sur l'activation de groupe hydroxyle dans ce solvant à l'aide des acides (tel que l'acide triflique, chlorure de fer(III), etc.) en quantités catalytiques. Egalement, cette méthode a été appliquée à l'ouverture catalytique des cyclopropanes activés par des groupements donneur et accepteur, ainsi que des cyclopropanes portant uniquement un de ses groupements. Les études des mécanismes détaillées de ces processus ont été réalisées aussi. Ces travaux ont été publiés dans trois publications dans les journaux scientifiques internationaux, et deux autres sont en cours de préparation.

Alcools benzyliques désactivés

Alcools benziliques
α-CF_3

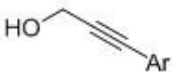
Alcools propargyliques
α-CF_3



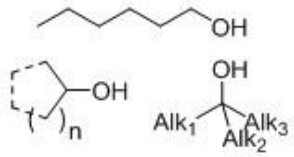


Cyclopropanes
"Non D-A"

Cyclopropanes
D-A



Alcools propargyliques
1°

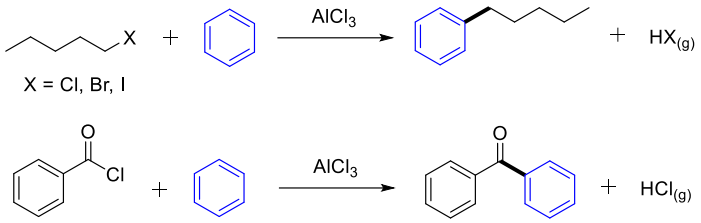


Alcools aliphatiques
1°, 2° et 3°

CHAPTER 1.
GENERAL INTRODUCTION

1. 1. General aspects of Friedel-Crafts reactions

The discovery of Friedel-Crafts reactions was reported in 1877 by French chemist Charles Friedel and American chemist James Mason Crafts.[1] At first, a general method of alkylation of benzene by alkyl halides (chlorides, bromides and iodides) was discovered in the presence of the corresponding aluminum halides. In the following report,[2] Friedel and Crafts presented the first example of benzene acylation by benzoyl chloride, again in the presence of $AlCl_3$ (Scheme 1.1). In the same study they stated the limitations of their method: substrates such as alcohols and carboxylic acids did not undergo analog reactions.



Scheme 1.1. First examples of Friedel-Crafts alkylation and acylation

Over the years, Friedel-Crafts reactions have proved to be practically limitless in terms of scope and usefulness, and they are still gaining interest among organic, theoretical, industrial and other chemists.[3] The use of more "green" substrates emerged, such as alkenes (styrenes) or alcohols,[4] which would not result in side-product formation, or would give water as the only byproduct, respectively. After more than one century from their discovery, first efforts were made by Fukuzawa[5] in 1996 and Shimizu[6] in 1997 to significantly lower the loading of Lewis and Brønsted acids that had been used as catalysts mostly in superstoichiometric quantities up to that point. However, some of the limitations that Friedel and Crafts noticed more than 140 years ago have still remained unsolved. For example, primary aliphatic alcohols still resist becoming synthetically useful substrates for Friedel-Crafts reactions, due to the rearrangement of the

[1] Friedel C., Crafts J.-M. *Compt. Rend. Acad. Sci.* Paris, **1877**, 84, 1392-1395
[2] Friedel C., Crafts J.-M. *Compt. Rend. Acad. Sci.* Paris, **1877**, 84, 1450-1454
[3] (a) Rueping M., Nachtsheim B. J. *Belstein J. Org. Chem.* **2010**, 6, No. 6. doi:10.3762/bjoc.6.6, (b) Dryzhakov M., Richmond E., Moran J. *Synthesis*, **2016**, 48, 935-959
[4] (a) Mckenna, J. F.; Sowa, F. J. *J. Am. Chem. Soc.* **1938**, 60, 124-125, (b) Oesper, P. F., Smyth C. P., Kharasch M. S., *J. Am. Chem. Soc*. **1942**, 64, 937-940
[5] Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-i. *Synlett*, **1996**, 6, 557-559
[6] Shimizu, I.; Khien, K. M.; Nagatomo, M.; Nakajima, T.; Yamamoto, A. *Chem. Lett*. **1997**, 26, 851-852

intermediate carbocation.[7] Also, there have been very few reports published about the use of non-functionalized carboxylic acids as starting compounds in Friedel-Crafts chemistry.[8]

1. 1. 1. Substrates in Friedel-Crafts reactions

Friedel-Crafts reactions consist of two main types of reactions: alkylation and acylation. In most cases, alkylation is done by employing alkyl halides, especially chlorides, bromides and iodides. Very few reports have been published about catalytic Friedel-Crafts reactions of primary[9] and tertiary alkyl fluorides.[10] However, in all these reactions, equivalents of halogenated byproducts are produced. In this regard, "cleaner" substrates are alkenes and alcohols. Alternatively, Friedel-Crafts alkylation can also be driven by the internal strain of cyclopropanes.[11] For Friedel-Crafts acylation, acyl halides, anhydrides of carboxylic acids, esters or amides have been mostly used.[12] In the past several years, new modes of Friedel-Crafts reactivity have been found, such as proton catalyzed, silane-fueled Friedel-Crafts coupling of fluoroarenes.[13]

1. 2. Dehydrative functionalizations of alcohols

Alcohols represent an attractive class of chemical compounds from the point of view of an organic chemist, due to the versatile reactivity of their hydroxyl group functionality. In basic conditions they can form alkoxide anions, which would subsequently act as strong bases or good nucleophiles. On the other hand, in the presence of Lewis or Brønsted acids, the hydroxyl group

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[7] Roberts R. M., Lin Y.-T., Anderson G. P. Jr. *Tetrahedron*, **1969**, 25, 4173-4182

[8] (a) Singh A. P., Pandey A. K., *J. Mol. Catal. A: Chem*. **1997**, 123, 141-147, (b) Zarei A., Hajipour A. R., Khazdooz L. *Tetrahedron Lett.* **2008**, 49, 6715-6719

[9] (a) Olah G. A., Yamato T., Hashimoto T., Shih J. G., Trivedi N., Singh B. P., Piteau M., Olah J. A. *J. Am. Chem. Soc*. **1987**, 109, 3708-3713, (b) Lühmann N., Panisch R., Müller T. *Appl. Organometal. Chem*. **2010**, 24, 533-537

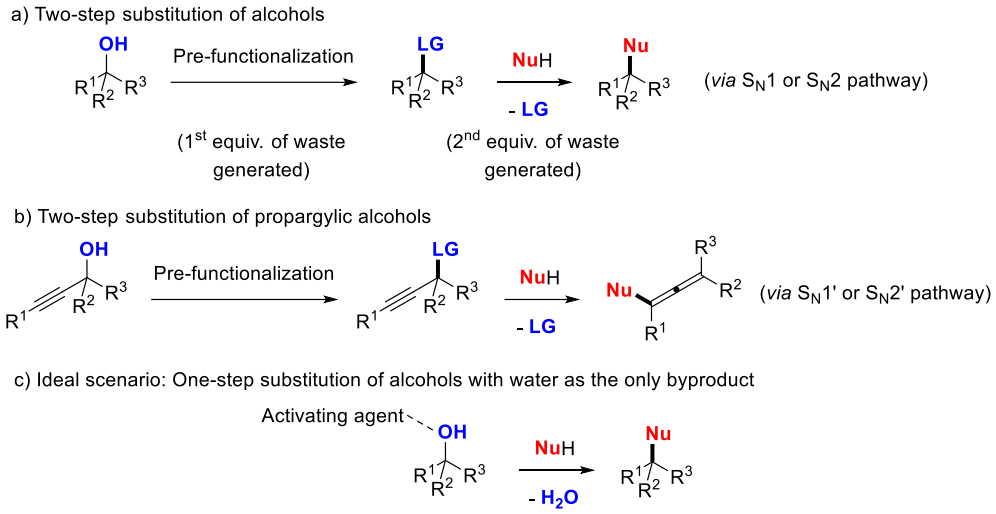
[10] Dryzhakov M., Moran J., *ACS Catal*. **2016**, 6, 3670-3673

[11] (a) Pinnick H. W., Brown S. P., McLean E. A., Zoller L. W. III, *J. Org. Chem*. **1981**, 46, 3758-3760, (b) Huang J.-W., Shi M. *Tetrahedron Lett.* **2003**, 44, 9343-9347, (c) Wales S. M., Walker M. M., Johnson J. S., *Org. Lett*. **2013**, 15, 2558-2561, (d) Dulin C. C., Murphy K. L., Nolin K. A. *Tetrahedron Lett.* **2014**, 55, 5280-5282, (e) Kim A., Kim S.-G. Eur. *J. Org. Chem*. **2015**, 6419-6422, (f) Kaicharla T., Roy T., Thangaraj M., Gonnade R. G., Biju A. T. *Angew. Chem. Int. Ed*. **2016**, 55, 10061-10064, (g) Meloney T. P., Murphy K. L., Mainsah T. L., Nolin K. A. *Tetrahedron Lett.* **2018**, 59, 18-21

[12] Tachrim Z. P., Wang L., Murai Y., Yoshida T., Kurokawa N., Ohashi F., Hashidoko Y., Hashimoto M. *Catalysts*, **2017**, 7, 40

[13] Allemann O., Duttwyler S., Romanato P., Baldridge K. K., Siegel J. S. *Science*, **2011**, 332, 574-577

is activated, and the remaining alkyl moiety acts as an electrophile. The hydroxy group is a poor leaving group, and in order to be substituted, it has to be previously activated or functionalized. As it has already been mentioned, activation is typically achieved by use of Lewis or Brønsted acids, while functionalization is achieved by forming corresponding halides, mesylates, esters, etc. Afterwards, in the second step, nucleophilic substitution can occur *via* two different pathways (Scheme 1.2.a): monomolecular (S_N1) or bimolecular (S_N2). Alternatively, in the case of allylic and propargylic alcohols, the substitution can also occur *via* an S_N1' or S_N2' mechanism (Scheme 1.2.b) on the γ-carbon to the hydroxyl group.



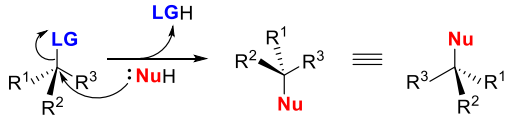
Scheme 1.2. Existing methods for nucleophilic substitution of alcohols

Nevertheless, the majority of described transformations proceed in a two-step sequence, and generate therefore at least two equivalents of (waste) byproducts. A more preferable and atom-economical approach would be based on a single-step reaction of non-prefunctionalized substrates, where catalysts (ideally in substoichiometric loading) would activate the OH group, allowing them to be recovered upon reaction completion (Scheme 1.2.c).

1. 2. 1. Substitution of alcohols *via* an S_N2 pathway

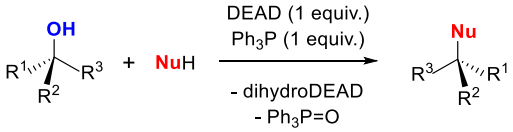
In the majority of cases, nucleophilic substitution of pre-functionalized primary and secondary alcohols proceeds through an S_N2 pathway (i. e. "synchronous mechanism"). After the

transformation of the hydroxyl group into a better leaving group (for example, to mesylate or tosylate), the nucleophile attacks from the side opposite to the leaving group, while the carbon-leaving group bond is simultaneously being broken (Scheme 1.3). Because of the concerted manner of formation of the new carbon-nucleophile bond and cleavage of the carbon-leaving group bond, the reaction is bimolecular, and its rate will depend on both the concentrations of the nucleophile and the starting product bearing the leaving group. These reactions are therefore stereospecific and represent a typical example of Walden inversion.



Scheme 1.3. General representation of the S_N2 mechanism

An example of such reactivity is the Mitsunobu reaction.[14]



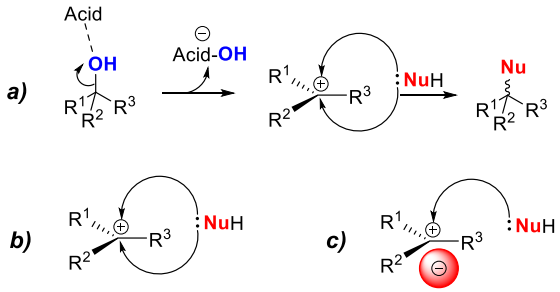
Scheme 1.4. General scheme of the Mitsunobu reaction

1. 2. 2. Direct substitution of alcohols *via* an S_N1 pathway

The mechanism of monomolecular nucleophilic substitution (S_N1, or "prior dissociation mechanism") of different classes of alcohols (mainly benzylic, allylic, propargylic and tertiary aliphatic alcohols) has been well studied.[15] In the initial phase, the hydroxyl group is activated by a Lewis or Brønsted acid, followed by polarization and (slow) cleavage of the carbon-oxygen bond, which is the rate-determining step (Scheme 1.5a). In this manner, a carbocation with planar geometry is formed, being available for nucleophilic attack from both sides of its plane. Once the carbocation is formed, the nucleophile can attack from either of the two sides (in the case of the "naked" carbocation, Scheme 1.5b), forming an equimolar mixture of enantiomers (i. e. diastereomers if the initial alcohol contains other stereocenters) in general case. This step is

[14] Mitsunobu O. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2380-2382
[15] Starting from Ingold C. K., Rothstein E. *J. Chem. Soc.* **1928**, 1217-1221

faster than the previous one (C–O bond cleavage). Therefore, the reaction rate in this case depends on the concentration of the initial activated alcohol, and it does not depend on the nucleophile concentration. However, although the carbocation itself is not chiral, the ion pair of the carbocation and its counterion is chiral. Therefore, the probability of the nucleophile attack in the case of the carbocation-counterion pair from both sides of the carbocation is not the same (Scheme 1.5c), since one side of the carbocation is already occupied with the counterion. Also, in the case of non-classical carbocations the outcome will also depend on the rearrangement rate within the carbocation itself. All in all, these effects can have significant influence on reaction kinetics.[16]



Scheme 1.5. General representation of the S_N1 mechanism (a). The attack of the nucleophile on the carbocation without (b) and with (c) a counterion.

1. 2. 3. Distinguishing an S_N1 from an S_N2 process

Although the first (correct) ideas[17] about possible mechanism of nucleophilic substitution have been present since 1911, it was only in 1933 that first clear experimental distinction between mono- and bimolecular nucleophilic substitution (and elimination) was achieved.[18] Apart from different molecularity of S_N1 and S_N2 reactions (mono- and bimolecular, respectively) that can be derived from reaction progress monitoring, other methods for distinguishing these two mechanisms exist:

- determination of the enantiomeric excess of the reaction product: if the substitution reaction took place on an enantiopure substrate, then the S_N2 process will result in enantiopure product, whereas the S_N1 process will result in complete loss of chirality at this stereocenter.

[16] Winstein S., Clippinger E., Fainberg A. H., Heck R., Robinson G. C. *J. Am. Chem. Soc.* **1956**, 78, 328-335
[17] Le Bel J.-A. *J. Chim. Phys*. **1911**, 9, 323-324
[18] Hughes E. D., Ingold C. K., Patel C. S. *J. Chem. Soc*. **1933**, 526-530

- linear free energy relations (LFER), and especially Hammett plot – illustrates the influence of substituents present in the substrate on the reaction rate, i. e. on the reaction activation energy, i. e. on the energy of the transition state. The method is based on the equation:

$$\log\frac{k}{k_{\mathrm{o}}} = \sigma\,\rho\,,$$

where k and k_{o} are the rate constants of the reactions with the molecule bearing a substituent different from hydrogen and bearing hydrogen, respectively, σ - is the substituent-dependent parameter of the given substituent, and ρ - is the reaction parameter. By plotting $\log(k/k_{\mathrm{o}})$ values against the σ parameter, a linear graph should be obtained, where the slope equals to the ρ parameter. Since the S_N1 process proceeds through a carbocationic intermediate, and the rate-determining step involves an electron transfer from the alkyl group to the leaving group, a large kinetic polar effect[19] should be observed in the reactions of this type. This means that in S_N1 processes, substituents will have greater impact on the reaction rate than in S_N2 reactions, which will result in a wider range of reaction rate values within a series of substituted compounds. This will finally result in Hammet plots with steeper slopes, i. e. higher absolute values of ρ parameters (around 5) than in S_N2 processes (closer to 0).[20]

- determination of the transition state thermodynamic parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) from an Eyring plot. This method is based on the Eyring equation[21] that relates the transition state Gibbs energy ($\Delta G^{\neq}$) with the chemical reaction rate constant (k):

$$k = \frac{\kappa\, k_{\mathrm{B}}\, T}{h}\, e^{-\frac{\Delta G^{\neq}}{RT}},$$

where κ - is the fraction of molecules reaching the transition state which proceeds to the formation of the products, k_{B} - Boltzmann's constant, T - thermodynamic temperature, h - Planck's constant, and R - universal gas constant. By expressing $\Delta G^{\neq}$ as difference of $\Delta H^{\neq}$ and $T\Delta S^{\neq}$, it can be deduced that:

$$\ln\frac{k}{T} = -\frac{\Delta H^{\neq}}{R}\cdot\frac{1}{T} + \ln\frac{\kappa\, k_{\mathrm{B}}}{h} + \frac{\Delta S^{\neq}}{R}.$$

Therefore, by determining reaction rate constants k at different temperatures, and plotting $\ln(k/T)$ against $1/T$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ can be determined from the intercept and the slope. Activation

[19] Polar effect = electronic effect.
[20] Wurst J. M., Liu G., Tan D. S. *J. Am. Chem. Soc*. **2011**, 133, 7916-7925
[21] (a) Eyring H. *J. Chem. Phys*. **1935**, 3, 107-115, (b) Glasstone, S., Laidler, K. J., and Eyring, H. "The Theory of Rate Processes", **1941**, McGraw-Hill, New York

entropies are in general more positive for monomolecular (S_N1 and E1) than for corresponding bimolecular processes (S_N2 and E2).[22]

- observation of kinetic isotope effect, that is defined as:

$$KIE = \frac{k_H}{k_D},$$

where k_H - is the reaction rate constant where compounds with protium are involved, and k_D - is the reaction rate constant of the same reaction where some of the protium atoms are replaced with deuterium. The same principle can be used for any other pair of isotopes.[23]

- measurement of kinetic solvent isotope effect (KSIE), that is defined in the same manner as kinetic isotope effect, only in this case the different isotope is introduced in solvent molecules.

- combination of Eyring analysis and KSIE. Although $\Delta G^{\neq}$ values for reactions involving protiated and deuterated compounds do not differ much, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ do. Regardless of the mechanism, the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ will be greater in deuterated solvent. Let $\delta\Delta S^{\neq}$ be:

$$\delta\Delta S^{\neq} = \Delta S^{\neq}(\text{deuterated}) - \Delta S^{\neq}(\text{protiated}), \text{ and correspondingly:}$$
$$\delta\Delta H^{\neq} = \Delta H^{\neq}(\text{deuterated}) - \Delta H^{\neq}(\text{protiated}).$$

Then, since an S_N1 process requires higher degree of reorganization of solvent molecules than S_N2 process, $\delta\Delta S^{\neq}$ will be higher, and consequently $\delta\Delta H^{\neq}$ as well, in an S_N1 scenario than in an S_N2 case. [24]

- rate of the S_N1 process depends more on the ionizing power of the solvent than the rate of an S_N2 process depends on it.

- rapid insight into the molecularity of the rate-determining step of the mechanism can be achieved by carrying out the reaction with double concentrations of both reactants. If the reaction rate doubles, the mechanism is monomolecular, and if it increases four times, the mechanism is bimolecular. If the reaction rate stays unchanged, then the reaction is zero order in both reactants.

[22] Schaleger L. L., Long F. A. *Adv. Phys. Org. Chem*. **1969**, 1, 1-33
[23] For detailed review on kinetic isotope effects in S_N2 reactions read: Westaway K. C. *Adv. Phys. Org. Chem*. **2006**, 41, 217-273
[24] Treindl L., Robertson R. E., Sugamori S. E. *Can. J. Chem*. **1969**, 47, 3397-3404

Based on all previously stated, several general descriptive trends for an S_N1 and S_N2 process can be established (Table 1.1), although the exceptions from these trends have been reported.[25]

Table 1.1. General trends in nucleophilic substitution reactions[26]

	Primary alkyl derivate	Secondary alkyl derivate	Tertiary alkyl derivate	Expected for S_N2	Expected for S_N1
Effect of the added nucleophile	Large	Large	Small	Large	Small
Effect of solvent polarity	Small	Medium	Large	Small	Large
Effect of solvent nucleophilicity	Large	Medium	Small	Large	Small
Stereochemistry	100% inversion	100% inversion	~50% inversion ~50% retention	100% inversion	50% inversion 50% retention

At the very end of this subchapter, it is necessary to mention that the terms such as "nucleophile", "electrophile", "heterolytic", "homolytic" were all coined by Sir Cristopher K. Ingold.[27] Since modern chemistry cannot be imagined without these terms, it is clear that his discoveries and terminology completely changed the way of thinking of the scientific community about chemical reactions and mechanisms during the 20th century. He practically invented the field of the experimental mechanistic investigation of chemical reactions. It is thus more than obvious that these achievements should have been acknowledged at least with a Nobel prize, and it is truly regrettable that this had never happened.

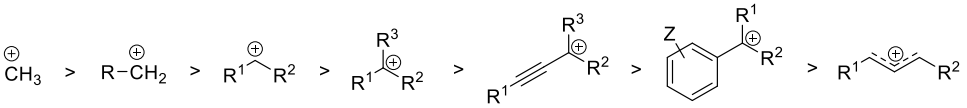
1. 2. 4. Carbocationic intermediates and their reactivity

Although it was as early as in 1922 that carbocations were postulated as possible intermediates in chemical reactions,[28] it was only in 1958 that they were experimentally identified by NMR spectroscopy.[29] The main challenges in the experimental detection of carbocations are their short lifetime and low concentration in the reaction medium.[30] From 1962

[25] Pronin S. V., Reiher C. A., Shenvi R. A. *Nature*, **2013**, 501, 195-199
[26] Taken from: Raber D. J., Harris J. M. *J. Chem. Educ*. **1972**, 49, 60-64
[27] Ridd J. H. *ACS Symposium Series*, **2017**, 1262, 207-218
[28] Meerwein H., von Emster K., Joussen J. *Berichte Deutsch. Chem. Gesalsch*. **1922**, 55B, 2500-2528
[29] Doering W von E., Saunders M., Boyton H. G., Earhart H. W., Wadley E. F., Edwards W. R., Laber G. *Tetrahedron*, **1958**, 4, 178-185
[30] The remark about low concentration refers to the reactions where carbocations intervene as intermediates.

onwards, in his remarkable work George Olah succeeded to overcome these limitations by use of the superacidic media and to detect and determine the structure of a number of different carbocations, starting with *tert*-butyl carbocation.[31]

Concerning the general trend in reactivity of carbocations, it can be depicted as in Scheme 1.6. In the aliphatic series of carbocations, the most reactive is methyl cation, followed by other primary, secondary and tertiary carbocations. The trend further expands to the series of π-carbocations, where the most reactive ones are benzylic and allylic, followed by propargylic cations.[32]



Scheme 1.6. General trend in reactivity of carbocations

Still, when we speak about carbocation reactivity, the next question that logically rises is: reactivity towards what? Once the carbocation is formed, it can be captured by a nucleophile, it can undergo an elimination in order to form a π-bond, or it can rearrange. Which one of these processes will be dominant will depend on the carbocation structure itself, as well as the reaction partners and surrounding medium. It has been considered for long time that more reactive the chemical species is, less selective it is, and vice versa. However, this is not always true,[33] and among a number of studies that proved it, the most distinguished ones are the findings of Mayr and Patz.[34] Based on the rates of the carbocations with nucleophiles, they proposed the following formula:

$$\log k = s\,(N + E)\,,$$

where k - is the rate constant of a nucleophile and electrophile reaction at 20 ^{o}C, s - nucleophile-specific slope parameter, N - electrophile-independent nucleophilicity parameter, and E - nucleophile-independent electrophilicity parameter. It was proved that this formula is universal for all kinds of nucleophiles: n-nucleophiles (e. g. amines, phosphines), π-nucleophiles (e. e.

[31] Olah G. A., Tolgyesi W. S., Kuhn S. J., Moffatt M. E., Bastien I. J., Baker E. B. *J. Am. Chem. Soc*. **1963**, 85, 1328-1334

[32] Exceptions from this general trend can be observed depending on the electron-withdrawing or -donating nature of the substituents attached to the corresponding alkyl and aryl groups.

[33] Mayr H., Ofial A. R. *Angew. Chem. Int. Ed*. **2006**, 45, 1844-1854

[34] Mayr H., Patz M. *Angew. Chem. Int. Ed. Engl*. **1994**, 33, 938-957

alkenes, benzene ring) and σ-nucleophiles (e. g. hydrides). Then, for the construction of the average general scale of nucleophilicity and electrophilicity (Figure 1.1), the electrophilicity parameter *E* of bis(*p*-methoxyphenyl)methyl cation was set at 0, and the slope parameter *s* of 2-methyl-1-pentene at 1. Values of *s*, *N* and *E* parameters for other nucleophiles and electrophiles were derived from the relative rate constants with these two reference compounds.[35] A standard temperature of 20 °C was chosen, and for all reactions that were followed at different temperature, conversion to 20 °C was made by using transition state thermodynamical parameters. Although the solvent effect and steric effects were neglected, so far the Mayr-Patz equation has proved to be valid for 1118 nucleophiles and 319 electrophiles.[36]

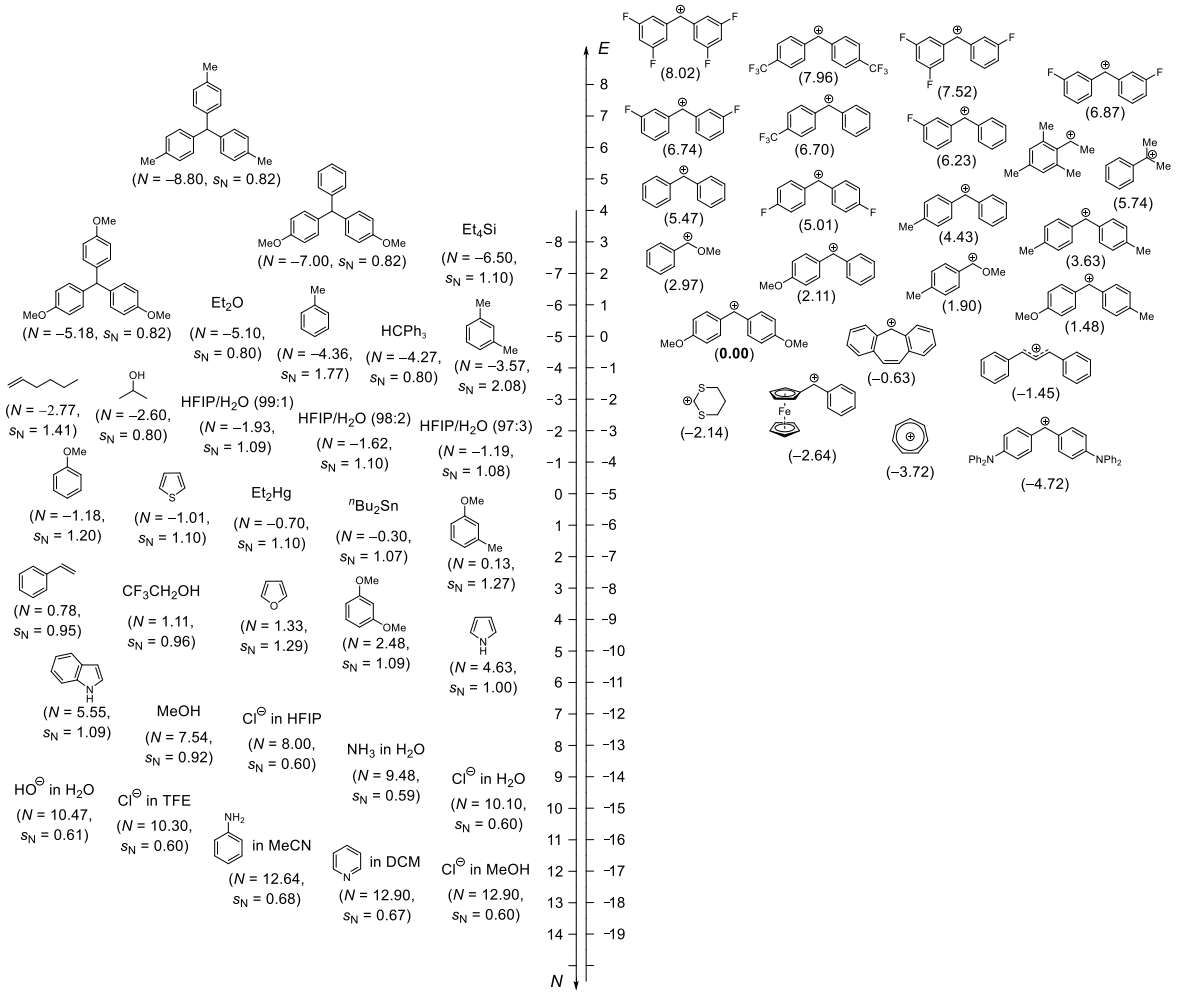


Figure 1.1. Extract from Mayr's electrophilicity-nucleophilicity scale

[35] Once the scales were established, the values of *s*, *N* and *E* parameters were also determined from reactions with other nucleophiles and electrophiles and correlated accordingly.

[36] According to the Database on Herbert Mayr's research group's website: http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank2/

This scale not only shows the relative trends of nucleophilicity and electrophilicity of a range of different chemical species, but it also allows the prediction of reactions of certain electrophiles with certain nucleophiles. Therefore, if the nucleophilicity and electrophilicity axes are aligned in opposite directions so that $N + 5 = -E$, the nucleophiles from the left side that are in the same line with electrophiles on the right side will prefer to react rapidly one with another at room temperature. "Rapidly" in this context refers to the rule:

$$E + N > -5$$

i. e. the rate constants between 10^{-6} and 10^{-3} L mol^{-1} s^{-1}, which are the limiting values when taken into account that for the most of nucleophiles *s* parameter lies between 0.6 and 1.2.[34] Although the generality of Mayr's approach is proved by many publications since then,[37] the universal prediction of nucleophilic substitution reactions is still not reachable.

1. 2. 5. The "ease" of carbocation formation

Carbocations are the intermediates in S_N1 reactions of alcohols, but is the S_N1 reactivity of alcohols exclusively dependent on the corresponding carbocation stability? To respond this question, Samec and Biswas within their study[38] systematically investigated the S_N1 reactivity of different classes of alcohols and nucleophiles (Figure 1.2) with various catalysts (Brønsted acid, Lewis acids, redox metals).

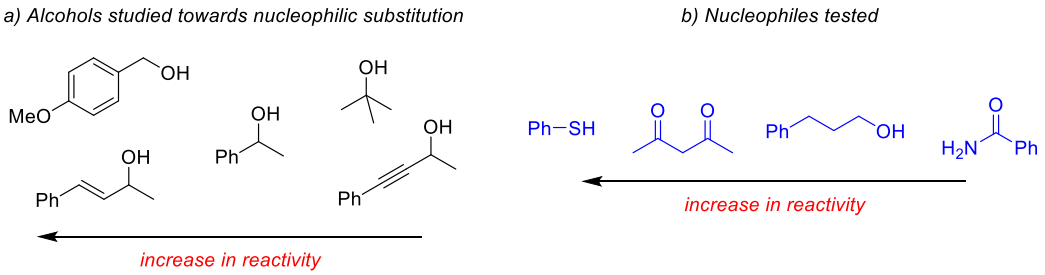


Figure 1.2. Alcohols and nucleophiles tested in Samec's and Biswas' study

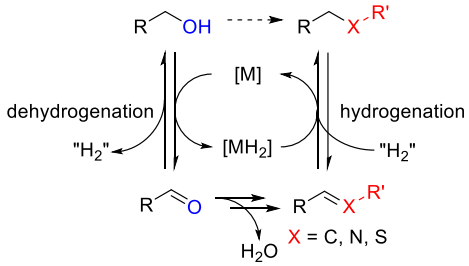
[37] (a) Roth M., Mayr H. *Angew. Chem. Int. Ed. Engl*. **1995**, 34, 2250-2252; (b) Mayr H., Kempf B., Ofial A. R. *Acc. Chem. Res.* **2003**, 36, 66-77; (c) Mayr H., Ofial A. R. *Pure Appl. Chem*. **2005**, 77, 1807-1821; (d) Mayr H., Ofial A. R. *J. Phys. Org. Chem*. **2008**, 21, 584-595

[38] Biswas S., Samec J. S. M. *Chem. Asian J.* **2013**, 8, 974-981

The conclusion of the study is therefore that "the *selectivity* of the alcohols to produce the desired substitution products was found to be independent of the electrophilicity of the generated carbocations, but highly dependent on the *ease* of formation of the cation." However, as it will be shown later in this thesis, this does not have to be necessarily true.

1. 2. 6. Functionalization of alcohols *via* a hydrogen borrowing strategy

It is worth to mention another way of alcohol functionalization - the "borrowing hydrogen" strategy, although it cannot be considered as substitution on a saturated carbon atom. This method describes a one-pot multi-step sequence starting with the alcohol dehydrogenation, followed by certain intermediate reaction(s), leading to the final hydrogenation step (Scheme 1.7). Apart from alcohols, this strategy has successfully been applied for functionalization of other classes of chemical compounds as well, such as alkanes and amines.[39]



Scheme 1.7. General scheme of borrowing hydrogen methodology

1. 2. 7. Catalysts for direct dehydroarylative substitution of alcohols

For direct substitution of alcohols in Friedel-Crafts reactions, Brønsted and Lewis acids have been used as catalysts. The first attempts to use Brønsted acids employed concentrated[40] (in 1936) and fuming[4b] (in 1942) sulfuric acid as solvents in order to drive intramolecular and intermolecular dehydroarylative transformations of tertiary alcohols, respectively. The first systematic study[41] of the use of alcohols in Friedel-Crafts reactions with 1-2 equiv. of $AlCl_3$ as catalyst was published in 1939. The first use of substoichiometric amount of Lewis acid (50

[39] Corma A., Navas J., Sabater M. J. *Chem. Rev*. **2018**, 118, 1410-1459
[40] Orcutt R. M., Bogert M. T. *J. Am. Chem. Soc.* **1936**, 58, 2055-2056
[41] Norris J. F., Sturgis B. M. *J. Am. Chem. Soc.* **1939**, 61, 1413-1417

mol% BF_3) as catalyst for Friedel-Crafts reactions of alcohols was published just a year before[4a], in 1938. However, it took more than 50 years from that time to find more efficient catalysts for alkylation of benzenes starting from alcohols. In 1996 it was disclosed that $Sc(OTf)_3$ and other lanthanide triflates[42] can catalyze Friedel-Crafts reactions of benzyl alcohols in lower substoichiometric loading (10 mol%).[5] After this groundbreaking work, other classes of alcohols were successfully involved in dehydroarylative reactions under substiochiometric Lewis or Brønsted acid catalysis as well, especially propargylic and allylic alcohols.

Apart from homogenous catalysis, Friedel-Crafts reactions under heterogenous catalysis are possible as well. One of the widely explored classes of heterogenous catalysts are zeolites.[43]

1. 3. HFIP as solvent and co-solvent in organic chemistry

1,1,1,3,3,3-hexafluoro-2-propanol or hexafluoroisopropanol (HFIP) was first synthesized most probably in the late fifties of the last century. The earliest reference[44] that mentions HFIP was submitted in 1960 (published in 1961), and it states that at the time "the synthesis of HFIP by reaction of hexafluoroacetone with Grignard reagent has already been known".[45] The reference further proposes another method for the synthesis of HFIP by reduction of hexafluoroacetone with sodium borohydride. From that time, more than six thousand references have cited the use of HFIP (Figure 1.3).

HFIP is a volatile, toxic colorless liquid with a sharp smell. Compared to its non-fluorinated analog, it has a lower boiling point and twice the density. Relative dielectric constants of HFIP and isopropanol do not differ significantly (Table 1.2), however, the ε_r of HFIP is twice as big as the ε_r of 2,2,2-trifluoroethanol (TFE). If we compare the acidity constant values, we observe that HFIP is 10^8 times more acidic than isopropanol. HFIP also has the

[42] In 1988, the efficiency of $B(OTf)_3$, $Al(OTf)_3$ and $Ga(OTf)_3$ as catalysts (with 50 mol% catalyst loading) for Friedel-Crafts alkylations from alkyl fluorides was revealed (read: Olah G. A., Farooq O., Farnia S. M. F., Olah J. A., *J. Am. Chem. Soc.* **1988**, 110, 2560-2565). This finding most probably influenced further development of metal triflates as catalysts for Friedel-Crafts reactions of alcohols.
[43] Sartori G., Maggi R. *Chem. Rev*. **2011**, 111, PR181-PR214
[44] Knunyants I. L., Krasuskaya M. P., *Byull. Izobretenii*, **1961**, No. 11, 25, Patent No. SU 138604
[45] Translation of the original text from the patent: "Способ получения гексафторизопропилового спирта взаимодействием гексафторацетона с реактивом Гриньера известен."

highest hydrogen bond donor ability from the majority of solvents (α = 1.96), however, it is the weakest hydrogen bond acceptor (β = 0.00).

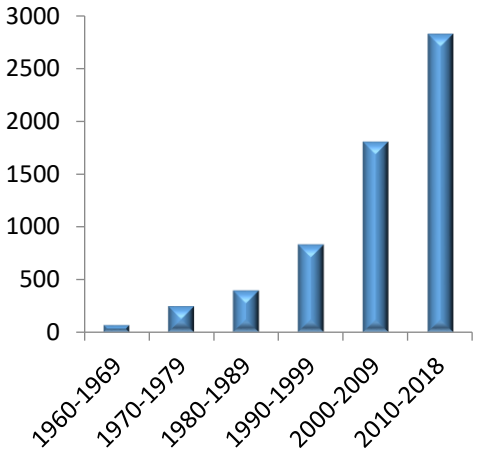


Figure 1.3. Number of citations of the use of hexafluoroisopropanol per decade since its first synthesis[46]

Due to its unique properties, HFIP has found a role in many areas of chemistry and biochemistry. It has been used as a solvent for metal-free[47] and metal-catalyzed[48] activation of C–H bonds. Its redox stability made it suitable to be used as solvent in electrochemistry.[49] Also, it was found that HFIP stabilizes secondary structures of proteins, which led to its application in protein structure and folding studies.[50] Since it has a relatively low boiling point (59 ºC), it can be easily removed by distillation, and several methods for its removal from reaction mixtures have been developed, including its co-distillation with alkenes on large scale.[51]

[46] Based on the search of the SciFinder database. Key words entered for the search: "hexafluoroisopropanol", "hexafluoroisopropyl alcohol", "1,1,1,3,3,3-hexafluoro-2-propanol", "HFIP".

[47] (a) Mfuh, A. M., Nguyen V. T., Chhetri B., Burch J. E., Doyle J. D., Nesterov V. N., Arman H. D., Larionov O. V. *J. Am. Chem. Soc*. **2016**, 138, 8408–8411; (b) Adams, A. M., Du Bois, J. *Chem. Sci*. **2014**, 5, 656–659

[48] (a) Wencel-Delord J., Colobert F. *Org. Chem. Front*. **2016**, 3, 394-400; (b) Dherbassy Q., Schwertz G., Chessé M., Hazra C. K., Wencel-Delord J., Colobert F. *Chem. Eur. J*. **2016**, 22, 1735-1743; (c) Jerhaoui S., Djukic J.-P., Wencel-Delord J., Colobert F. *Chem. Eur J.* **2017**, 23, 15594-15600; (d) Jerhaoui S., Poutrel P., Djukic J.-P., Wencel-Delord J., Colobert F. *Org. Chem. Front*. **2018**, 5, 409-414

[49] (a) Francke, R., Cericola, D., Kötz, R., Weingarth, D., Waldvogel, S. R. *Electrochim. Acta*, **2012**, 62, 372–380; (b) Ayata, S., Stefanova, A., Ernst, S. & Baltruschat, H. *J. Electroanal. Chem*. **2013**, 701, 1–6; (c) Beil S. B., Müller T., Sillart S. B., Franzmann P., Bomm A., Holtkamp M., Karst U., Schade W., Waldvogel S. R. *Angew. Chem. Int. Ed.* **2018**, 57, 2450-2454

[50] (a) Chiti F., Taddei N., Webster P., Hamada D., Fiaschi T., Ramponi G., Dobson C. M. Nat. Struct. Biol. 1999, 6, 380-387; (b) Sirangelo I., Dal Piaz F., Malmo C., Casillo M., Birolo L., Pucci P., Marino G., Irace G. *Biochemistry*, **2003**, 42, 312-319; (c) Kumar Y., Muzammil S., Tayyab S. *J. Biochem*. **2005**, 138, 335-341; (d) Mandal P., Molla A. R., Mandal D. K. *J. Biochem*. **2013**, 154, 531-540

[51] Hutton D. G. Patent No. 3284348, Ser. No. 439972, U. S. Patent Office, **1966**

Table 1.2. Key physico-chemical properties of isopropanol, HFIP, 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropyl methyl ether

Property	*i*PrOH	HFIP	TFE	HFIP-ME
Boiling point[52] [°C]	82	59	74	[50]
Freezing point[52] [°C]	–88	–4	–44	-
Density at 25 °C [g mL^{-1}]	0.782	1.596	(1.384)	[1.39]
Relative dielectric constant ε_r at 20 °C	(18.2)	17.8[53]	(8.6)	15.4[54]
pK_a	17.1[55]	9.3[56]	12.8	-
Ionizing power parameter[57] Y_{OTs}	–2.83	3.79	1.80	-
Hydrogen bond donor parameter[58] α	0.76	1.96	1.51	-
Hydrogen bond acceptor parameter[58] β	0.95	0.00	0.00	-

1. 3. 1. Carbocations in HFIP

In recent chemical literature, it can be often read that HFIP stabilizes carbocations, and that this is due to its high dielectric constant and low nucleophilicity.[59] It has already been used for the study of highly reactive carbocations, since it prolongs their lifetime.[60] In this regard, we can ask several fundamental questions: how exactly does HFIP stabilize carbocations? Is it a bulk effect of the solvent, or are there some interactions involved in this stabilization process? If we compare the relative dielectric constants of HFIP and isopropanol, we notice that they are almost the same. Therefore, the origin of the carbocation stabilization lies elsewhere. If we consider the ionizing ability of HFIP measured by 2-adamantyl tosylate method,[61] we observe it is the highest between all organic solvents[57] (Y_{OTs} = 3.79). This value is very close to the ionizing power of water[62] (Y_{OTs} = 4.1). Thus, the Y_{OTs} parameter alone cannot be relevant for explaining

[52] CRC Handbook of chemistry and physics, 87th edition, 2006-2007 (except for HFIP-ME)
[53] Fioroni M., Burger K., Mark A. E., Roccatano D., *J. Phys. Chem. B*, **2001**, 105, 10967-10975
[54] Nakazawa N., Kawamura M., Sekiya A., Ootake K., Tamai R., Kurokawa Y., Murata J. *Trans. of the JSRAE*, **2001**, 18, 263-271
[55] Serjeant E. P., Dempsey B. *Ionisation constants of organic acids in aqueous solutions*, **1979**, Pergamon Press
[56] Eberson L., Hartshorn M. P., Persson O. *J. Chem. Soc., Perkin Trans.* **1995**, 2, 1735-1744
[57] Bentley T. W., Carter G. E. *J. Org. Chem.* **1983**, 48, 579-584
[58] Kamlet M. J., Abboud J.-L. M., Abraham M. H., Taft R. W. *J. Org. Chem*. **1983**, 48, 2877-2887
[59] Colomer I., Chamberlain A. E. R., Haughey M. B., Donohoe T. J. *Nat. Rev*. **2017**, 1, Article No. 88
[60] Pezacki J. P., Shukla D., Lusztyk J., Warkentin J. *J. Am. Chem. Soc*. **1999**, 121, 6589-6598
[61] This method is based on the measurement of rate constants of hydrolysis of 2-adamantyl tosylate in different solvents. The ionizing ability parameter Y_{OTs} is defined as: $\log(k/k_0) = Y_{OTs}$, where k - is rate constant of the hydrolysis in the examined medium, and k_0 - rate constant of the hydrolysis in the mixture of 80% EtOH and 20% H_2O (v/v).
[62] Bentley, T. W.; Bowen, C. T.; Brown, H. C.; Chloupek, F. J. *J. Org. Chem*. **1981**, 46, 38-42

the stabilization effect of HFIP either (nor any nucleophilicity parameters that are calculated with the aid of Y_{OTs}, for example, N_{OTs}), otherwise, one could expect that water could stabilize carbocations even better than HFIP.

On the other hand, a study of Mayr and Ammer[63] offers a more detailed explanation. These authors postulated that for each mixture of two solvents there is a critical concentration of one of them where S_N2 processes change to S_N1 for a given electrophile. In other words, an electrophile can react *via* an S_N1 mechanism in one solvent and *via* S_N2 in another, depending on the nucleophilic properties of a given solvent. Less nucleophilic solvents will therefore "give more space" to the development of the positive charge on the involved substrates and favor an S_N1 mechanism, whereas more nucleophilic solvents will be involved in an S_N2 process. To explain this change in mechanism, the Mayr-Patz equation for solvents can be used:

$$\log k_1 = s_N (N_1 + E) \text{ ... (eq. 1.1)}$$

where k_1 - is the first order rate constant for the reactions of electrophiles (i. e. carbocations) with solvents at 20 ^oC, s_N and N_1 - nucleophilic kinetic parameters of the solvent, and E - electrophilic kinetic parameter of the electrophile. By using a series of substituted benzhydrylium ions (ranging from stabilized carbocations with $E \sim 2$ to the most reactive carbocations with $E \sim 8$) with known electrophilicity parameters E, they were able to determine the nucleophilicity parameters[64] N_1 and s_N for the series of HFIP/water mixtures (Table 1.3).

Table 1.3. Mayr's solvent nucleophilic parameters of a series of HFIP/water mixtures

Solvent composition (w/w)	s_N	N_1
50% HFIP/50% H_2O	1.03	1.50
70% HFIP/30% H_2O	0.96	1.65
90% HFIP/10% H_2O	0.93	0.96
93% HFIP/7% H_2O	0.96	0.34
95% HFIP/5% H_2O	0.97	–0.10
97% HFIP/3% H_2O	0.97	–1.19
98% HFIP/2% H_2O	1.10	–1.62
99% HFIP/1% H_2O	1.09	–1.93

[63] Ammer J., Mayr H. *J. Phys. Org. Chem.* **2013**, 26, 59-63

[64] Higher values of N and N_1 parameters refer to increased nucleophilicity of the observed species, or solvent, respectively. Analogously, higher E parameters indicate increased electrophilic character.

From the data shown in Table 1.3, it is obvious that the nucleophilicity of the solvent mixture strongly decreases with augmenting the molar ratio of HFIP in the mixture, leading to negative values of N_1 parameter for HFIP.[65] Not only is this value negative, but it is the lowest one, compared to other solvents[66] (Table 1.4).

Table 1.4. Mayr's nucleophilicity values for different solvents. Slope parameter $s = 0.9$ is recommended for these solvents. Solvent compositions are given as v/v percentages, except for TFE and HFIP mixtures (w/w).

Solvent	N_1
70% EtOH/30% H_2O	6.5
80% 1,4-dioxane/20% H_2O	6.1
95% acetone/5% H_2O	6.1
CH_3COOH	4.1
HCOOH	3.1
97% TFE /3% H_2O	1.8
97% HFIP/3% H_2O	–1.2

Still, all these considerations do not allow for explaining the transition from an S_N1 to S_N2 process in different solvents. In order to achieve that, we should take into account one key feature that distinguishes these two mechanisms – the existence of carbocations. In general, we can claim that an intermediate exists if its lifetime is longer than the duration of one bond vibration[67] (approximately 10^{-13} s). Therefore, if the lifetime of a carbocation is at least 10^{-13} s, we can consider the process as S_N1. Otherwise, the process is S_N2. Taking this into account, the values of s_N and N_1 parameters for HFIP can be used to estimate critical E values that an electrophile should have in order to be involved in an S_N1 process as follows:

The rate constant in Mayr's experiments represents the number of carbocations trapped by solvent per second, and therefore the carbocation lifetime can be expressed as: $\tau = 1/k$. From the critical value of the carbocation lifetime $\tau \geq 10^{-13}$ s, we can calculate the critical value of the carbocation trapping rate constant: $k \leq 10^{13}$ s^{-1}, and the critical value of its logarithm: $\log k \leq 13$. By replacing "$\log k$" term with "$s_N (N_1 + E)$" (cf. eq. 1.1) in the previous expression, we get:

[65] In laboratory conditions HFIP always contains traces of water, therefore parameters found for 99% pure HFIP containing 1% of water can be considered with high degree of reliability as if they were found for HFIP that is used in laboratory conditions.
[66] Minegishi S., Kobayashi S., Mayr H., *J. Am. Chem. Soc*. **2004**, 126, 5174-5181
[67] Cox R. A. Int. *J. Mol. Sci.* **2011**, 12, 8316-8332

$$s_N\,(N_1 + E) \leq 13 \text{ ... (eq. 1.2).}$$

Finally, by replacing the values $s_N = 1.09$ and $N_1 = -1.93$ for 99% HFIP from Table 1.3 in the eq. 1.2, we obtain the critical value of the electrophilicity parameter: $E \leq 14$. This means that electrophiles with $E \leq 14$ will react *via* an S_N1 pathway in HFIP, whereas electrophiles with E greater than 14 will undergo an S_N2 reaction. Since the highest E parameters determined so far reach values of 8 for benzhydrylium ions substituted with two fluorines or one trifluoromethyl group on each phenyl ring,[68] the critical value of 14 is far beyond the electrophilicity values of the most electrophilic carbocations that have been measured so far. This leads us to the conclusion that generally in HFIP S_N2 processes on highly reactive carbocations (still with $E \leq 14$) cannot be observed, i. e. that these carbocations will always react *via* S_N1 mechanism in HFIP in nucleophilic substitution reactions.

Although Mayr's study provided deeper, more detailed and quantitative insight into the nature of the "HFIP effect" on stabilization of carbocations, these results do not, however, explain *why* HFIP has such a low value of its nucleophilicity parameter N_1, i. e. the *cause* of this interesting property of HFIP. Also, they do not consider any possible steric or self-association effects. However, with these results in hand, one can argue if HFIP actually *stabilizes* (stabilization = thermodynamic phenomenon) carbocations at all, or just "allows" them to exist longer (kinetic phenomenon) due to its extremely low nucleophilicity (and possibly other inherent features).

1. 3. 2. Self-association in HFIP

Although HFIP has been present in chemists' laboratories for almost 60 years, the scientific community has just recently started getting deeper insights into its structural features in the condensed phase. This happened thanks to the discovery of the effect that HFIP exhibited in alkene epoxidation. Although it has been known that fluorinated compounds such as hexafluoroacetone accelerate alkene epoxidation with H_2O_2 since 1979,[69] it was discovered only

[68] Data taken from the database at Mayr's research group website: http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html

[69] (a) Heggs R. P., Ganem B. *J. Am. Chem. Soc.* **1979**, 101, 2484-2486; (b) Biloski A. J., Heggs R. P., Ganem B., *Synthesis*, **1980**, 810-811; Ganeshpure P. A., Adam W. *Synthesis*, **1996**, 179-188

in 1999 by Sheldon and coworkers[70] that the same reaction can be run in TFE, with significant reduction of metal catalyst loading. This lead to the subsequent discovery of Neimann and Neumann[71] that the same reactivity could be achieved without any catalyst when HFIP is employed as solvent. Since in that case no metals were involved in the process of H_2O_2 activation, it could have only have happened through a new, purely organocatalytic mode of activation. Soon after, Berkessel and coworkers followed up with a series of quantitative studies of this "HFIP effect". They showed that the alkene epoxidation reaction is 10^5 times faster when run in HFIP instead of in 1,4-dioxane in the absence of additional catalysts.[72] Further kinetic studies revealed that the reaction order of solvent in this case is 2-3, suggesting that the situation is a bit more complicated than it was initially proposed by Neimann and Neumann (Figure 1.4.a). This result indicated that aggregates of 2-3 molecules of HFIP act in a cooperative manner to activate H_2O_2, and motivated Berkessel and coworkers to explore the crystal structure of HFIP. It was found that HFIP forms infinite helices in the solid state, in which HFIP molecules are interconnected by hydrogen bonds[73] (Figure 1.4. b and c). Unlike the gas phase where HFIP molecules mostly exist in an antiperiplanar (ap) conformation, in the solid state HFIP molecules adopt synclinal (sc) to synperiplanar (sp) conformations with a HCOH torsional angle around 31° and a maximal dipole moment (Figure 1.4.d). These findings are in accordance with detailed conformational analysis that has revealed that monomeric HFIP exhibits its highest hydrogen bond donor ability and lower σ^*_{OH} orbital energy in this form. Further computational studies of HFIP oligomers revealed that the association of two and three HFIP molecules leads to increased polarization of the OH groups, i. e. an increase of the terminal OH proton partial charge. In other words, aggregation in HFIP enhances its ability to form hydrogen bonds with more significant covalent character. However, for oligomers bigger than trimers this effect becomes insignificant. All these findings match excellently with the reaction order of HFIP being 2 to 3 in epoxidation reactions, explaining why in particular 2 to 3 molecules of HFIP coordinate with one molecule of H_2O_2 in order to form the active catalytic species for oxygen transfer to the alkene. Finally, all these conclusions are supported by the experimental determination of the activation entropy

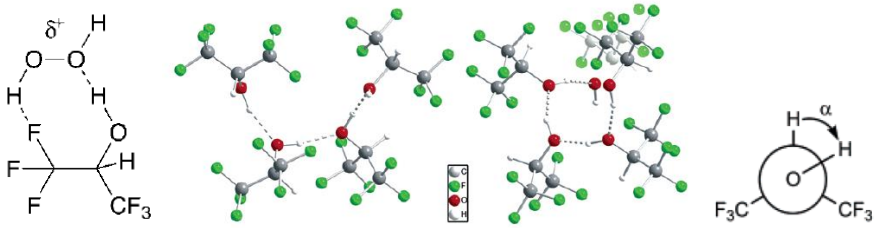
[70] (a) van Vliet, M. C. A., Arends, I. W. C. E., Sheldon, R. A. *Chem. Commun*. **1999**, 821-822 (b) van Vliet, M. C. A., Arends, I. W. C. E., Sheldon, R. A. *Chem. Commun*. **1999**, 263-264. (c) Shryne, T. M., Kim, L. US Patent 4024165, 1977

[71] Neimann, K.; Neumann, R. *Org. Lett*. **2000**, 2, 2861-2863

[72] Berkessel A., Andreae M. R. M. *Tetrahedron Lett.* **2001**, 42, 2293-2295

[73] Berkessel A., Adrio J. A., Hüttenhein D., Neudörfl J. M. *J. Am. Chem. Soc*. **2006**, 128, 8421-8426

being $\Delta S^{\neq} = -39$ cal mol^{-1} K^{-1}, which suggests a highly ordered transition state in the rate determining step.[74]



(a) (b) (c) (d)

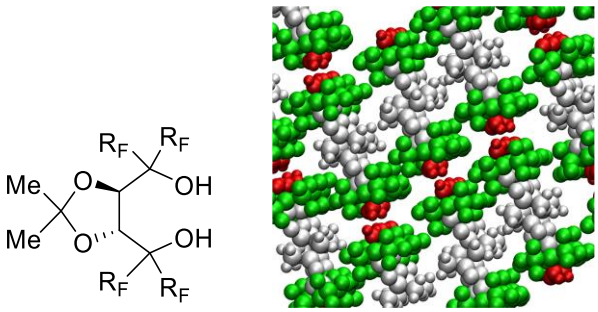
Figure 1.4. Rough proposition of the electrophilically activated H_2O_2 intermediate by Neimann and Neumann (a). Helical structures in crystal structure of HFIP: view perpendicular to the helix axis (b) and view along the helix axis (c). Newman representation of the synclinal conformation of HFIP with torsional angle α (d).

From the crystal structure it can be noticed that formation of HFIP helices results in the "division" of the crystal in two microphases. The core of the each helix forms a *polar microphase* along the axe of the helix, where hydroxyl groups are involved in the hydrogen bond network. Outer, surface parts of the helices by means of which the helices are in contact, form a *fluorous microphase*, consisting of CF_3 groups. When the olefin and H_2O_2 are added to HFIP, H_2O_2 joins the polar microphase, whereas olefin molecules form the third, *non-polar microphase*. This separation of microphases best resembles the microdomaines that can be observed in crystals of highly fluorinated analogue of tartrate-derived TEFDDOLs[75] (α,α,α′,α′-tetrakis(perfluoroaryl/alkyl)-2,2′-dimethyl-1,3-dioxolane-4,5-dimethanols) (Figure 1.5).

Therefore, although macroscopically the reaction mixture of an alkene and H_2O_2 in HFIP appears homogenous, in reality it contains three different types of micro-domains, and therefore the epoxidation reaction in this system can be regarded as interfacial or phase-transfer process. This is confirmed by molecular dynamics simulations and small-angle X-ray scattering (SAXS) experiments.[76] Neighbor counts[77] and surface coverage analysis[78] provided deeper insight into

[74] Berkessel A., Adrio J. A., *J. Am. Chem. Soc.* **2006**, 128, 13412-13420
[75] Berkessel, A.; Vormittag, S. S.; Schlörer, N. E.; Neudörfl, J. M. *J.Org. Chem.* **2012**, 77, 10145-10157
[76] Hollóczki O., Berkessel A., Mars J., Mezger M., Wiebe A., Waldvogel S. R., Kirchner B. *ACS Catal*. **2017**, 7, 1846-1852

the relative positions of groups at the interfaces of these domains, and allowed to propose solvation patterns of active and "inactive" catalytic species for the reaction of cyclooctene epoxidation by H_2O_2 in HFIP (Figure 1.6).



(a) (b)

Figure 1.5. (a) The structure of TEFDDOLs. (b) Segregation of polar (hydroxyl groups, red), nonpolar (the CH_3 units and the cyclooctene rings, gray) and fluorous (CF_3-C-CF_3 units, green) phases in the crystal structure of TEFDDOL

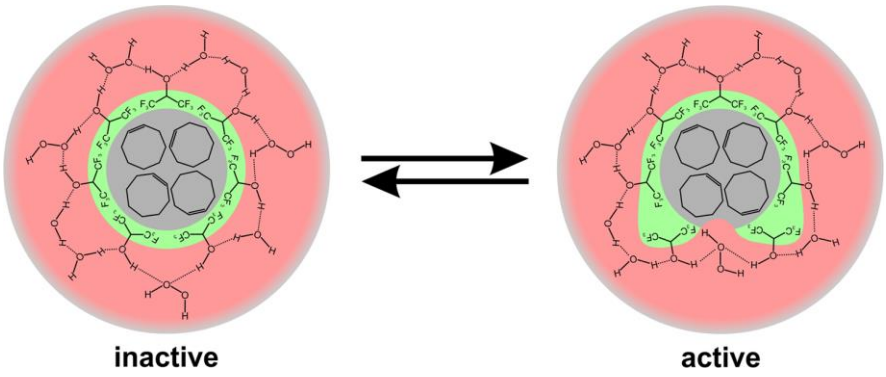


Figure 1.6. Proposed solvent patterns in the reaction mixture of cyclooctene and H_2O_2 in HFIP

1. 3. 3. Acid-induced aggregation in solvents

In the previous subchapter, we have seen that kinetic experiments can give us valuable insights into the nature of intermediate species in chemical reactions, and that they can help detect aggregation phenomena in solvents. Another example of such reactivity is found in the

[77] Neighbor counts is the number of certain kinds of molecules sharing a face with the observed molecule at a time. It is calculated based on Voronoi tessellation analysis (for application to water clathrates, see for example: Chakraborty S. N., Grzelak E. M., Barnes B. C., Wu D. T., Sum A. K. *J. Phys. Chem. C*, **2012**, 116, 20040-20046)
[78] Surface coverage analysis represents the surface percentage of a given molecule that is shared with another observed molecule.

work of Pocker and coworkers. In a simple reaction of hydrohalogenation of alkenes, one would expect that the reaction order in the acid HX equals one, as well as the reaction order in alkene. Interestingly, in 1960 Pocker and coworkers[79] found that this is not the case when nitromethane was used as solvent - reaction order of alkene was indeed one, but reaction order in acid was 2. Particularly, for addition of hydrogen chloride to isobutene in nitromethane they found the rate law to be:

$$v_{\text{addition}} = k\,[\text{alkene}]\,[\text{HCl}]^2 \ldots \text{(eq. 1.3)}.$$

Rather than investigating further the role of the solvent, they concluded (based on conductivity measurements) that ions HCl_2^- were formed in process

$$2HCl \rightleftharpoons H^+ + HCl_2^-,$$

and that the reaction proceeded afterwards with the following mechanism:

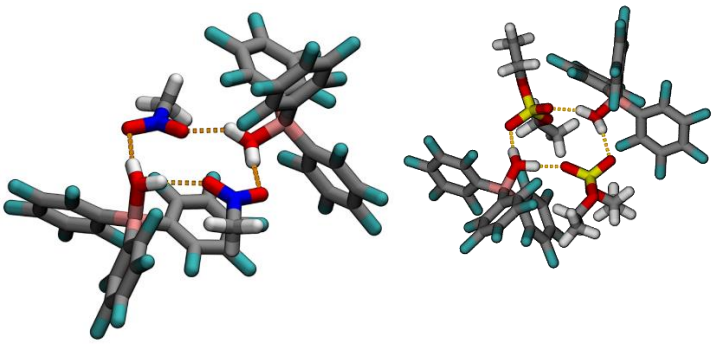
$$Me_2C{=}CH_2 + H^+ \rightleftharpoons Me_3C^+ \text{ (step 1)},$$

$$Me_3C^+ + HCl_2^- \rightleftharpoons Me_3CCl + HCl \text{ (step 2)},$$

which satisfied the explanation of the second reaction order in acid. However, in this study no further quantitative investigations of the nitromethane effect were conducted.

More than half a century later, Moran and coworkers[80] found similar rate dependence while they were investigating $B(C_6F_5)_3{\cdot}H_2O$ catalyzed azidations of tertiary alcohols in nitromethane. Similarly, they found the reaction order of the catalyst to be 2, and moreover, the reaction order in solvent to be 2 as well. IR studies revealed the existence of hydrogen bonds between the OH group of the catalyst and nitro group of nitromethane, suggesting the presence of catalyst-solvent aggregates in the rate-determining step. Furthermore, it was found that this phenomenon is not related just to nitromethane, but is more general, and applies to sulfates, since the O-S-O angle in sulfates is very similar to O-N-O angle in nitro-compounds (Figure 1.7).[81]

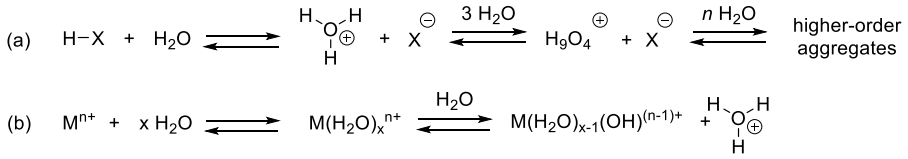
[79] Pocker Y. *J. Chem. Soc*. **1960**, 1292-1297
[80] Dryzhakov M., Hellal M., Wolf E., Falk F. C., Moran J. *J. Am. Chem. Soc*. **2015**, 137, 9555-9558
[81] Montalvo-Acosta J. J., Dryzhakov M., Richmond E., Cecchini M., Moran J., *Under review*



(a) (b)

Figure 1.7. (a) Complex of $B(C_6F_5)_3 \cdot H_2O$ and nitromethane. (b) Complex of $B(C_6F_5)_3 \cdot H_2O$ and diethylsulfate.

It is also worth mentioning at this point that Brønsted and Lewis acids exist in the form of aggregates in water (Scheme 1.8). Upon dissociation in water, Brønsted acid forms range of clusters[82], which can be represented in a simplified manner as H_3O^+, or more precisely as $H_5O_2^+$ or $H_9O_4^+$. On the other hand, Lewis acids, such as metal cations, coordinate several molecules of water and form *aquo* complexes[83]. Furthermore, in the process of hydrolysis these complexes release protons, which immediately become hydrated, forming the same water-proton clusters.[84]



Scheme 1.8. Formation of hydronium clusters in water (a) and metal *aquo* complexes (b)

[82] Wicke E., Eigen M., Ackermann Th. *Zeitschrift für Physikalische Chemie*, **1954**, 1, 340-364
[83] (a) Scham T. K., Hastings J. B., Perlman M. L. *J. Am. Chem. Soc*. **1980**, 102, 5906-5908; (b) Kallies B., Meier R. *Inorg. Chem*. **2001**, 40, 3101-3112
[84] For example: Brosset C., Biedermann G., Sillén L. G. *Acta Chem. Scand*. **1954**, 8, 1917-1926

1. 4. Brønsted acids, Lewis acids and superacids as catalysts and reaction media

Brønsted acids can be involved in catalysis in two possible manners: general and specific:

1) General acid catalysis – the reaction of the substrate X is catalyzed by a general acid HA, and the acid intervenes in the rate-determining step to form a reactive protonated intermediate HX^+:

$$X + HA \xrightarrow{k_1} HX^+ + A^- \ldots \text{(step 1)}.$$

Still, the acid HA can dissociate in the medium, and therefore the reaction will occur if the protons from the acid HA exist in the medium as well:

$$X + H^+(\text{solvated}) \xrightarrow{k_2} HX^+ \ldots \text{(can occur in parallel with the step 1)}.$$

The next step(s) is (are) formation of the reaction product from the intermediate HX^+. Therefore, the reaction rate in this case will depend both on the concentration (activity) of the acid HA and on the H^+ ions activity (pH), i. e. on the total acid concentration, and the overall rate is as follows:

$$v = k_1 [X] [HA] + k_2 [X] [H^+] = [X] (k_1 [HA] + k_2 [H^+]) .$$

2) Specific acid catalysis – in this case, the catalyst is exclusively proton, i. e. protonated form of the solvent, which is involved in fast equilibrium first step where the reactive protonated intermediate HX^+ is formed:

$$X + H^+(\text{solvated}) \rightleftharpoons HX^+ \ldots \text{(step 1)}.$$

This is followed by formation of the product, which is the rate determining step:

$$HX^+ + Y \xrightarrow{k_2} \text{product} \ldots \text{(step 2, RDS)}.$$

Therefore, unlike the previous case, the reaction rate will depend on the concentration of the reactive intermediate HX^+:

$$v \sim k_2 [HX^+].$$

If the step 2 is bimolecular, the reaction rate expression will be: $v = k_2 [HX^+] [Y]$. If the step 2 is monomolecular, the reaction rate expression stays: $v = k_2 [HX^+]$, which means that in the case of specific acid catalysis, the reaction rate depends only[85] on the concentration of the protonated intermediate. Since HX^+ in the step 1, its concentration strongly depends on the concentration of the specific acid, i. e. on the concentration of the H^+(solvated) species, which is equal to pH.[86] Therefore, the rate of the specific acid catalyzed reaction is exclusively pH-dependent.

When discussing the Lewis acid catalyzed reactions, one should be very careful, because "hidden" Brønsted acid catalysis can be the actual cause of the catalytic activity due to the hydrolysis process (Scheme 1.8b). For example, it was found that in some cases when metal triflates were used as "catalysts", the catalytic activity actually arose from the small amounts of triflic acid generated in the medium, and even led to the same reaction yields as metal triflates.[87] Another example is tris(pentafluorophenyl)borane catalyst, which when hydrated, acts as strong Brønsted acid.[80]

A century ago, it was noticed that dimerization of acids increases their acidity[88]. Since then, chemists were interested in increasing the acidity of acids further and discovering new (hyper-) strong acids. This lead to the development of superacids, which were defined by Gillespie as the acids stronger[89] than 100% sulfuric acid.[90] Olah extensively used superacids such as "magic acid" (FSO_3H/SbF_5 1:1 mixture) and $HSbF_6$ for study of various carbocations.[91]

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[85] If the concentration of the other reactant Y is kept constant, this is also true for the bimolecular process.

[86] More precisely, the reaction rate will depend on the *activity* of the protonated solvent species, not on the concentration.

[87] (a) Evans P. A., Cui J., Gharpure S. J., Hinkle R. J. *J. Am. Chem. Soc*. **2003**, 125, 11456-11457; (b) Rosenfeld D. C., Shekhar S., Takemiya A., Utsunomiya M., Hartwig J. F. *Org. Lett.* **2006**, 8, 4179-4182

[88] Meerwein H., Hammel O., Serini A., Vorster J. *Justus Liebigs Annalen der Chemie*, **1927**, 16-47

[89] "Stronger" in the sense of superacids refers to Hammet function (H_o) values lower than –12.

[90] Gillespie R. J., Peel T. E. *Adv. Phys. Org. Chem*. **1971**, 9, 1-24

[91] For example: (a) Olah G. A., Pittman C. U. *J. Am. Chem. Soc.* **1966**, 88, 3310-3312; (b) Commeryas A., Olah G. A. *J. Am. Chem. Soc*. **1969**, 91, 2929-2942; (c) Olah G. A., Shen J. *J. Am. Chem. Soc*. **1973**, 95, 3582-3585; (d) Olah G. A., DeMember J. R., Mo Y. K., Svoboda J. J., Schilling P., Olah J. A. *J. Am. Chem. Soc*. **1974**, 96, 884-892; (e) Olah G. A., Schilling P., Staral J. S., Halpern Y., Olah J. A. *J. Am. Chem. Soc.* **1975**, 97, 6807-6810; (f) Olah G. A., Surya Prakash G. K., Barzaghi M., Lammertsma K., Von R. Schleyer P., Pople J. A. *J. Am. Chem. Soc*. **1986**, 108, 1032-1035;

However, the interest for superacid chemistry did not decrease since then. Recently, the crystal structure of fluoroantimonic acid ($HSbF_6$), the strongest superacid known, was published by Gandon and coworkers (Figure 1.8).[92]

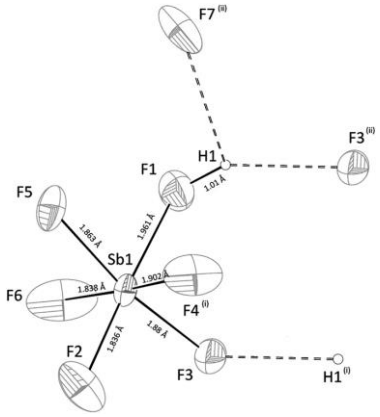
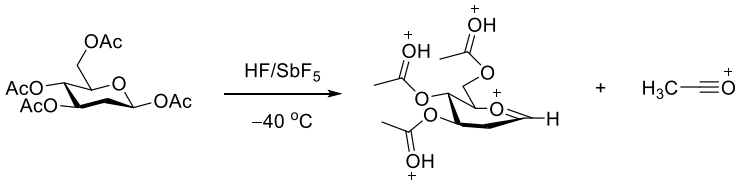


Figure 1.8. An $HSbF_6$ molecule with intermolecular hydrogen bonds in the crystal

This superacid was also used by Thibaudeau and coworkes for the first experimental detection of the glucosyl cations (Scheme 1.9).[93]



Scheme 1.9. The use of $HSbF_6$ for capture of the glucosyl cation

The same group reported use of the HF/SbF_5 superacidic medium for trifluoromethyl-thiolation[94], fluorination[95], chlorofluorination[96] of aromatic amines[97], as well as for cellulose depolymerization.[98] Triflic acid was also used with DCM as reaction medium for cascade

[92] Bour C., Guillot R., Gandon V. *Chem. Eur. J*. **2015**, 21, 6066-6069
[93] Martin A., Arda A., Désiré J., Martin-Mingot A., Probst N., Sinaÿ P., Jiménez-Barbero J., Thibaudeau S., Blériot Y. *Nat. Chem*. **2016**, 8, 186-191
[94] Milandou L. J. C. B., Carreyre H., Alazet S., Greco G., Martin-Mingot A., Nkounkou Loumpangou C., Ouamba J.-M., Bouazza F., Billard T., Thibaudeau S. *Angew. Chem. Int. Ed*. **2017**, 56, 169-172
[95] Martin-Mingot A., Compain G., Liu F., Jouannetaud M.-P., Bachmann C., Frapper G., Thibaudeau S. *J. Fluor. Chem*. **2012**, 134, 56-62
[96] Liu F., Martin-Mingot A., Jouannetaud M.-P., Bachmann C., Frapper G., Zunino F., Thibaudeau S. *J. Org. Chem*. **2011**, 76, 1460-1463
[97] Le Darz A., Castelli U., Mokhtari N., Martin-Mingot A., Marrot J., Bouazza F., Karam O., Thibaudeau S. *Tetrahedron*, **2016**, 72, 674-689
[98] Martin-Mingot A., De Oliveira Vigier K., Jérôme F., Thibaudeau S. Org. Biomol. Chem. 2012, 10, 2521-2524

cationic polycyclization.[99] The group of Vasilyev has very recently reported on use of triflic acid as reaction medium for various kinds of chemical transformations.[100] Not less interesting certainly are Lewis superacids, defined as Lewis acids stronger[101] than monomeric SbF_5 in the gas phase.[102]

1. 5. Trifluoromethyl group in organic molecules

Interest for fluorinated, perfluorinated, and particularly trifluoromethylated compounds has been high among chemists for more than half of the century so far. Fluorine is the most electronegative atom,[103] and when introduced in a molecule in the place of a hydrogen, it brings many new physico-chemical and pharmaceutically relevant properties to the molecule. Thanks to its negative inductive effect, it raises the acidity of the adjacent groups.[104] This change in the pK_a usually leads to dramatic change in pharmacokinetic properties (such as bioavailibility[105]) and binding affinity of the molecule.[106] C–F bond is the strongest covalent single carbon-heteroatom bond[107] (447 kJ mol^{-1}), and although polar, it is non-polarizable. This property has extensively been used to increase the metabolic stability of pharmaceuticals.[108] The length of a C–F bond (141 pm) is closer to the length of a C–O bond (143 pm) than to the C–H bond (109 pm).[109]

[99] Theunissen C., Métayer B., Henry N., Compain G., Marrot J., Martin-Mingot A., Thibaudeau S., Evano G. *J. Am. Chem. Soc*. **2014**, 136, 12528-12531

[100] (a) Golushko A. A., Sandzhieva M. A., Ivanov A. Yu., Boyarskaya I. A., Khoroshilova O. V., Barkov A. Yu., Vasilyev A. V. *J. Org. Chem.* **2018**, 83, 10142-10157; (b) Iakovenko R. O., Kazakova A. N., Boyarskaya I. A., Gurzhiy V. V., Avdontceva M. S., Panikorovsky T. L., Muzalevskiy V. M., Nenajdenko V. G., Vasilyev A. V. *Eur. J. Org. Chem.* **2017**, 5632-5643; (c) Saulnier S., Lozovskiy S. V., Golovanov A. A., Ivanov A. Yu., Vasilyev A. V. *Eur. J. Org. Chem*. **2017**, 3635-3645; (d) Zalivatskaya A. S., Ryabukhin D. S., Tarasenko M. V., Ivanov A. Yu., Boyarskaya I. A., Grinenko E. V., Osetrova L. V., Kofanov E. R., Vasilyev A. V. *Belstein J. Org. Chem*. **2017**, 13, 883-894; (e) Saulnier S., Golovanov A. A., Vasilyev A. V. *RSC Adv*. **2016**, 6, 103546-103555

[101] In case of Lewis superacids, "stronger" means lower values of enthalpy of fluoride ion binding, i. e. higher fluoride ion affinity (FIA).

[102] Müller L. O., Himmel D., Stauffer J., Steinfeld G., Slattery J., Santiso-Quiñones G., Brecht V., Krossing I. *Angew. Chem. Int. Ed.* **2008**, 47, 7659-7663

[103] Pauling L. *J. Am. Chem. Soc*. **1932**, 54, 3570-3582

[104] Schlosser M. *Angew. Chem. Int. Ed.* **1998**, 110, 1496-1513

[105] Bioavailability is the percentage of the dose that reaches the circulatory system.

[106] Böhm H.-J., Banner D., Bendels S., Kansy M., Kuhn B., Müller K., Obst-Sander U., Stahl M. *ChemBioChem*, **2004**, 5, 637-643

[107] Smith D. W. *J. Phys. Chem. A*, **1998**, 102, 7086-7087

[108] Purser S., Moore P. R., Swallow S., Gouverneur V. *Chem. Soc. Rev.* **2008**, 37, 320-330

[109] Dunitz J. D., Schweizer W. B. *Chem. Eur. J*. **2006**, 12, 6804-6815

Therefore, the C–F bond is bioisosteric with C–OH and C=O group[110] and even with C–OCH_3 fragment.[111]

It is therefore clear that the introduction of the trifluoromethyl group will also bring new interesting properties to a molecule, compared to its non-trifluoromethylated analog. Although exchange of one hydrogen for a fluorine atom does not affect significantly molecular size (van der Waals radius of fluorine is 147 pm, and of hydrogen 120 pm),[108] introduction of the trifluoromethyl group does change the molecular shape significantly, since its van der Waals volume is estimated to be approximately the same as the volume of the ethyl group.[112]

While the majority of chemists would intuitively expect the electronic properties of the CF_3 group to be exclusively electron-withdrawing, this is not completely true.[113] It was found that the inductive effect that fluorine atom provokes in molecules decays in an alternate manner:

δ– δ+ δδ– δδ+
F←C←C←C

and this is so called "β-effect".[114] This effect is well studied in aliphatic,[115] as well as in aromatic compounds.[116] Therefore, the replacement of a hydrogen atom with the trifluoromethyl group leads to the increased electron deficiency in the remaining part of the molecule as a whole, but the α-atom, adjacent to the CF_3-group, will still be partially negatively charged. This would mean that the CF_3 group actually exhibits an electropositive rather than an electronegative effect on the adjacent atom, but still acts as a highly electronegative group on a remote atom. Still, the situation is not that straightforward, since the electronegativity of the CF_3 group strongly depends on the method used for its calculation, as well as on the process that is observed.[117] Nevertheless, due to its overall effect on the electron charge density in a molecule, the presence

[110] Biffinger J. C., Kim H. W., DiMagno S. G. *ChemBioChem*, **2004**, 5, 622-627
[111] Schweizer E., Hoffmann-Röder A., Schärer K., Olsen J. A., Fäh C., Seiler P., Obst-Sander U., Wagner B., Kansy M., Diderich F. *ChemMedChem*, **2006**, 1, 611-621
[112] Müller K., Faeh C., Diderich F. *Science*, **2007**, 317, 1881-1886
[113] Tomashenko O. A., Grushin V. V. *Chem. Rev*. **2011**, 111, 4475-4521
[114] Pople J. A., Gordon M. *J. Am. Chem. Soc*. **1967**, 89, 4253-4261
[115] (a) Davis D. W., Banna M. S., Shirley D. A. *J. Chem. Phys*. **1974**, 60, 237-245; (b) Palmer M. H., *J. Mol. Str. Theochem*, **2000**, 500, 225-243
[116] Holmes, S. A.; Thomas, T. D. *J. Am. Chem. Soc*. **1975**, 97, 2337-2341
[117] True J. E., Thomas T. D., Winter R. W., Gard G. L. *Inorg. Chem*. **2003**, 42, 4437-4441

of the CF_3 group in aliphatic chains decreases their lipophilicity. On the other hand, the attachment of the CF_3 group to an aromatic moiety increases its lipophilicity.[118]

1. 6. Conclusion of Chapter 1 and the aim of the thesis

In this chapter, basic notions of Friedel-Crafts and nucleophilic substitution reactions were described. Special attention was drawn to the explanation of carbocation reactivity. Accent was also put on the Brønsted acid and superacid catalysis, as well as on the acid-induced aggregation phenomena in solvents. Finally, the interest of introduction of the trifluoromethyl group into organic molecules was discussed. Therefore, the aim of this chapter is to summarize key elements of previous findings relevant to this thesis and give the theoretical context for the work that will be further presented in the chapters 2-5.

In 2007, the ACS Green Chemistry Institute Pharmaceutical Roundtable highlighted OH group activation for nucleophilic substitution and Friedel-Crafts reactions on unactivated substrates as two out of 30 key research directions in modern chemistry.[119] The work presented in this thesis presents a modest contribution to these two areas of organic chemistry. The main aims that the author of this thesis has been seeking to accomplish are following:

1. to push the boundaries of the electronically deactivated benzylic alcohol reactivity in Friedel-Crafts reactions,

2. to explain the key specific properties of the catalytic system (Brønsted superacid catalysts in hexafluoroisopropanol) that promotes the reactivity mentioned in the previous line,

3. to apply these findings for improving the scope of Friedel-Crafts reactivity of propargylic alcohols, aliphatic alcohols and substituted cyclopropanes.

[118] Smart B. E. *J. Fluor. Chem.* **2001**, 109, 3-11

[119] Constable D. J. C., Dunn P. J., Hayler J. D., Humphrey G. R., Leazer J. L. Jr., Linderman R. J., Lorenz K., Manley J., Pearlman B. A., Wells A., Zaks A., Zhang T. Y. *Green Chem.* **2007**, 9, 411-420

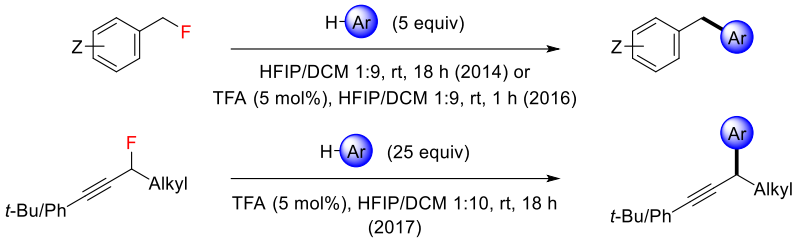
CHAPTER 2

CATALYTIC DEHYDROARYLATIVE REACTIONS OF DEACTIVATED BENZYLIC ALCOHOLS[120]

[120] Parts of this chapter have been published: Vuković V. D., Richmond E., Wolf E., Moran J. *Angew. Chem. Int. Ed.* **2017**, 56, 3085-3089

2. 1. Scientific background and context

A recent report about Friedel-Crafts reactions of benzyl fluorides in the presence of HFIP under extremely mild conditions (room temperature 6-18 h) and without any additional catalyst was published in 2014 by Paquin and coworkers.[121] Just two years after this study, the same group reported improvement of the reactivity by employing trifluoroacetic acid as catalyst – the reaction time was shortened to 1 h.[122] Finally, in 2017 they reported on activation of secondary propargyl fluorides under the same reaction conditions with trifluoroacetic acid as catalyst.[123]



Scheme 2. 1. Summary of Paquin's work on benzyl and propargyl fluorides activation

In parallel with these studies, the use of HFIP as solvent for intramolecular[124] and intermolecular[125] Friedel-Crafts acylation from acyl chlorides under remarkably mild conditions (room temperature, 2-5 h) was reported by Aubé and coworkers. They also found that employment of HFIP as solvent in the presence of catalytic amount of TFA can replace TFA as solvent in hydroarylation reactions of α,β-unsaturated carboxylic acids.[126] Also, Nájera *et al.* reported in 2012 the use of HFIP and TFE as solvents in nucleophilic substitution of allylic alcohols with *N*-, *C*- and sylilated nucleophiles.[127]

In 2015, the year when the work on this thesis was started, the state of the art in Friedel-Crafts reactions of benzylic alcohols was mostly defined by the work of Hall and coauthors. At that point they published a study about Friedel-Crafts reactions of benzylic alcohols catalyzed by 2,3,4,5-tetrafluoroboronic[128] and ferroceneboronic acid[129] in HFIP/$MeNO_2$ mixture of solvents.

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[121] Champagne P. A., Benhassine Y., Desroches J., Paquin J.-F. *Angew. Chem. Int. Ed*. **2014**, 53, 13835-13839
[122] Hemelaere R., Champagne P. A., Desroches J., Paquin J.-F. *J. Fluor. Chem*. **2016**, 190, 1-6
[123] Hamel J.-D., Beaudoin M., Cloutier M., Paquin J.-F. *Synlett*, **2017**, 28, 2823-2828
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[127] Trillo P., Baeza A., Nájera C. *J. Org. Chem*. **2012**, 77, 7344-7354
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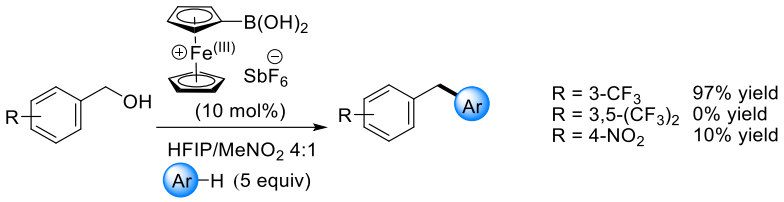


Scheme 2.2. Hall's work on activation of benzylic alcohols using ferrocene-based boronic acid as catalyst

Therefore, we were interested to find out if simple Brønsted acids can be used as catalysts instead of boronic acids in dehydroarylative reactions of benzylic alcohols with the same (or at least approximate) efficiency.

2. 2. Choice of the model substrate and reaction optimization

The investigations were started with the use of different Lewis, Brønsted and boronic acids as catalysts for the reaction of 1-phenylethanol with mesitylene in HFIP/$MeNO_2$ as solvent mixture at room temperature. This Friedel-Crafts reaction was reported[128] to be catalyzed by neutral, commercially available boronic acids **1a** and **1b** (Figure 2.1). To our surprise, the described reactivity was not observed in either case using boronic acids **1a** and **1b** acquired from Sigma-Aldrich, nor from Alfa Aesar (Table 2.1, entries 1-4). After recrystallization from dilute aqueous HCl, **1a** did furnish compound **5** in 36% yield (entry 5), however the same acidified catalyst in the presence of 5 mol% Proton Sponge was completely inactive (entry 6). Employment of another boron-based catalyst that acts as strong Brønsted acid lead to higher yield (entry 7). Several strong Brønsted acids were also tested (entries 8-11) in 20 times lower catalyst loading, resulting in higher yields. Finally, Lewis acid bismuth triflate was also able to provide the reaction product in almost quantitative yield (entry 12).

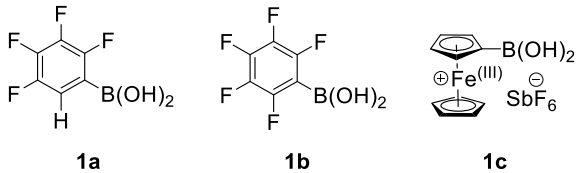
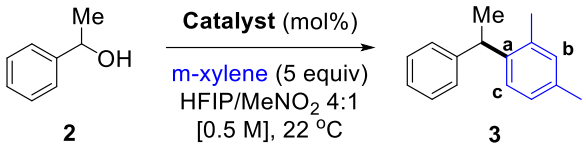


Figure 2.1. Boronic acid based catalysts used in the initial study.

[129] Mo X., Yakiwchuk J., Dansereau J., McCubbin J. A., Hall D. G., *J. Am. Chem. Soc*. **2015**, 137, 9694-9703

Table 2.1. Comparison of boronic, Brønsted and Lewis acids for the Friedel-Crafts reaction of **2** with *m*-xylene to give **3a**+**3b**+**3c**.[a]



2 **3**

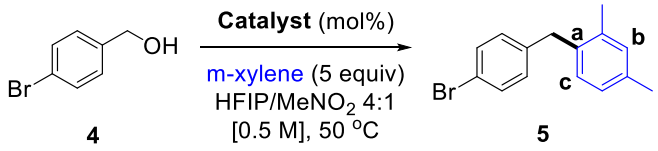
Entry	Catalyst	mol%	*t* (h)	Yield **3a**+**3b**+**3c** (%)
1	**1a**[b]	20	1.5	0[c]
2	**1a**	20	36	11
3	**1b**	20	1.5	0
4	**1b**	20	36	18
5	**1a**[d]	20	24	36
6	**1a**[e]	20	36	0
7	$B(C_6F_5)_3{\cdot}H_2O$	20	1.5	79
8	HCl	1	0.5	82
9	CF_3CO_2H	1	20	98
10	$HSbF_6{\cdot}6H_2O$	1	0.25	95
11	TfOH	1	0.25	88
12	$Bi(OTf)_3$	1	0.25	98

[a]Isolated yields after silica gel chromatography. [b]Purchased from Sigma-Aldrich and from Alfa Aesar. [c]78% of the starting alcohol was recovered. [d]For this run, **1b** was recrystallized from aq. 6 M HCl prior to the reaction. [e]Conducted in the presence of 20 mol% Proton Sponge.

Despite these unexpected results, it remained unclear whether Brønsted acid catalysis might be responsible for the alcohol substitution reactions reported to be catalyzed by neutral boronic acids. Therefore, a second set of control experiments with more challenging primary benzylic alcohol substrate **4** was run at 50 °C (Table 2.2). This reaction has already been reported to proceed with an iron(III) boronic based catalyst **1c** (Figure 2.1).[129] To test the previously mentioned hypothesis, iron(III) chloride (entries 1-2) and hexafluoroantimonic acid (entries 3-8) were employed as catalysts, in order to understand the catalytic role of the metallic center and the conjugate acid of the counterion of the catalyst **1c**. Surprisingly, simple iron(III) chloride furnished the reaction products in 67% yield after only 30 minutes (entry 1). With the same catalyst loading, hexafluoroantimonic acid was able to catalyze the reaction after 1 h up to 87% yield (entry 3). This result suggested that Brønsted acid catalysis is the driving force for the investigated reaction. Indeed, triflic acid was a successful catalyst too (entry 9). Only a slight

change in reactivity was noticed when lower catalyst loadings of hexafluoroantimonic acid were used (entries 4-6), which suggested that even the traces of the Brønsted acid (that might result from the formation of a metal hydrate or from the hydrolysis of the catalyst **1c**) could drive the reaction forward. In order to check this, the reaction was ran with bismuth triflate, a salt of another strong Brønsted acid. The reaction proceeded smoothly resulting in 81% yield after 1 h (entry 10). Addition of the Proton Sponge completely shut down the reactivity, confirming the crucial role of protons in the catalytic process (entry 8). Less acidic trifluoroacetic acid was not able to furnish the product in satisfying yield (entry 11). Interestingly, hydrofluoric acid was able to catalyze the reaction up to 82% yield (entry 12), most probably due to the formation of HF-dimers.

Table 2.2. Comparison of boronic, Brønsted and Lewis acids for the Friedel-Crafts reaction of **4** with *m*-xylene to give **5a**+**5b**+**5c**.[a]



4 **5**

Entry	Catalyst	mol%	*t* (h)	Yield **5a**+**5b**+**5c** (%)
1	$FeCl_3$	10	0.5	67
2	$FeCl_3$	1	48	25
3	$HSbF_6{\cdot}6H_2O$	10	1	87
4	$HSbF_6{\cdot}6H_2O$	5	2	85
5	$HSbF_6{\cdot}6H_2O$	1	2.5	82
6	$HSbF_6{\cdot}6H_2O$	0.5	48	77
7	$HSbF_6{\cdot}6H_2O$[b]	10	18	80
8	$HSbF_6{\cdot}6H_2O$[c]	10	96	0[d]
9	TfOH	10	0.25	72
10	$Bi(OTf)_3$	10	1	81
11	CF_3CO_2H	10	24	<2
12	$HF_{(50\%\ aq)}$	10	18	82

[a]Isolated yields after silica gel chromatography. [b]Conducted at 23 °C. [c]Conducted in the presence of 10 mol% Proton Sponge. [d]90% of the starting alcohol was recovered.

To understand better the behavior of acids in HFIP/$MeNO_2$ as catalysts for Friedel-Crafts reactions of benzylic alcohols, a third substrate **6** (3,5-bis(trifluoromethyl)benzyl alcohol[130]) was chosen, that did not react at all under Hall's conditions.[129] A third set of experiments was run at 100 ^{o}C (Table 2.3). Delightfully, fluoroantimonic acid furnished modest yield of **7** (entry 1), which was improved by using HFIP as a sole solvent (entry 2). In order to test other Brønsted acids, triflic acid was employed, which resulted in major improvement of the reaction yield (entry 3). This result is rather surprising if we consider the fact that fluoroantimonic acid is stronger than triflic acid. However, at higher temperatures fluoroantimonic acid decomposes, whereas triflic acid is extremely thermally stable.[131] Lewis acid, such as iron(III) chloride, yielded the product in only 18% yield (entry 4), whereas the bismuth salt of triflic acid was very efficient as catalyst (entry 5). Addition of proton sponge (entry 6) or employment of simple sodium hexafluoroantimonate salt (entry 7) completely shut down the reactivity. This was also the case with weaker Brønsted acids, such as trifluoroacetic acid (entry 8). The decrease in the equivalents of the arene nucleophile did not change the yield significantly, so further experiments were continued with 3 equiv of *m*-xylene instead of 5 (entry 9). The solvent influence was then investigated (entries 10-15). Whereas other fluorinated alcohols, such as 2,2,2-trifluoroethanol (entry 10) and perfluoro-*tert*-butanol (entry 11) resulted in moderate reactivity, nitromethane, THF and toluene resulted in no reactivity (entries 12-14). It was therefore concluded that the observed reactivity is also due to the specific properties of HFIP.

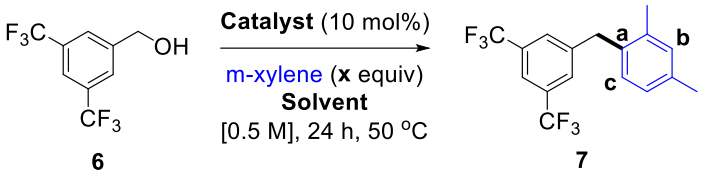
Finally, in order to investigate if free OH groups of HFIP play crucial role in the catalysis of the designed model reaction, the reaction was carried out in hexafluoroisopropyl methyl ether (HFIPME). Complete shutdown of the reactivity was expected, but the reaction surprisingly worked better than in HFIP itself (entry 15). This result led to the conclusion that OH groups in HFIP are not solely responsible for the remarkable result observed in entry 3, but other factors play a significant role as well. From Table 1.2 it is seen that not many relevant physico-chemical constants have been determined for HFIPME, and that the lower dielectric constant cannot explain the above mentioned result (if this were the case, the reaction would be even more efficient in TFE). The other bulk parameters of HFIPME are therefore most probably not

[130] Another reason why 3,5-bis(trifluoromethyl)benzyl alcohol was chosen is the particular interest of 3,5-bis(trifluoromethyl)benzyl group to pharmaceutical chemistry. See for example: Swain C., Rupniak N. M. J. *Ann. Rep. Med. Chem*. **1999**, 34, 51-60

[131] Haszeldine R. N., Kidd J. M. *J. Chem. Soc*. **1954**, 4228-4232

relevant either. On the other hand, one could try to rationalize this result in the context of the nucleophilicity of this solvent. What contributes to the nucleophilicity parameter N_1 of a solvent?

Table 2.3. Optimization and control experiments with 3,5-bis(trifluoromethyl)benzyl alcohol (**6**)



Entry	Catalyst	Solvent	x	Yield[a] **7a**+**7b**+**7c** (%)
1	$HSbF_6{\cdot}6H_2O$	HFIP/$MeNO_2$[b]	5	28
2	$HSbF_6{\cdot}6H_2O$	HFIP	5	39
3	TfOH	HFIP	5	90
4	$FeCl_3$	HFIP	5	18
5	$Bi(OTf)_3$	HFIP	5	90
6	$HSbF_6{\cdot}6H_2O$[c]	HFIP	5	<1
7	$NaSbF_6$	HFIP	5	<1
8	TFA	HFIP	5	<1
9	TfOH	HFIP	3	83
10	TfOH	CF_3CH_2OH	3	19
11	TfOH	$(CF_3)_3COH$	3	69
12	TfOH	$MeNO_2$	3	<1
13	TfOH	THF	3	<1
14	TfOH	Toluene	3	<1
15	TfOH	$(CF_3)_2CHOMe$	3	98

[a]Reaction conditions: Isolated yields after silica gel chromatography. [b]HFIP/$MeNO_2$ 4/1 (v/v) mixture. [c]Conducted in the presence of 10 mol% Proton Sponge.

On one hand, positive inductive effects of the adjacent groups can increase the nucleophilicity of a single molecule. On the other hand, if a solvent is more acidic, it will contain more anions, and therefore "bulk nucleophilicity" will be higher. If we now compare HFIP and HFIPME in these two aspects, the methyl group of HFIPME would certainly make it more nucleophilic than HFIP,[132] whereas in terms of "bulk nucleophilicity" HFIPME would be less nucleophilic than HFIP. Therefore, if we suppose that HFIPME has lower Mayr's ("bulk") nucleophilicity

[132] However, in these considerations, steric effects were not taken into account.

parameter N_1 than HFIP, it would allow carbocations in HFIPME to live longer. This means that the probability that a carbocation will meet the arene nucleophile is higher, and therefore the reaction is faster than in HFIP.

Nevertheless, if the "bulk nucleophilicity" is higher due to higher concentration of anions in the media, then the "bulk electrophilicity" will be higher as well, due to the increased corresponding number of counterions. On the first sight it might seem that in preceding discussion the rise of "bulk electrophilicity" is neglected. Actually, since HFIPME does not have any acidic protons (unlike HFIP), it would not be possible to compare their "bulk electrophilicities".

All in all, the results summarized in the previous three tables illustrate the importance of the right choice of the model substrate for optimization experiments. Also, the change of the temperature proved to be of minor importance for the selected transformations, as long as a strong Brønsted acid is used as catalyst in combination with HFIP as solvent. The results also suggest that the reaction mechanism is slightly more complex than a simple Brønsted acid catalyzed reaction (whether it is specific or general acid catalysis). Although the best result during optimization was achieved with HFIPME as solvent, it was decided to use HFIP in further studies, due to its availability and lower cost.

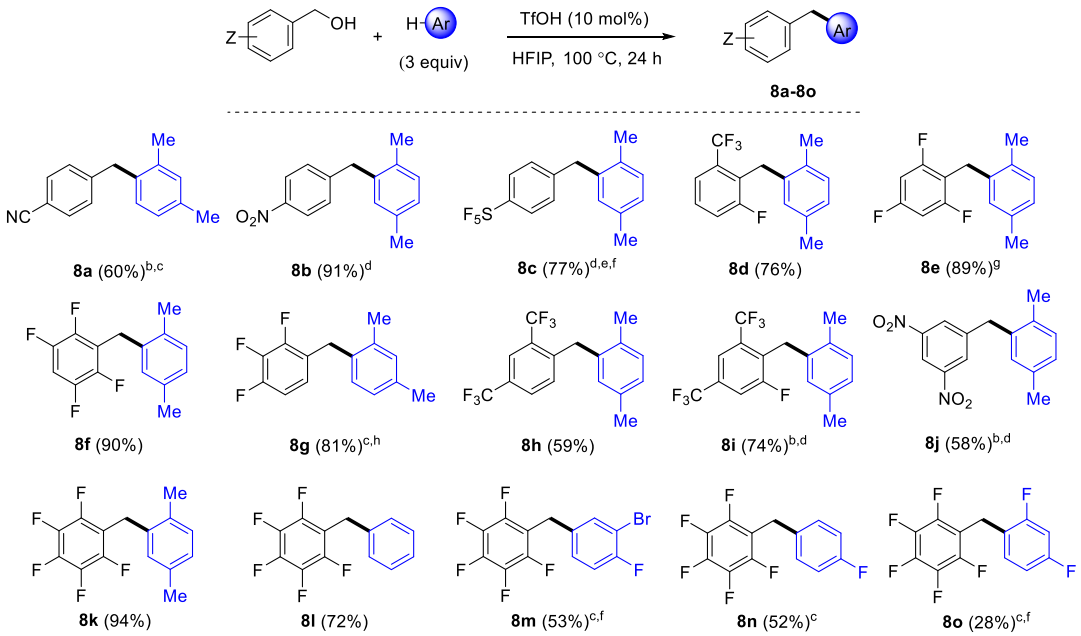
2. 3. Scope of deactivated benzylic alcohols

After establishing optimal conditions as: 10 mol% triflic acid (catalyst), 3 equiv of the arene nucleophile, 100 ^{o}C and 24 h, the scope of primary benzylic alcohols bearing electron withdrawing groups on the phenyl ring was explored (Table 2.4).

Monosubstituted primary benzylic alcohols bearing cyano-, nitro- and pentafluorothio- moiety all reacted in good to excellent yields (entries **8a**-**8c**). Maximal previously reported yields for the reactions of 4-cyano- and 4-nitrobenzylic alcohol were respectively 12% and 46%,[129] which is respectively five and two times lower than in this study. Fluoro- and trifluoromethyl bearing substrates also reacted in moderate to excellent yields (**8d**-**8g**). Impressively, substrates bearing up to two trifluoromethyl or two nitro groups were well tolerated as well (**8h**-**8j**). Finally, pentafluorobenzyl alcohol was able to react with number of very weak nucleophiles,

such as benzene, fluorobenzene, and even 1,3-difluorobenzene, furhishing corresponding products in excellent to moderate yields (**8k**-**8o**).

Table 2.4. The scope of electronically deactivated primary benzylic alcohols



[a]Isolated yields after column chromatography over silica. [b]Performed with 20 mol% TfOH. [c]Combined yield of regioisomers. [d]Reaction time was 48 h. [e]Performed with 10 mol% $HSbF_6 \cdot 6H_2O$ as catalyst, 80 °C. [f]Performed with 5 equiv of nucleophile. [g]Performed at 50 °C, 30 min. [h]Performed at 50 °C, 1 h.

Under standard conditions from the Table 2.4, weak aromatic nucleophiles 1,4-difluorobenzene, 1-bromo-3,5-difluorobenzene, 1-bromo-2,4-difluorobenzene also furnished corresponding products with pentafluorobenzyl alcohol, albeit in ~10% yield. Use of methoxybenzene derivatives resulted in no reaction and returned unchanged starting materials. The attempts to employ heterocyclic aromatic nucleophiles (such as 2-methylfuran, 2-methylthiophene, benzimidazole) in reactions with 1-phenylethanol at 50 °C failed. In order to understand why these nucleophiles were unsuccessful under these reaction conditions, an NMR titration of benzimidazole with TfOH in HFIP was performed (Figure 2.2).

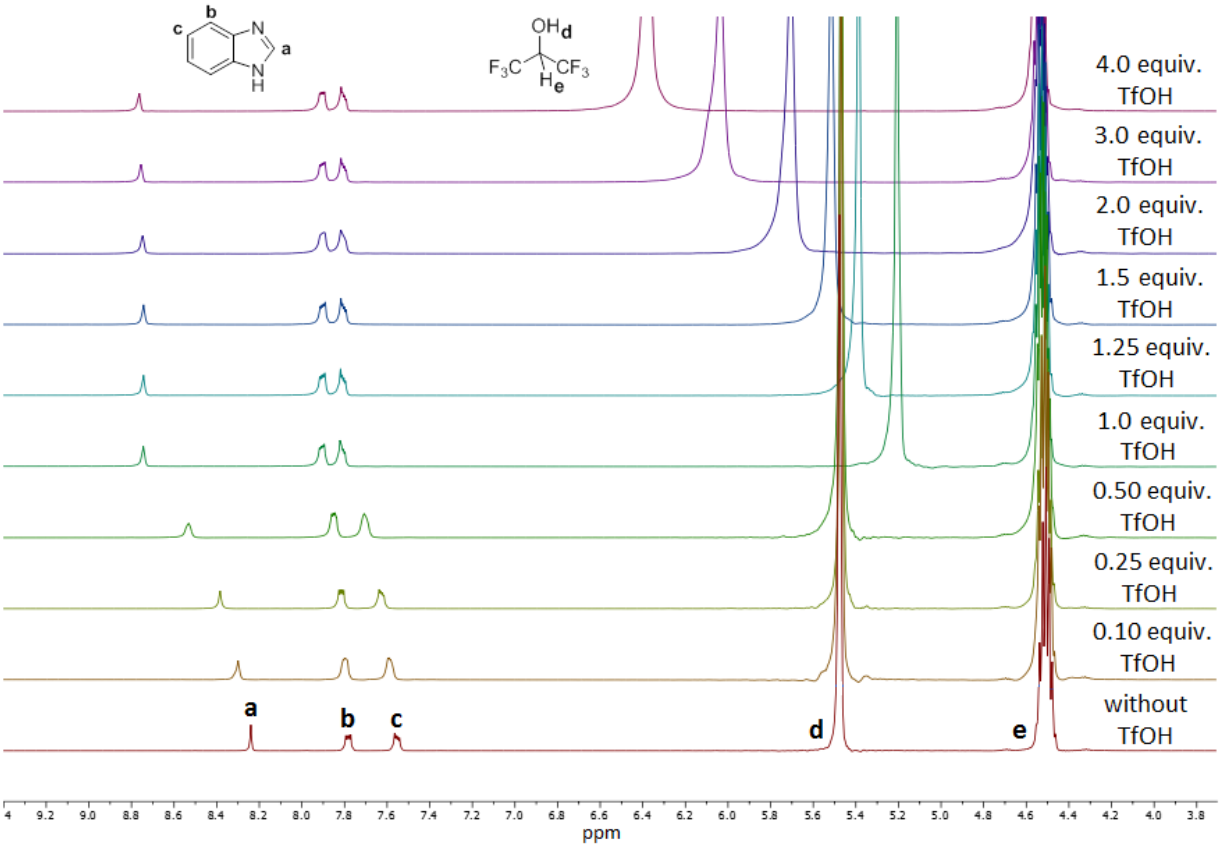


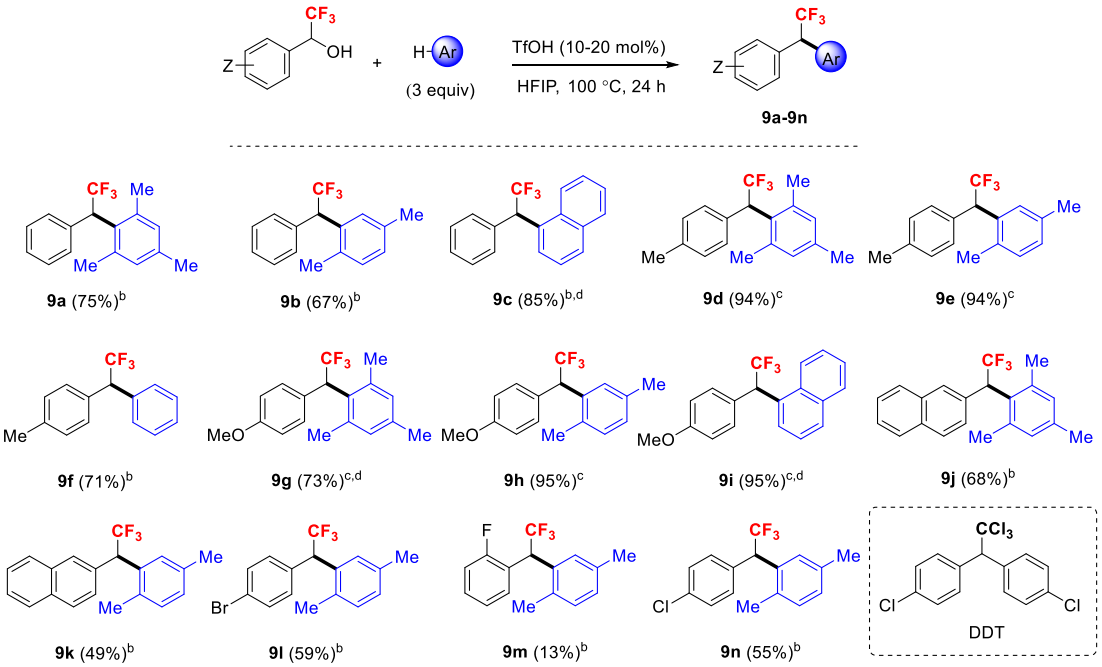
Figure 2.2. ^{1}H-NMR titration of benzimidazole in HFIP with TfOH

As soon as small amounts of triflic acid were added, a downfield shift for signals of aromatic protons of benzimidazole was observed. These signals continued to shift downfield until 1 equiv of the acid was added. From that point, by addition of additional 2, 3 and 4 equiv of TfOH, the benzimidazole protons did not shift, and only the changes of the chemical shifts for the solvent protons were observed. These findings imply that benzimidazole is therefore interacting with the catalyst (quenching it), which is the reason of the observed non-reactivity with heteroaromatic nitrogen-containing nucleophiles.

Success with highly deactivated benzylic alcohols prompted the exploration of more challenging possibility, that carbenium ions with adjacent electron-withdrawing groups might be generated and trapped directly from the alcohols in a catalytic manner. α-Trifluoromethyl cations

are synthetically valuable intermediates,[133] that have previously only been accessed by stepwise or *in situ* pre-activation of alcohols using stoichiometric activating agents,[134] or in concentrated strong Brønsted acids.[135] In this regard, Table 2.5 summarizes the scope of substituted 2,2,2-trifluoro-1-phenylethanols for nucleophilic substitution under TfOH/HFIP conditions.

Table 2.5. Scope of α-trifluoromethyl secondary benzylic alcohols



[a]Isolated yields after column chromatography over silica. [b]Performed with 20 mol% TfOH. [c]Performed with 10 mol% TfOH. [d]Combined yield of regioisomers. [d]Reaction performed at 75 °C.

α-Trifluoromethyl benzylic alcohol and its analogs bearing activating methyl and methoxy group on the phenyl ring showed good to excellent reactivity towards Friedel-Crafts nucleophiles, such as benzene (**9f**), naphthalene (**9c**, **9i**), mesitylene (**9a, 9d, 9g, 9j**) and *p*-xylene (**9b, 9e, 9h, 9k**). Substrates with bromine and chlorine on the phenyl ring were modestly tolerated (**9l, 9n**), whereas the fluorophenyl substrate showed poor reactivity under the reaction

[133] Creary X. *Chem. Rev*. **1991**, 91, 1625-1678

[134] a) Allen A. D., Ambridge I. C., Che C., Michael H., Muir R. J., Tidwell T. T. *J. Am. Chem. Soc*. **1983**, 105, 2343-2350; b) Allen A. D., Girdhir R., Jansen M. P., Mayo J. D., Tidwell T. T. *J. Org. Chem*. **1986**, 51, 1324-1329; c) Richard J. P. *J. Am. Chem. Soc*. **1986**, 108, 6819-6820; d) Richard J. P. *J. Chem. Soc. Chem. Commun*. **1987**, 1768-1769; e) Richard J. P. *J. Am. Chem. Soc*. **1989**, 111, 1455-1465; f) Richard J. P. *Tetrahedron Lett*. **1989**, 30, 23-26; g) Kwong-Chip J., Tidwell T. T. *Tetrahedron Lett*. **1989**, 30, 1319-1322

[135] a) Olah G. A., Pittman C. U. Jr. *J. Am. Chem. Soc*. **1966**, 88, 3310-3312; b) Koshy K. M., Roy D., Tidwell T. T. *J. Am. Chem. Soc*. **1979**, 101, 357-363

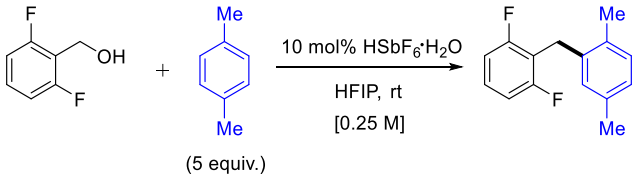
conditions (**9m**). All products represent fluorinated analogs of DDT (last entry of the Table 2.5), and products **9l-9n** offer possibilities for further functionalization *via* metal-catalyzed cross-coupling reactions.

2. 4. Mechanistic studies

In order to get deeper insight into details of the reaction mechanism, a series of various kinetic experiments was performed, along with NMR titrations, determination of kinetic solvent isotope effects, and other experiments.

2. 4. 1. Kinetic studies

In the initial phase of kinetic studies, 2,6-difluorobenzyl alcohol and *p*-xylene were chosen as model substrates to react in the presence of 10 mol% $HSbF_6 \cdot 6H_2O$ as catalyst. The solvent was a mixture of HFIP with $CDCl_3$. The concentration of nucleophile was varied by keeping the total reaction mixture volume constant, and by the method of initial reaction rates, the reaction order in *p*-xylene was determined to be 0 (exact value of the slope is –0.03) (Figure 2.3).



Scheme 2.3. Model reaction for determination of reaction order in *p*-xylene

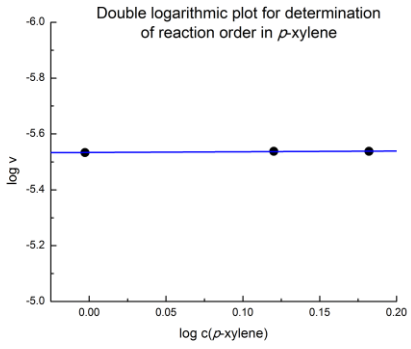
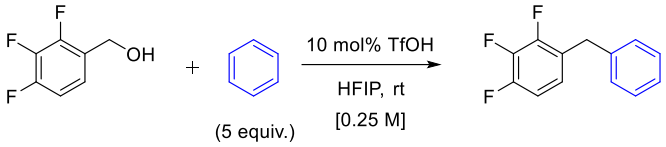


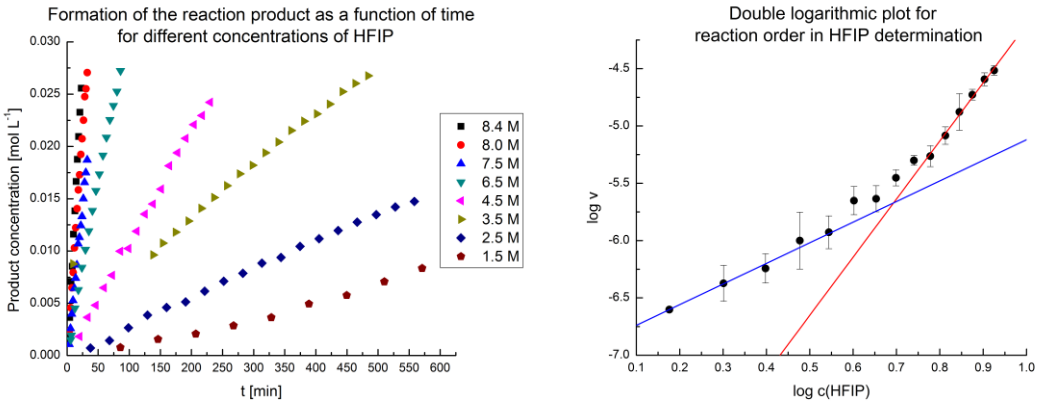
Figure 2.3. Double logarithmic plot for determination of reaction order in *p*-xylene

Since these model substrates turned out to be not optimal for the determination of the reaction order of HFIP, kinetic studies were continued with another substrate that was more suitable (Scheme 2.4).



Scheme 2.4. Model reaction for determination of reaction order in HFIP and TfOH

For reaction order determination of HFIP, the concentration of HFIP was varied, and the initial rates of the reaction was monitored (Figure 2.4a). *n*-Pentane was used as a neutral "dummy" solvent so that the volume of the reaction mixture could have been kept constant throughout all kinetic experiments. The double logarithmic plot for HFIP shows that the reaction order in HFIP changes as a function of its concentration (Figure 2.4b). For higher concentrations of HFIP [5.5 mol L^{-1} - 8.4 mol L^{-1} (pure solvent)] the reaction order in HFIP equals **5.1 ± 0.3** (R^2 = 0.9903, red line on the double logarithmic plot). For lower concentrations of HFIP [1.5 mol L^{-1} - 4.5 mol L^{-1}] the reaction order in HFIP is **1.80 ± 0.07** (R^2 = 0.9942, blue line on the double logarithmic plot). Similar higher order dependent behavior of HFIP has already been reported by Berkessel and Adrio.[136]

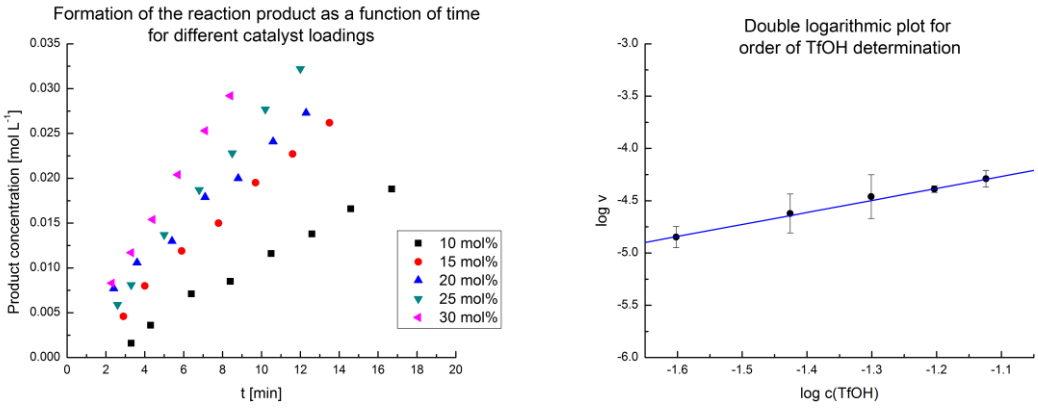


(a) (b)

Figure 2.4. (a) Reaction progress dependence on the HFIP concentration. (b) Double logarithmic plot for determination of reaction order in HFIP.

[136] Berkessel A., Adrio J. A. *Adv. Synth. Catal*. **2004**, 346, 275-280

On the other hand, calculated reaction order in catalyst (TfOH) is **1.15 ± 0.04** (R^2 = 0.9966, blue line on Figure 2.5b).



(a) (b)

Figure 2.5. (a) Reaction progress dependence on the TfOH concentration. (b) Double logarithmic plot for determination of reaction order in TfOH.

Based on this kinetic analysis, it can be concluded that under the examined reaction conditions, the reaction order in arene nucleophile is 0, the reaction order in catalyst (TfOH) is 1 and the reaction order in solvent (HFIP) is 5. These results therefore show high order overall reaction order of the rate determining step, i. e. suggest that one molecule of catalyst (one solvated proton) and five molecules of HFIP are involved in the transition state. Alternatively, this result could also mean that multiple rate-determining steps are involved in the mechanism. In any case, this result implies the existence of higher order interactions between TfOH and HFIP. When the concentration of HFIP is lower, only the two molecules of HFIP participate in these interactions, whereas at higher concentration, 5 molecules of HFIP participate. The shape of the double logarithmic plot suggests that there is certain critical concentration (around 5 mol L^{-1}) when this change happens. Since such critical concentration exists, and the change does not happen more gradually (the concentration range of this change is rather narrow, from 4.5 to 5.5 mol L^{-1} approximately), this suggests high cooperativity of the TfOH/HFIP interaction.

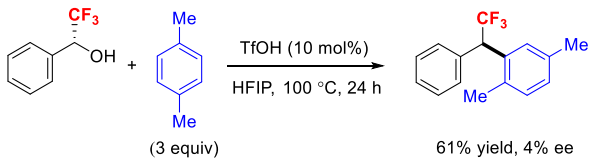
In the section 1. 3. 2. of this thesis it was mentioned that association of two to three molecules of HFIP leads to higher degree of polarization of the terminal OH groups of the cluster.[74] The result of the present kinetic analysis correlates well with these findings in lower HFIP concentration regime, when the reaction order is found to be around 2. By analogy, it can

be therefore assumed that this polarization effect spans over 5 molecules of HFIP rather than only 2 or 3 in the presence of TfOH in high concentrations of HFIP, and that these (transitory) clusters are involved in the catalysis of the Friedel-Crafts reactions of alcohols in HFIP. This would further imply that these five HFIP + one TfOH molecule clusters have acidity superior to the 2-3 HFIP molecule clusters, and that this effect might be cause of the efficient activation of highly deactivated alcohols in the TfOH/HFIP system.

The analogy can be expanded even further. Remarkable similarity with the proton diffusion process in water[137] can be postulated. Whereas in (acidified) water clusters $H(H_2O)_4^+$ form,[138] in HFIP, analogously, clusters $H(HFIP)_5^+$ form, and the proton "hopping" process occurs between them. In water, the hydrogen bond network inside of which this "hopping" process occurs spans over the whole volume of water. In HFIP, however, this hydrogen bond network spans only across the polar microphase. If we compare the Hammett functions of the solutions of the same total molarity of the acid in water and HFIP, in that case, solution in HFIP will behave as more acidic medium.[139] This effect was previously rationalized by lower proton solvation in HFIP,[139] as well as with high anion stabilization in HFIP.[140] However, if we take into account recent findings of Berkessel et al.[76] this might also be due to the higher *effective* concentration of protonated clusters in HFIP in polar microphase. Equally, this would explain remarkable catalytic properties of TfOH in HFIP.

2. 4. 2. Enantiomeric excess of the reaction product determination

(–)-2,2,2-Trifluoro-1-phenylethanol was subjected to the reaction conditions from the Table 2.5 in order to investigate the stereochemical outcome of the reaction. Almost complete loss of the stereochemical information was observed (Scheme 2.5).



Scheme 2.5. Friedel-Crafts reaction of an enantioenriched α-trifluoromethyl benzyl alcohol

[137] Marx D., Tuckerman M. E., Hutter J., Parrinello M. *Nature*, **1999**, 397, 601-604
[138] Of course, this is just averaged picture, clusters with 3 or 5 or more molecules of water exist as well.
[139] Carre B., Devynck J. *Anal. Chim. Acta*, **1981**, 131, 141-147
[140] Fărcaşiu D., Ghenciu A., Marino G., Kastrup R. V. *J. Mol. Catal. A: Chem*. **1997**, 126, 141-150

The outcome of this experiment leads to a clear conclusion that there is a carbocationic intermediate formed in the course of the reaction, and that the type of the mechanism is therefore S_N1. Once it has been proved that under these conditions the carbocation is formed at the α-position to the CF_3-group, it can be argued if the CF_3 group has the stabilizing or destabilizing effect on the carbocation that is formed. The fact that reactions of dehydroarylative nucleophilic substitutions of α-CF_3 benzylic alcohols proceed at much higher temperatures than their methylated analogs proves that it is difficult to form the carbocation, i. e. the kinetic barrier for its formation is too high. This can only be due to the negative induction effect of the CF_3 group (Figure 2.6.a). If β-effect were pronounced, then the substitution would be possible at room temperature (Figure 2.6.b), since the effect of the CF_3 group is for an order of magnitude more pronounced than the effect of the CH_3 group (Figure 2.6.c).[114,141]

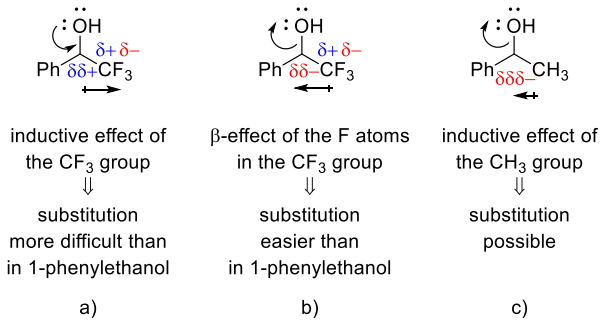


Figure 2.6. (a) Inductive effect of the CF_3 group on the alcohol reactivity. (b) β-effect of the CF_3 group on the alcohol reactivity. (c) Inductive effect of the methyl group on the alcohol reactivity.

On the other hand, one could be led to the conclusion that lower stability of the α-CF_3 carbocation that is formed (i. e. its short living time) is the cause of the lack of Friedel-Crafts reactivity of the α-CF_3 benzylic alcohols at room temperature. This can be the case only if there is destabilizing inductive effect present (Figure 2.7.a). If β-effect were there, the carbocation would have been more stabilized (Figure 2.7.b) than the corresponding methyl derivate (Figure 2.7.c), and the nucleophile attack would have been possible even at room temperature.

[141] As it will be shown in the Chapter 4. of this thesis, secondary alcohols react in nucleophilic substitution reactions under milder conditions than α-trifluoromethyl benzylic alcohols.

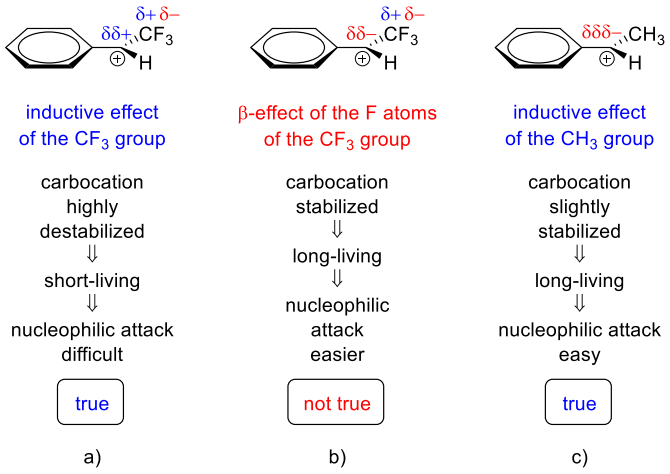
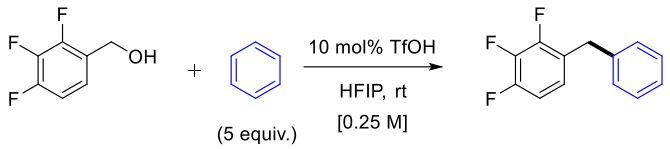


Figure 2.7. (a) Inductive effect of the CF_3 group on the carbocation stability. (b) β-effect of the CF_3 group on the carbocation stability. (c) Inductive effect of the methyl group on the carbocation stability.

However, the fact that higher temperature is needed for the Friedel-Crafts reactions of α-CF_3 benzylic alcohols does not tell anything about the stability of the carbocation that is formed. It can only offer the information about the ease of the carbocation formation, as it is discussed in the Figure 2.6. In the case of the formation of the carbocation (i. e. C–O bond cleavage), therefore, the inductive effect of the fluorine atoms dominates over β-effect. In the case of carbocation stability, it cannot be established which effect predominates based on the experiments performed. Although it can be supposed that in this case also inductive effect predominates, this can be only found out by determining the Mayr's electrophilicity parameters for α-CF_3 benzylic cations.

2. 4. 3. Kinetic solvent isotope effect

Additional kinetic studies were carried out in deuterated hexafluoroisopropanols. First, the following reaction:



was followed in HFIP-d_2, and the following kinetic solvent isotope effect was observed:

$$KSIE_{d2} = \frac{v_{\mathrm{H}}}{v_{\mathrm{D}}} = \frac{1.42 \cdot 10^{-5}\ \mathrm{mol\ L^{-1}s^{-1}}}{3.1 \cdot 10^{-5}\ \mathrm{mol\ L^{-1}s^{-1}}} = 0.46$$

and thus, $KSIE_{\mathrm{d2}}^{-1}$ = 2.2, which means that the reaction is 2.2 times faster in HFIP-d_2 than in protiated HFIP. Therefore, an inverse kinetic solvent isotope effect is observed.

In order to better understand the deuteration effect of the hydroxyl group and of the methine proton of HFIP, the same reaction was carried out in HFIP-d_1(OD) under identical conditions. The kinetic solvent isotope effect in this case was:

$$KSIE_{\mathrm{OD}} = \frac{v_{\mathrm{H}}}{v_{\mathrm{D}}} = \frac{1.42 \cdot 10^{-5}\ \mathrm{mol\ L^{-1}s^{-1}}}{3.01 \cdot 10^{-5}\ \mathrm{mol\ L^{-1}s^{-1}}} = 0.47$$

which is practically the same value as it was obtained in dideuterated HFIP-d_2. Hence, the origin of the kinetic effect is at the hydroxyl group deuterium of HFIP.

A possible explanation of the observed effect is as follows. The first step is protonation of the benzylic alcohol substrate, and the second step is the rate determining step of C–O bond cleavage:

(1) $ROH + H^+ \rightleftharpoons ROH_2^+$ and (1') $ROD + D^+ \rightleftharpoons ROD_2^+$

(2) $ROH_2^+ \rightarrow R^+ + H_2O$ and (2') $ROD_2^+ \rightarrow R^+ + D_2O$.

Then, the overall rate constant is $k = K_1k_2$, where K_1 is the equilibrium constant of the first reaction, and k_2 - rate constant of the second step. Since heteroatom-deuterium bonds are stronger than corresponding heteroatom-protium bonds, the equilibrium 1' is shifted more towards right than the equilibrium 1, and therefore: $K_1' > K_1$. This means that the resulting effect is: $k' > k$.

Another possible explanation would be that deuterated HFIP stabilizes the transition state of the step 2' more than protiated HFIP stabilizes the transition state of the step 2, since the deuterium bonds are stronger than corresponding hydrogen bonds, especially in dimers and trimers.[142] However, the stabilization might also be due to the geometric isotope effect – change

[142] Scheiner S., Čuma M. *J. Am. Chem. Soc*. **1996**, 118, 1511-1521

of the hydrogen bond geometry due to deuteration.[143] Interestingly, the observed value of the KSIE is in the range of KSIE for acid-catalyzed reactions in H_2O and D_2O.[144]

2. 4. 4. NMR titration of pentafluorobenzyl alcohol in HFIP with triflic acid

To better understand the interaction of triflic acid with HFIP and substrates, a ^{1}H-NMR titration of 2,3,4,5-pentafluorobenzyl alcohol in HFIP/C_6D_6 (5:2, v/v) solution with triflic acid was performed (Figure 2.8). Upon addition of catalytic amounts of TfOH, fast exchange between the OH proton of HFIP, triflic acid proton and pentafluorobenzyl alcohol OH proton was observed (signal **b**+**c**+**e**, spectrum 2). It was also noticed that the **b**+**c**+**e** signal at the spectrum 2 shifted upfield compared to the initial signal **c** at the spectrum 1. This means that HFIP and pentafluorobenzyl alcohol are both protonated (exchange protons with triflic acid), and the strength of the hydrogen bond decreased. With further addition of triflic acid (spectra 3-8), the intensity of the **b**+**c**+**e** signal proportionally increased, and it shifted downfield, meaning that the hydrogen bonds in the system became stronger. After addition of 1 equiv TfOH (spectrum 8), exchange of TfOH protons with benzene protons was observed (signal **f**+**e**), as well as formation of new product (spectrum 9), which is most probably the triflate ester of pentafluorobenzyl alcohol (signal **a'**, not visible at the picture due to its low intensity). Meanwhile, **b**+**c**+**e** signal still continued shifting downfield, becoming broader, and more intense, up to 8 equiv of TfOH added (spectrum 14). Then, the signal intensity increased again until the end of the titration, and total change of the chemical shift of the **b**+**c**+**e** proton during the titration was around 5.5 ppm. Also, a downfield shift of the methine proton of HFIP was noticed (signal **d**), as well as downfield shift of the benzylic protons of pentafluorobenzyl alcohol (signal **a**). It should be also mentioned that occasionally during the titration, an NMR spectrum with wide range (0 to 80 ppm) was acquired, and no additional signals at higher ppm values were observed.

[143] Shi C., Zhang X., Yu C.-H., Yao Y.-F., Zhang W. *Nat. Commun*. **2018**, 9, 481

[144] The rates of D^+ catalyzed reactions in D_2O are usually 2-3 greater than the rates of corresponding H^+ catalyzed reactions in H_2O. - Laidler K. J. "*Chemical Kinetics*", **1987**, Pearson Education Inc.

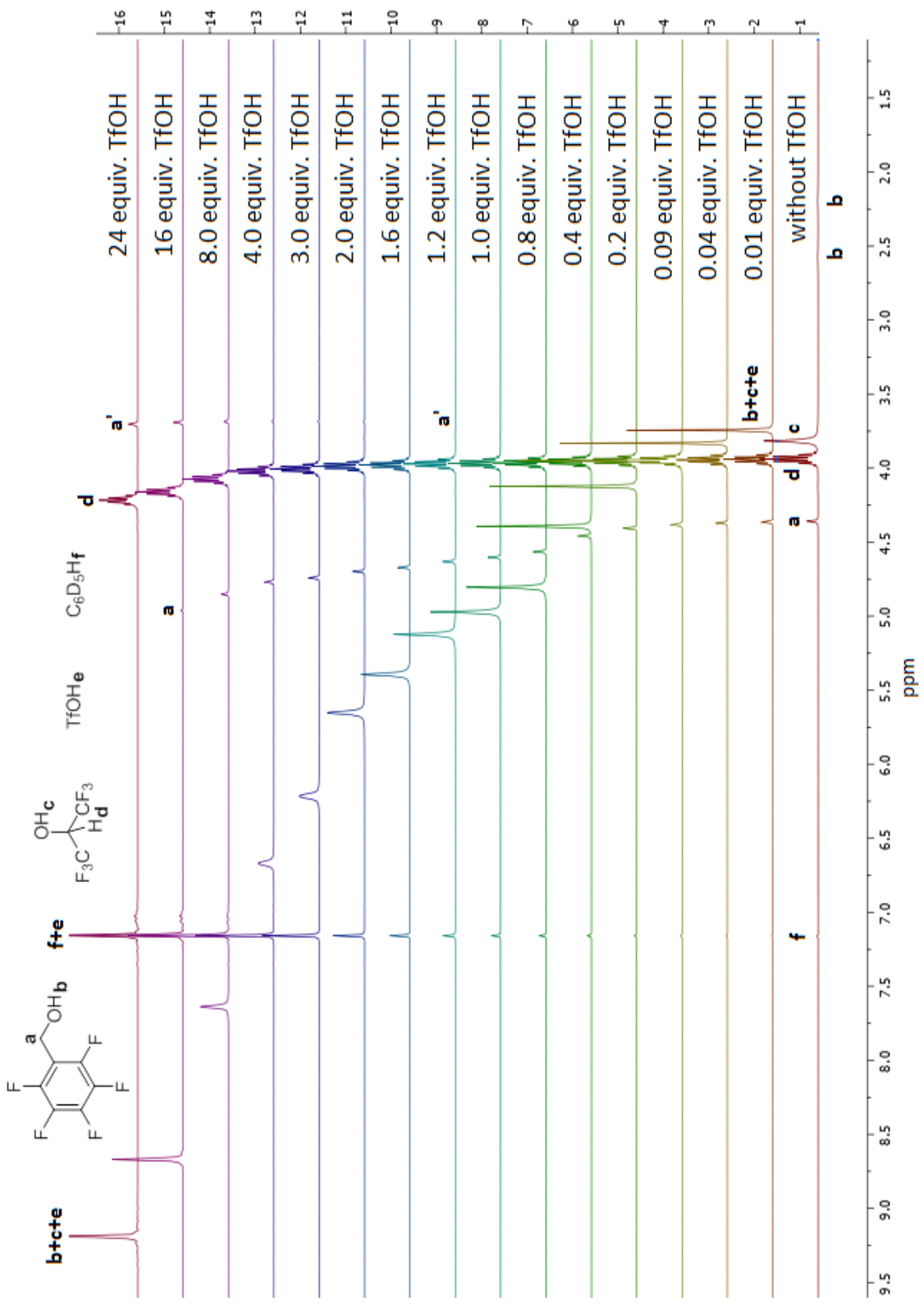


Figure 2.8. ^{1}H-NMR titration of 2,3,4,5-pentafluorobenzyl alcohol in HFIP/C_6D_6 with TfOH

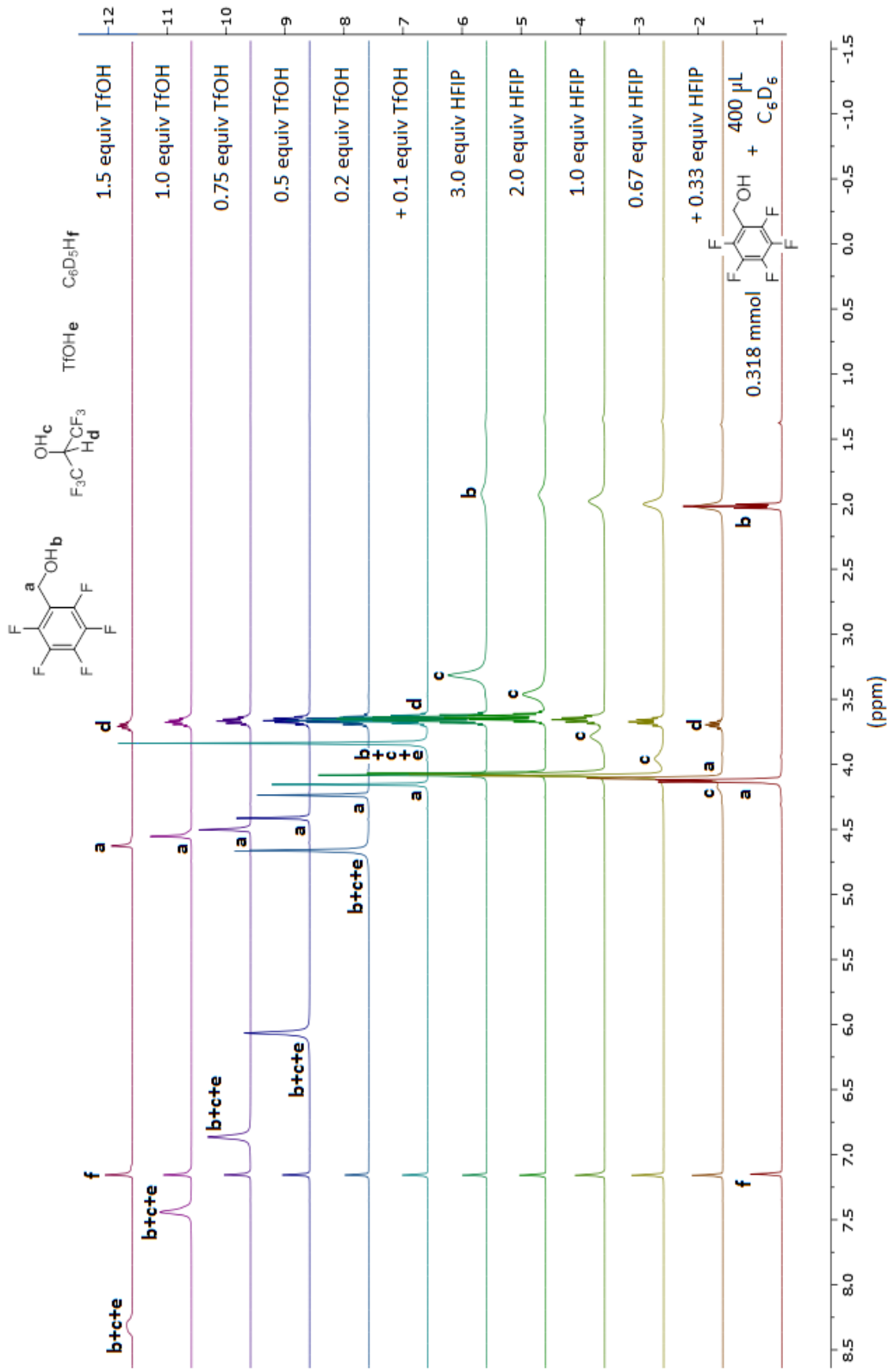


Figure 2.9. ^{1}H-NMR titration of 2,3,4,5-pentafluorobenzyl alcohol in C_6D_6 with HFIP and TfOH

To deconvolute the nature of interactions between these three species in the solution, a ^{1}H-NMR titration of pentafluorobenzyl alcohol with HFIP in C_6D_6 was first performed, followed by titration with TfOH (Figure 2.9). At first, it was noticed that there is no fast exchange between OH protons of HFIP and OH protons of pentafluorobenzyl alcohol (signals **c** and **b**, spectrum 2). With the addition of HFIP, upfield shift of the signals of HFIP OH protons was observed (signal **c**, spectra 3-6). After 3 equiv of HFIP were added, first increment of triflic acid was added (spectrum 7). Upon addition of just 0.1 equiv of triflic acid, all these three signals (**b**+**c**+**e**) combined to one (spectrum 7), which continued shifting downfield as triflic acid is added (spectra 8-12). Broadening of this peak near the end of the titration indicates existence of hydrogen-bond network (sample was well mixed before the spectrum acquisition, therefore broadening of peaks is not result of the non-homogenity in solution).

Therefore, this experiment showed that addition of TfOH leads to stronger hydrogen bonding within the hydrogen bond network, which is evidenced by the downfield shift of the OH proton signal of the HFIP. Still, greater wideness of the peaks would be expected for protons involved in hydrogen-bond network. The narrow shape of the peaks therefore suggests fast proton exchange between TfOH and HFIP. This fact, together with the downfield shift of the mentioned OH-HFIP proton, are in accordance with higher order cluster formation, which was postulated as result of kinetic experiments in the section 2. 4. 1. of this thesis. Additional experiments were performed in order to get an insight in the nature and strength of these hydrogen bonds.

To evaluate if fast exchange of the protons **b**, **c**, and **e** from Figure 2.8 indeed results in the formation of a hydrogen-bond network, the hydrogen-bond strength in the system constituted of pentafluorobenzyl alcohol, HFIP, TfOH and C_6D_6 was estimated. The method of variation of temperature coefficients ($\Delta\delta/\Delta t$) was used. The constituents of the system were dissolved in C_6D_6, and the temperature was gradually increased from room temperature to 90 ^{o}C. For each temperature, the reference C_6D_6 shift was corrected for value of 0.0009 ppm K^{-1} found in literature,[145] and the relative change of **b**+**c**+**e** chemical shift from Figure 2.10 was plotted against the temperature (Figure 2.11).

[145] Cross B. P., Schleich T. *Organic Magnetic Resonance*, **1977**, 10, 82-85

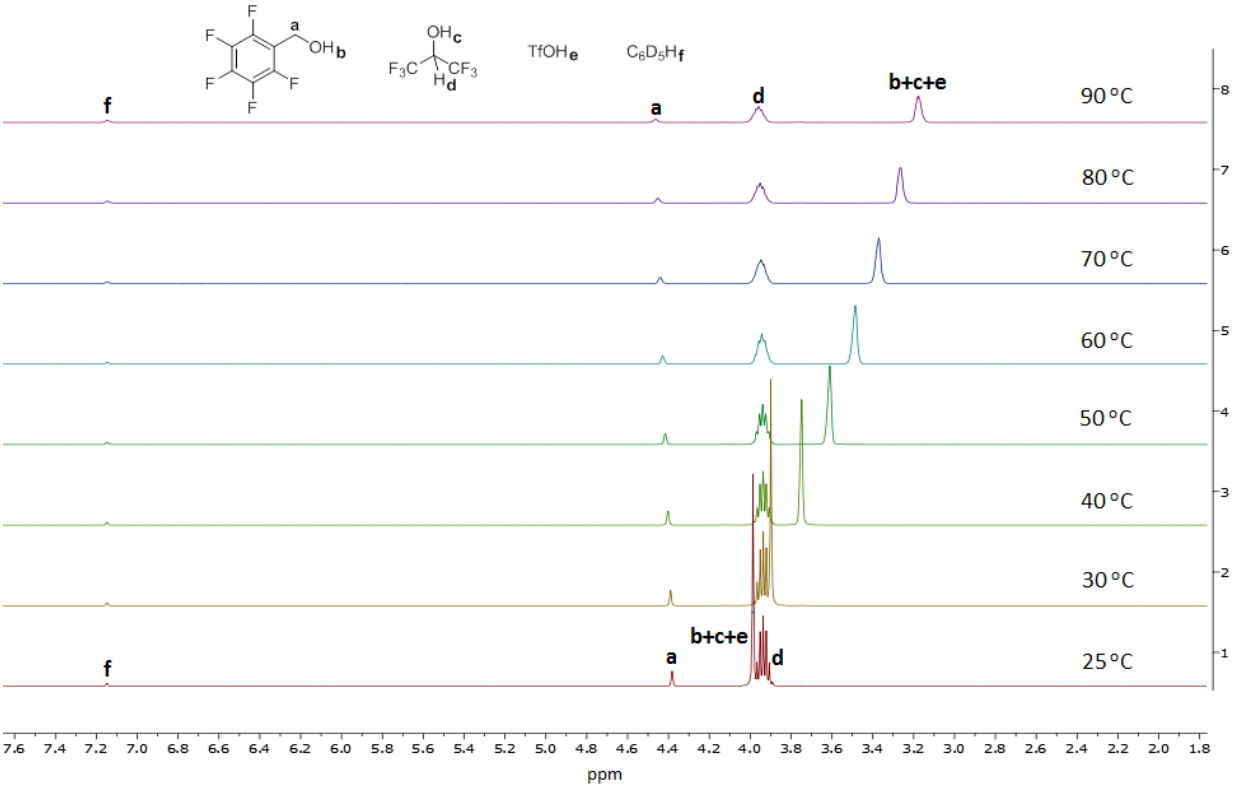


Figure 2.10. ^{1}H-NMR spectra of 2,3,4,5-pentafluorobenzyl alcohol, HFIP and TfOH in C_6D_6 at different temperatures

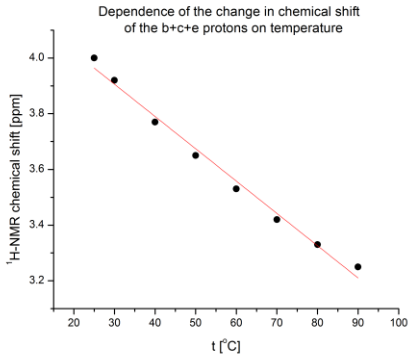


Figure 2.11. Dependence of the chemical shift of **b**+**c**+**e** protons on temperature

The slope of the linear graph that was obtained is the temperature coefficient $\Delta\delta/\Delta t$ that suggests the strength of hydrogen bonds. The bigger temperature coefficients are, the weaker the hydrogen bond, because the bigger difference in chemical shift with increased temperature

suggests easier breaking of the hydrogen bond.[146] Therefore, it was found that for this system the value of the temperature coefficient is:

$$\frac{\Delta\delta}{\Delta t} = (-11.6 \pm 0.5)\frac{\text{ppb}}{\text{K}}.$$

Then the same experiment was repeated, only this time uniquely with HFIP in C_6D_6. The corresponding NMR spectra can be seen in Figure 2. 12, and the change of the chemical shift on temperature dependence in Figure 2.13.

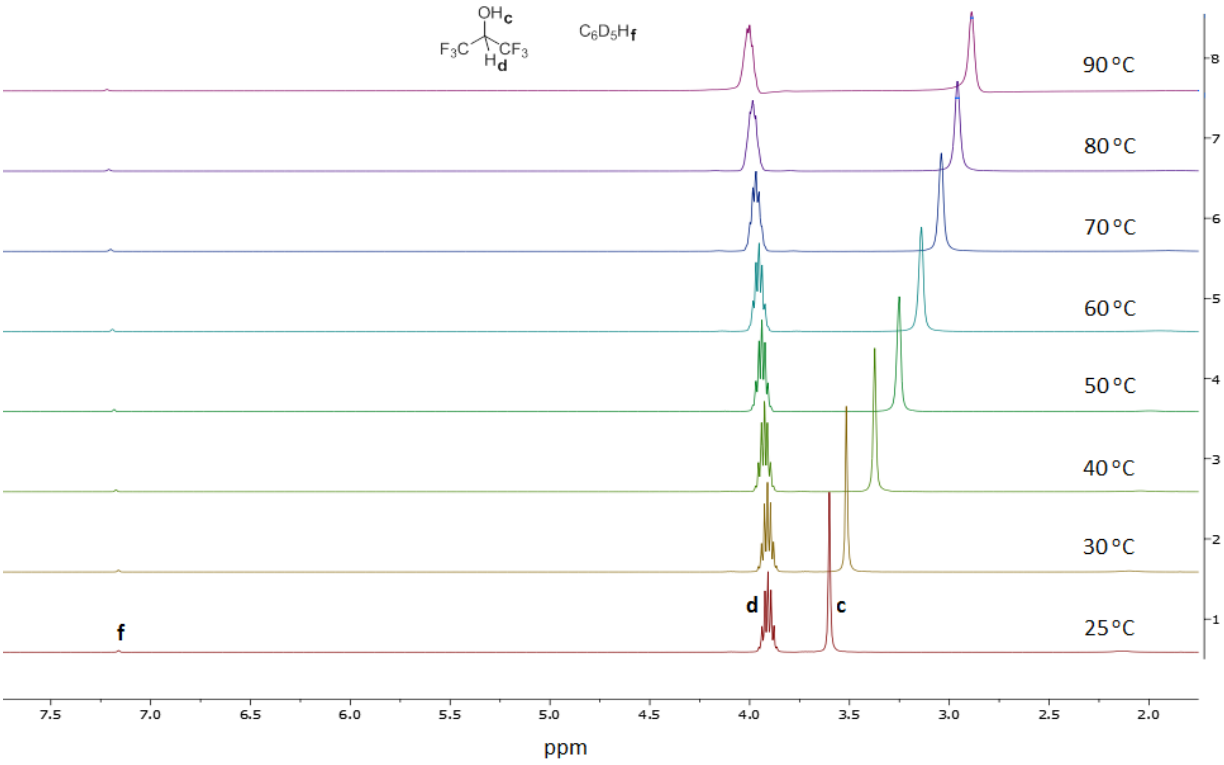


Figure 2. 12. ^{1}H-NMR spectra of HFIP in C_6D_6 at different temperatures

[146] Charisiadis P., Kontogianni V. G., Tsiafoulis C. G., Tzakos A. G., Siskos M., Gerothanassis I. P. *Molecules*, **2014**, 19, 13643-13682

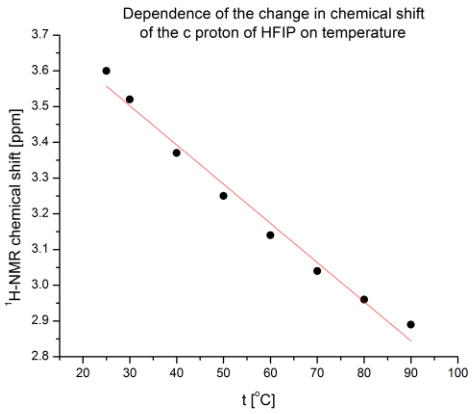


Figure 2.13. Dependence of the chemical shift of the proton **c** of HFIP on temperature

Practically the same value of the temperature coefficient was measured:

$$\frac{\Delta\delta}{\Delta t} = (-11.0 \pm 0.6)\frac{\text{ppb}}{\text{K}},$$

suggesting that the nature of the interaction established between the OH group of the benzylic alcohol substrates, HFIP and triflic acid is indeed a hydrogen bond. Therefore, all these experiments combined implied the existence of acid-induced supramolecular aggregates in solution.

2. 4. 5. Other factors that influence the reaction

The influence of water that is produced in the reactions. The acidity range in HFIP is influenced by the basicity of present water. However, it was found that this influence is negligible when the content of water in HFIP is less than 0.025% by weight.[139] If we consider that maximal amount of water that can be produced in the reaction of 0.25 mmol of the benzylic alcohol in 0.5 mL of HFIP equals the initial amount of the benzylic alcohol, the weight percent of the produced water in that solution is 0.56%. Therefore, production of water during the reaction strongly influences the acidity scale in the system, but evidently not enough to disturb the catalytic turnover.

Thermodynamics of the acid-induced cluster formation. Upon adding a catalytic amount of the acid, a benzylic alcohol and an arene to HFIP, formation of clusters is spontaneous ($\Delta G < 0$). The entropy change of this process should be highly negative, since the ordered structures are formed. But the proton "hopping" process in HFIP is more efficient than in water, therefore this effect should contribute to the increase of the entropy. On the other hand, total enthalpy change in the system should be significantly negative. New hydrogen bonds like O–H···O (OH from the benzylic alcohol, O from HFIP) and O–H···F (OH from the benzylic alcohol, F from HFIP) in polar microphase are formed. Also, π-π stacking interactions between arene nucleophiles and phenyl ring of the deactivated benzylic alcohols are possible in hydrophobous microphase, as well as fluorine-fluorine interactions in the fluorous microphase. There are no published references concerning these considerations in HFIP, therefore, this discussion is purely theoretical.

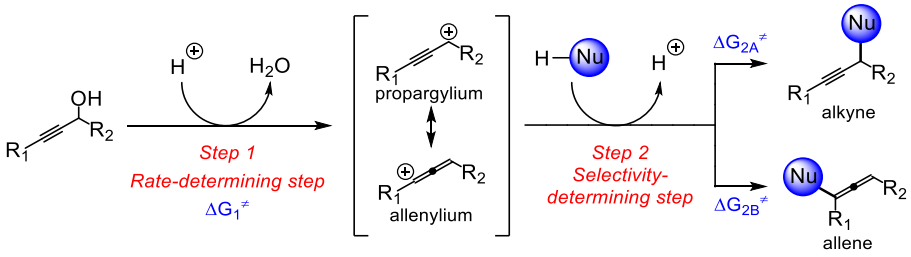
2. 5. Conclusion of Chapter 2 and perspectives

In this chapter, a general method of activation of extremely electronically deactivated benzylic alcohols in Firedel-Crafts reactions was described. The method is based on the use of 10-20 mol% TfOH in HFIP as solvent and 3-5 equiv of the arene nucleophile. Kinetic studies, NMR titrations, kinetic solvent isotope effect and other experiments suggest the S_N1 mechanism and involvement of approximately five molecules of HFIP in the catalytically active species. To get a deeper insight in the aggregation of the species in the solution, DOSY and NOESY NMR experiments are proposed to be done, especially fluorine NOESY. Hydrogen bond network between HFIP, benzylic alcohols and TfOH seems to have a significant role in catalysis as well. In order to further evaluate the strength of the hydrogen bonds in the system, the boiling points of mixtures of different composition of TfOH and HFIP could be determined.

CHAPTER 3
PROPARGYLIC ALCOHOLS AS VERSATILE SUBSTRATES IN FRIEDEL-CRAFTS REACTIONS

3. 1. Scientific background and context

Propargylic alcohols represent an attractive class of starting compounds for many chemical transformations. For example, the direct nucleophilic substitution of propargylic alcohols can result in two types of products: α-substituted alkyne or allene, due to two resonance forms of the intermediate carbocation: propargylium and allenylium (Scheme 3.1). The transformations towards alkynes are well studied, on the other hand, there are only few examples of the formation of allenes from propargyl alcohols.[147]



Scheme 3.1. Brønsted acid catalyzed formation of alkynes and allenes from propargyl alcohols *via* an S_N1' process

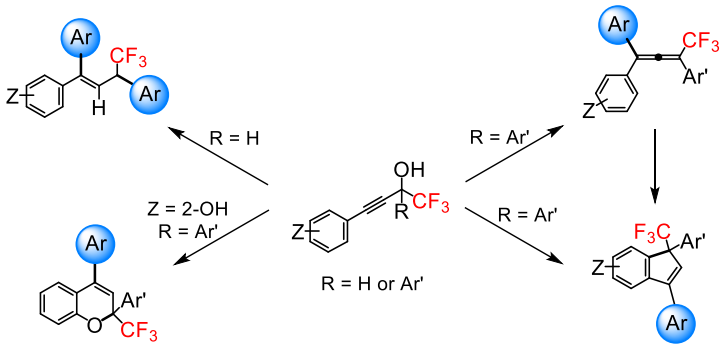
What are the factors that determine which one of these two products will form? From the Scheme 3.1. it can be seen that in the case of the S_N1' substitution of propargylic and allylic alcohols, the catalyst has a role of OH group activation and C–O bond polarization (i. e. lowers the $\Delta G_1^{\neq}$). Therefore, the change in selectivity can only be achieved with the catalysts that change the ratio of the two $\Delta G^{\neq}$ values of products formation steps ($\Delta G_{2A}^{\neq}$ and $\Delta G_{2B}^{\neq}$). To the best of this thesis' author's knowledge, experimental attempts to estimate the relative values of $\Delta G_{2A}^{\neq}$ and $\Delta G_{2B}^{\neq}$ for propargylic alcohols in the literature are not known. Combination of Mayr's nucleophilicity and electrophilicity parameters can be used to estimate one of these two values - the one for which the reaction is observed. For the other one, the $\Delta G^{\neq}$ value would have to be estimated by other means. Yet, Mayr's parameters for propargyl cations are not available.

Nevertheless, according to the study of Samec and Biswas,[38] reactivity and selectivity in the substitution of propargylic alcohols (analogously to allylic alcohols) are dependent on the ease of the carbocation formation (i. e. on the catalyst used) and on the nucleophile employed.

[147] To find out more about nucleophilic substitution of propargylic alcohols, see review: Dryzhakov M., Richmond E., Moran J., *Synthesis*, **2015**, 48, 935-959

They concluded that "the efficiency order of the electrophilic alcohols in terms of *selectivity* to form the desired substitution products was found to be governed by *the ease* of generating the corresponding carbocation rather than the electrophilicity of the generated cation." Since the ease of the carbocation depends on the step 1 (Scheme 3.1), and the selectivity on the step 2 (same scheme), in light of the previously exposed discussion, it is not clear how these conclusions could have been drawn without detailed analysis of reaction kinetic parameters. Furthermore, the same study claims that "*the efficiency of the reactions to generate the products was found to be highly dependent on the reactivity of the nucleophiles.*" This conclusion seems to be ambiguous as well, because no possible interactions of the nucleophiles with the catalysts were investigated.

Since it was shown in the previous chapter that α-trifluoromethylated benzylic alcohols are suitable substrates for Friedel-Crafts reactions in HFIP, the next step was to explore the reactivity of their propargylic analogs in HFIP under Brønsted and Lewis acid catalysis conditions. In this chapter it will be shown that CF_3-bearing propargyl alcohols are versatile substrates in dehydroarylative Friedel-Crafts reactions (Scheme 3.2), giving access to a number of trifluoromethyl allenes, alkenes, indenes and chromenes. Our method is therefore highly potent for diversity oriented synthesis of trifluoromethyl-functionalized compounds, which are of considerable interest to pharmaceutical research.[148]



Scheme 3.2. Transformations of α-CF_3 propargyl alcohols in HFIP presented in this chapter. Reaction conditions: 10 mol% TfOH or $FeCl_3$ (catalyst), 3-5 equiv. of aryl nucleophile, rt to 80 °C, 5 min to 24 h.

[148] See section 1. 5. of this thesis.

Recent interest and importance of synthesis and reactivity of allenes without trifluoromethyl group is evidenced by reports of Maruoka,[149] List,[150] Thomson and Schaus,[151] Ma[152] and others. Methods for synthesis of allenes bearing electron-withdrawing groups, such as keto, carboxy, ester, amide, cyano, sulfone and others are well documented.[153] Among them, the first synthesis of tetrakis(CF_3)allene reaches back in sixties,[154] followed by syntheses of geminal bis(CF_3)allenes.[155] Nevertheless, there are only two reports (Scheme 3.3a-b) about synthesis of monoaryl mono(CF_3) substituted allenes, starting from γ-CF_3 propargyl alcohols[156] and from propargyl bromodifluoroacetates.[157] There is also a limited number of methods allowing access to biaryl mono(CF_3) substituted allenes from γ-CF_3 propargyl alcohols[158] and prefunctionalized propargyl alcohols (Scheme 3.3c),[159] as well as by trifluoromethylation of alkynes,[160] propargyl halides[161] and propargyl acetates.[162] Finally, only one example of Pd-catalyzed synthesis of triaryl mono(CF_3) substituted allenes has been reported.[163] This is also so far the most general method to synthesize tetrasubstituted allenes bearing one CF_3 group and one to three aryl groups or one to three alkyl groups (Scheme 3.3d). But, no *general* methods allowing access to triaryl mono(CF_3) substituted allenes have been reported so far.

[149] Hashimoto T., Sakata K., Tamakuni F., Dutton M. J., Maruoka K. *Nat. Chem*. **2013**, 5, 240-244
[150] Tap A., Blond A., Wakchaure V. N., List B. *Angew. Chem. Int. Ed*. **2016**, 55, 8962-8965
[151] Jiang Y., Diagne A. B., Thomson R. J., Schaus S. E., *J. Am. Chem. Soc*. **2017**, 138, 1998-2005
[152] Wu P., Jia M., Lin W., Ma S., *Org. Lett*. **2018**, 20, 554-557
[153] Krause, N.; Hashmi, A. S. K.; Eds. Modern Allene Chemistry, Wiley-VCH: Weinheim, **2004**; Vols. 1 and 2.
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[157] Ambler B. R., Peddi S., Altman R. A. *Org. Lett*. **2015**, 17, 2506-2509
[158] Li J.-L., Yang X.-J., Jiang M., Liu J.-T. *Tetrahedron Lett.* **2017**, 58, 3377–3379
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[160] Ji Y.-L., Luo J.-J., Lin J.-H., Xiao J.-C., Gu Y.-C. *OrgLett*, **2016**, 18, 1000–1003
[161] Zhao T. S. N., Szabó K. J. *OrgLett.* **2012**, 14, 3966–3969
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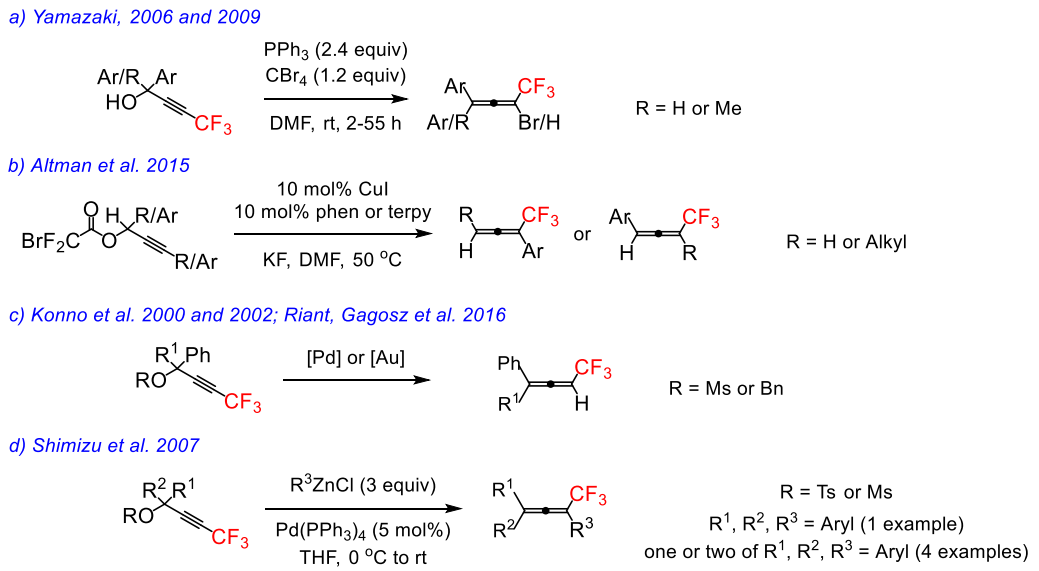
[163] Shimizu M., Higashi M., Takeda Y., Jiang G., Murai M., Hiyama T. *Synlett* **2007**, 7, 1163–1165



Scheme 3.3. Extract from the previous work on synthesis of trifluoromethyl substituted allenes

In general, allenes are considered as relatively reactive species, able to isomerize to various structures.[164] Photochemically induced,[165] Au(I)-catalyzed[166] and Brønsted acid catalyzed[167] isomerization of allenes to indenes have already been described, as well as Fe(II)-catalyzed oxidative transformation of allenes to indenes.[168] However, no analogous transformations to indenic cores bearing trifluoromethyl groups have been reported.

However, several other reaction pathways have been explored so far to obtain CF_3-substituted indenes. The earliest method was based on radical addition of alkylbenzene to hexafluoropropene,[169] following perfluoro-CF_3-containing indenes.[170] Other strategies comprise the treatment of indanones with perfluoroalkyl lithium reagents,[171] the use of α-(trifluoromethyl)allyl alcohols,[172] etc. A recent example from Vasilyev group describes the

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[169] (a) Kimoto H., Muramatsu H., Inukai K. *Nippon Kagaku Kaishi*, **1975**, 4, 665-671; (b) Kimoto H., Muramatsu H., Inukai K. *Bull. Chem. Soc. Jap.* **1976**, 49(6), 1642-1649
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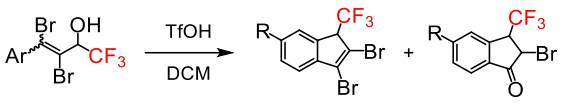
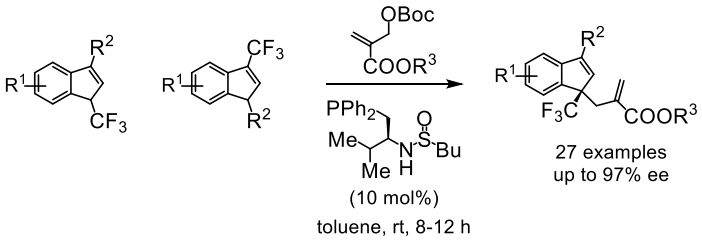
[172] Radix-Large S., Kucharski S., Langlois B. R. *Synthesis*, **2004**, 3, 456-465

synthesis of CF_3-indenes from brominated CF_3-enones[173] and brominated CF_3-substituted allyl alcohols[174] using superstoechiometric TfOH (Scheme 3.4).



Scheme 3.4. Access to bromo-indenes and indanones from bromoallyl alcohols (Vasilyev et al. 2017)

In another recent study, Zhang and coworkers showed formation of chiral CF_3-bearing indenes from *mix*-indenes (Scheme 3.5), where mix-indenes were synthesized from α-CF_3-allylic alcohols.[175]



Scheme 3.5. Enantioselective allylic alkylation of *mix*-CF_3 indenes (Zhang et al. 2017)

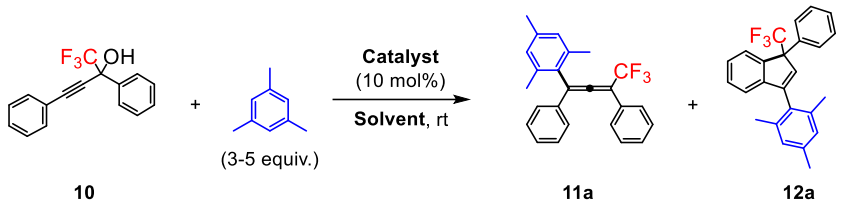
3. 2. Reaction discovery and optimization

We began our investigations with standard conditions for dehydroarylative reactions of benzylic alcohols in HFIP that were previously established (Table 2.3). Instead of direct nucleophilic substitution on the α-CF_3 carbon of the alcohol **10**, with TfOH as catalyst in HFIP at room temperature we observed the nucleophile attack on γ-carbon and formation of allene **11a** (Table 3.1, entry 1). Moreover, when the same reaction is conducted at higher temperature (50 ^oC), the formation of an additional product (CF_3-substituted indene, **12a**) was observed (entry 2). In order to verify the counteranion effect and Lewis acid catalysts, we tested $Sc(OTf)_3$, which did not furnish the allene in satisfactory yield (entry 3). Other Brønsted acids did not lead to the

[173] Iakovenko R. O., Kazakova A. N., Boyarskaya I. A., Gurzhiy V. V., Avdontceva M. S., Panikorovsky T. L., Muzalevskiy V. M., Nenajdenko V. G., Vasilyev A. V. *Eur. J. Org. Chem.* **2017**, 5632-5643
[174] Kazakova A. N., Iakovenko R. O., Boyarskaya I. A., Ivanov A. Yu., Avdontceva M. S., Zolotarev A. A., Panikorovsky T. L., Starova G. L., Nenajdenko V. G., Vasilyev A. V. *Org. Chem. Front.* **2017**, 4, 255–265
[175] Zhang J., Wu H.-H., Zhang J. *Org. Lett.* **2017**, 19, 6080–6083

formation of allene or indene (entries 3-7), apart from fluoroantimonic acid, that gave a mixture of allene and indene in an approximate ratio of 11:1 (entry 7). Although mostly efficient in yielding the allene, none of the tested Lewis acids were able to furnish the corresponding indene in significant yield (entries 8-11). Finally, at room temperature, in only 5 to 10 minutes, with $FeCl_3$ as catalyst we were able to observe formation of the allene in 93% isolated yield (entry 12). Heating at 80 °C and longer reaction time led to complete transformation to the corresponding indene (entry 13). By testing the same reaction in other solvents (entries 14-16),

Table 3.1. Reaction optimization and discovery



Entry	Catalyst	Solvent	Time	Allene - isolated yield [%]	Indene - isolated yield [%]
1	TfOH	HFIP	1 h	85	-
2[a]	TfOH	HFIP	45 min	50	43
3	$Sc(OTf)_3$	HFIP	24 h	9	-
4[a]	TFA	HFIP	24 h	60	-
5	H_3PO_4	HFIP	24 h	-	-
6	HCl	HFIP	5-10 min	traces	-
7	$HSbF_6 \cdot 6H_2O$	HFIP	5-10 min	87	8
8	SbF_5	HFIP	5-10 min	66	-
9[a]	$AlCl_3$	HFIP	45 min	24	10
10	$ZnCl_2$	HFIP	24 h	7	-
11	$AuCl_3$	HFIP	5-10 min	69	-
12	$FeCl_3$	HFIP	5-10 min	93	-
13[b]	$FeCl_3$	HFIP	24 h	-	94
14	$FeCl_3$	*i*-PrOH	5-10 min	-	-
15	$FeCl_3$	CF_3CH_2OH	5-10 min	39	-
16	$FeCl_3$	DCM	24 h	9	-
17	$FeCl_2$	HFIP	24 h	41	-
18	$FeCl_3$[c]	HFIP	3.5 h	5	-

[a]Reaction was performed at 50 °C. [b]Reaction performed at 80 °C.
[c]In the presence of 20 mol% Proton sponge.

we confirmed that this reactivity is most pronounced in HFIP and iron(III) chloride. Iron(II) chloride was not as efficient as iron(III) chloride in catalysis (entry 17). Addition of 20 mol% of Proton sponge completely shut down the reactivity (entry 18).

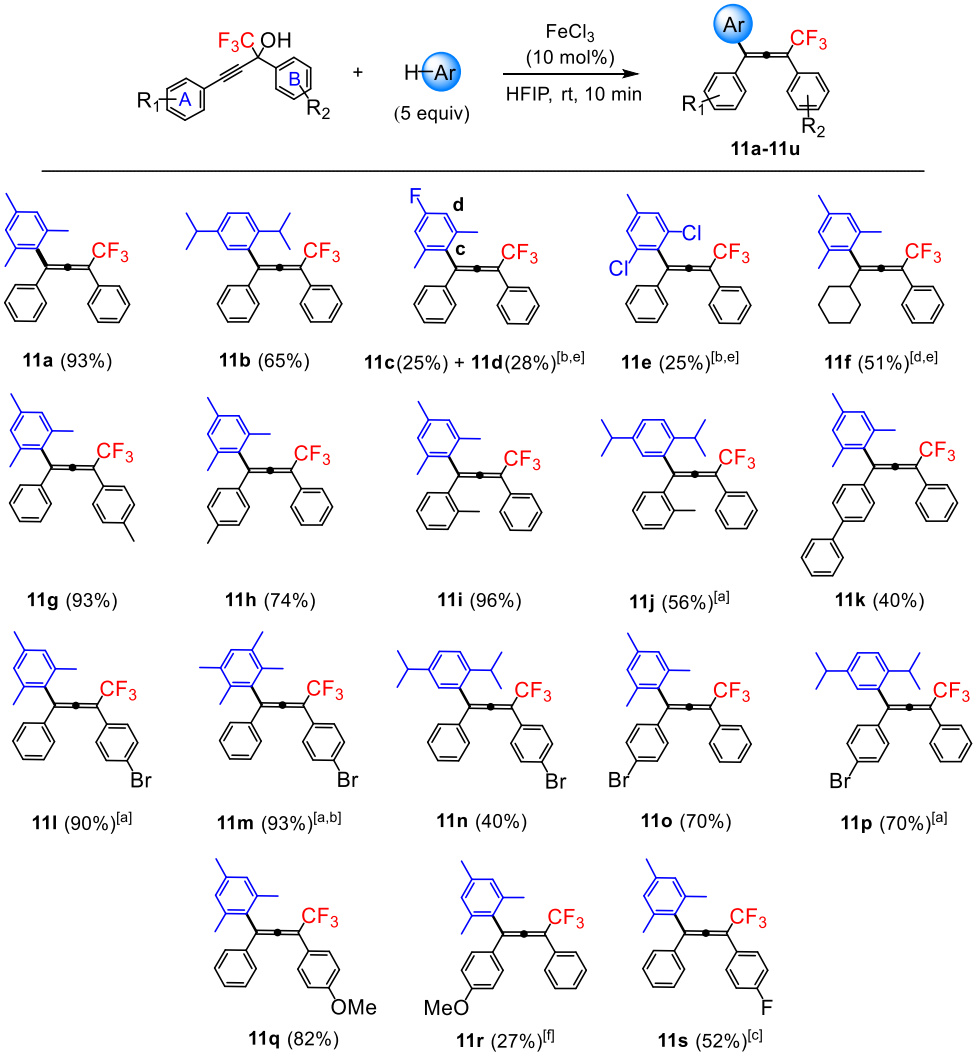
Why is iron(III) the best catalyst for the above mentioned transformation?[176] In the hydrolysis process, it can act like a hidden Brønsted acid catalyst, releasing traces of protons, which would efficiently protonate the hydroxyl group in HFIP. However, if this were the case, $FeCl_3$ and HCl would exhibit comparable effects, which was not the case. Therefore, the cause of such efficiency of $FeCl_3$ should be searched somewhere else. In fluorinated alcohols as solvents, the solvation of cations is minimal. Therefore, naked Fe^{3+} ion could act as Lewis acid stronger than in other media. Alternatively, Fe^{3+} ion might transiently form sandwich complexes coordinating the phenyl ring at the γ-position and the arene nucleophile, directing the attack.

3. 3. Scopes of allenes and indenes

Encouraged by the initial results, the scope of triaryl monotrifluoromethyl allenes was explored (Table 3.2). The parent 1,1,1-trifluoro-2,4-diphenyl-but-3-yn-1-ol furnished the corresponding allene **11a** with mesitylene as nucleophile in 93% yield. Bulkier nucleophiles, such as 1,4-diisopropylbenzene resulted in slight decrease of yield (entry **11b**), as well as nucleophiles bearing chlorine or fluorine (**11c-e**). Substitution of the phenyl ring A with cyclohexyl group lead to significant decrease in yield of **11f**. *p*-Methyl substituent on the phenyl ring B did not change the yield of **11g** compared to **11a**, but a *p*-methyl group on the phenyl ring A slightly decreased the yield of **11h**. However, an *o*-methyl group did not influence the yield of **11i**, compared to **11a**, but did decrease the yield of **11j** compared to **11b**. Introduction of another phenyl ring at the *para* position of the phenyl group A lowered the yield of **11k** compared to **11a**. A *p*-bromo substituent on the phenyl ring B slowed down the reaction in case of **11l-n**, which was also the case with *p*-bromophenyl ring A (**11o-p**). A *p*-methoxy group on phenyl ring B lead to only slight decrease in yield of **11q**, as well as the same substituent on the phenyl ring A (entry **11r**).

[176] Interestingly, Vasilyev et al. published analogous transformation of CF_3-allylic alcohols with $FeCl_3$ (or FSO_3H) as catalyst in DCM, giving CF_3-alkenes and CF_3-indanes. See: Kazakova A. N., Iakovenko R. O., Boyarskaya I. A., Nenajdenko V. G., Vasilyev A. V. *J. Org. Chem*. **2015**, 80, 9506-9517

Table 3.2. Scope of tetrasubstituted allenes bearing trifluoromethyl group



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

Although the yield shown for **11r** is only 27%, this is because the reaction was deliberately interrupted after only few minutes, in order to get the pure allene, since subsequent indene formation in this case is very rapid. Further heating of **11r** at 50 °C during 6 h only yielded the mixture of allene and indene in a 3:2 ratio. Finally, when fluorine is introduced in the *para* position on the phenyl ring B, the reaction slows down significantly (entry **11s**).

Therefore, based on the results from Table 3.2 it can be concluded that in general electron-withdrawing groups (fluorine, bromine, phenyl) introduced in *para* positions of both the

A and B-phenyl ring slow down the reaction, whereas the electron-donating groups (methoxy and methyl) in *para* positions of the both phenyl ring accelerate the reaction.

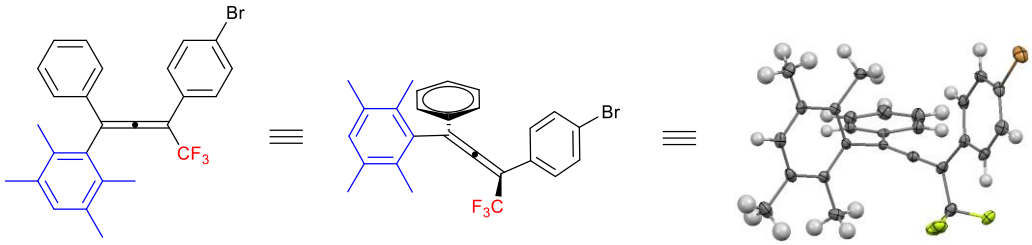


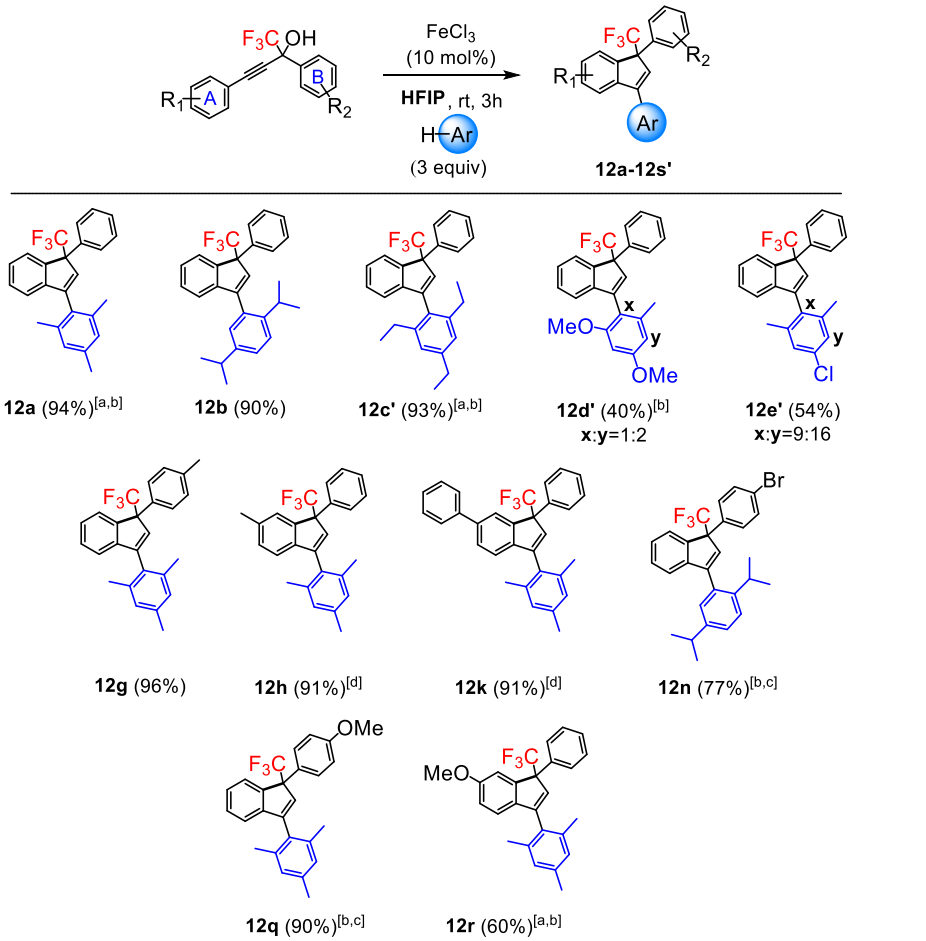
Figure 3.1. Crystal structure of one of the allenes

In the next step of the study, the scope of indenes was explored (Table 3.3). The indenes **12a** and **12b** were obtained *via* allenes **11a** and **11b** in excellent yields. In the case of **11c-e**, the nucleophiles employed were quite weak, so the corresponding indenes were difficult to form. 1,3,5-triethylbenzene proved to be another good nucleophile for formation of indenes (entry **12c'**). However, when methoxy- or chloro-bearing arenes are used, the yields dropped significantly (**12d'-e'**). The indenes **12g**, **12h** and **12k** bearing methyl or additional phenyl group were all obtained in excellent yields. When a methoxy group is attached in the *para* position on the phenyl ring B, the yield of the indene **12q** remained high, unlike the case of the *para* substituted phenyl ring A (**12r**). The reaction was also slowed down when a bromo-substituent was introduced in the phenyl ring B (**12n**).

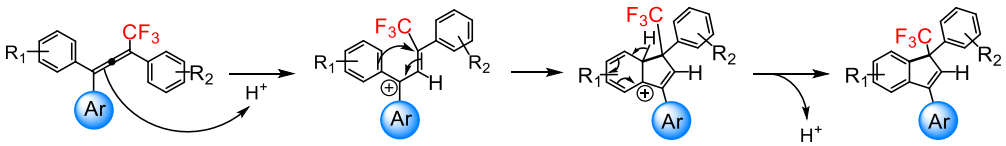
When a methyl group is in the *ortho* position on the phenyl ring A, like in the cases of **11i** and **11j**, the formation of the indene is disabled. *Para*-bromo substitution in the phenyl ring A of the starting alcohols also leads to significantly lower cyclization rates of **11o** and **11p**. Therefore, the following Nazarov-type cyclization mechanism can be proposed (similar cyclizations have already been reported with $Yb(OTf)_3$ as catalyst[177], as well as with AgOTf and TfOH[178]) in Scheme 3.6.

[177] Zhang X., Teo W. T., Hong Chan P. W. *Org. Lett*. **2009**, 11, 4990-4993
[178] Cordier P., Aubert C., Malacria M., Lacôte E., Gandon V. *Angew. Chem. Int. Ed*. **2009**, 48, 8757-8760

Table 3.3. Scope of indenes bearing trifluoromethyl group. Compounds with numbers containing an apostrophe (**12c'**, **12d'**, **12e'**, **12s'**) do not have corresponding allene analogs. All other compounds have corresponding allene analog with the same letter in Table 3.2.



[a]Reaction time was 24 h. [b]Heated at 80 ºC. [c]Reaction time was 1 h. [d]Run at 50 ºC during 6 h.



Scheme 3.6. Proposed mechanism of indene formation.

Reaction progress was monitored by gas chromatography (Figure 3.2). As described in Table 3.1, after only 5 minutes at room temperature, complete conversion of the starting propargylic alcohol **10** to the allene **11a** was observed (a-b), followed by conversion to the indene **12a** in several hours (c). When the allene **11a** was subjected to the same reaction

conditions without nucleophile, it was also transformed in the corresponding indene in just 2 h (d-f).

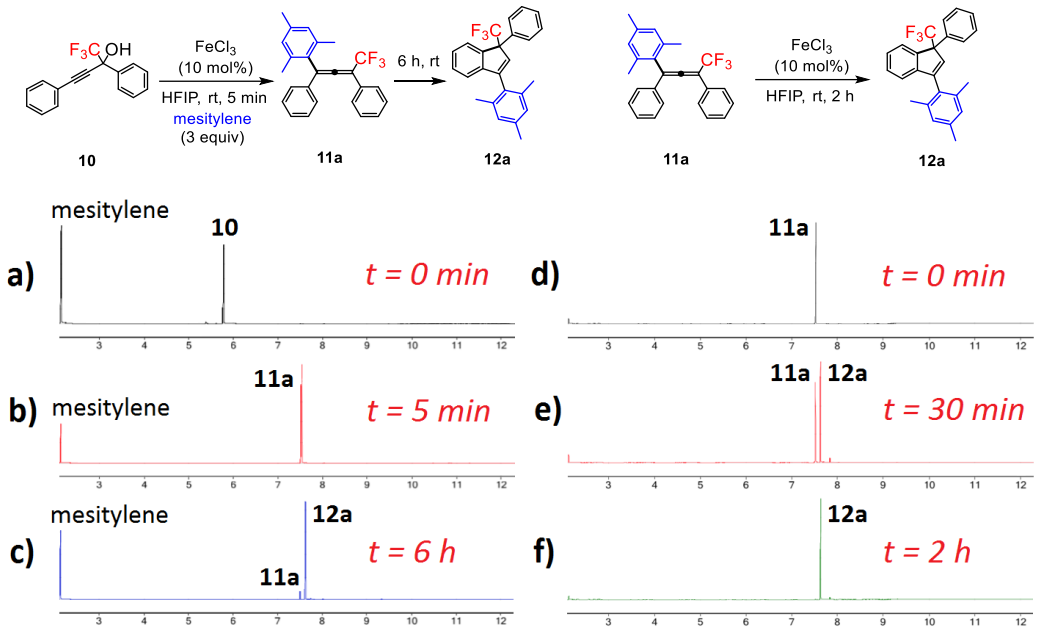


Figure 3.2. Reaction progress of the formation of the indene **12a** from propargylic alcohol **10** via allene **11a** (a-c) and reaction progress of the isomerization of the indene **11a** to allene **12a** (d-f)

3. 4. Scope of chromenes

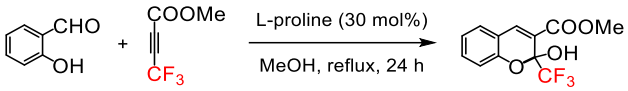
Chromenes (benzopyrans) are a class of organic compounds that exhibit various biological activities,[179] especially their trifluoromethylated derivates.[180] So far, five different methods for synthesis of 2*H*-2-trifluoromethyl chromenes have been described. Initially, the synthesis was accomplished by condensation of 3,4-dimethoxyphenol with a CF_3-containing acetal.[181] Numerous reports of condensation of salicylaldehyde with activated trifluoromethyl

[179] Pratap R., Ram V. J., *Chem. Rev*. **2014**, 114, 10476-10526

[180] (a) Wang J. L., Carter J., Kiefer J. R., Kurumbail R. G., Pawlitz J. L., Brown D., Hartmann S. J., Graneto M. J., Seibert K., Talley J. J. *Bioorg. Med. Chem. Lett*. **2010**, 20, 7155-7158 and 7159-7163 and 7164-7168; (b) Xing L., Hamper B. C., Fletcher T. R., Wendling J. M., Carter J., Gierse J. K., Liao S. *Bioorg. Med. Chem. Lett*. **2011**, 21, 993-996; (c) Zhang Y., Tortorella M. D., Wang Y., Liu J., Tu Z., Liu X., Bai Y., Wen D., Lu X., Lu Y., Talley J. J. *ACS Med. Chem. Lett*. **2014**, 5, 1162-1166; (d) Reddy K. R., Rao P. S., Dev G. J., Poornachandra Y., Kumar C. G., Rao P. S., Narsaiah B., *Bioorg. Med. Chem. Lett.* **2014**, 24, 1661-1663; (e) Zhang Y., Wang Y., He C., Liu X., Lu Y., Chen T., Pan Q., Xiong J., She M., Tu Z., Qin X., Li M., Tortorella M. D., Talley J. J. *J. Med. Chem*. **2017**, 60, 4135-4146

[181] Camps F., Coll J., Messeguer A., Pericás M. A., *J. Heterocyclic Chem*. **1980**, 17, 207-208

alkenes were published subsequently (Scheme 3.7),[182] and this has been far the most exploited method for synthesis of this scaffold. Three remaining studies offer alternative ways to access this class of chromenes: intramolecular cyclisation of phenoxypropenals;[183] condensation of N-unsubstituted imines of 2-hydroxyacetophenones[184] – analogously to the condensation of salicylaldehydes; and using propargyl alcohols as starting compounds[185]. The last strategy, however, was able to provide very few examples of 2*H*-2-trifluoromethyl chromenes.



Scheme 3.7. A representative method of synthesis of 2*H*-2-trifluoromethylchromenes (Zhang, Cao et al. 2016)

As part of our propargylic alcohol activation research program, we hypothesized that employing *o*-hydroxyphenyl group as a structural moiety of the starting propargyl alcohol might give access to corresponding 2*H*-2-trifluoromethyl chromenes. Indeed, when 1,1,1-trifluoro-4-(2-hydroxophenyl)-2-phenylbut-3-yn-1-ol (**13a**) was subjected to TfOH/HFIP reaction conditions, we were pleased to observe formation of **14a** in quantitative yield (Table 4). Other nucleophiles such as durene, pentamethylbenzene and 1,3,5-trimethoxybenzene prooved to be compatible with the reaction conditions (**14b-14d**). Slight modification of the electronic properties of the 2-phenyl ring (**14e** and **14f**), as well as complete substitution of the 2-aryl moiety with a 2-alkyl group did not influence the reactivity either (**14g**). Also, the *tert*-butyl-dimethylsilyl derivatives **13e'** and **13f** yielded the same product as their phenolic analogs (**13e**).

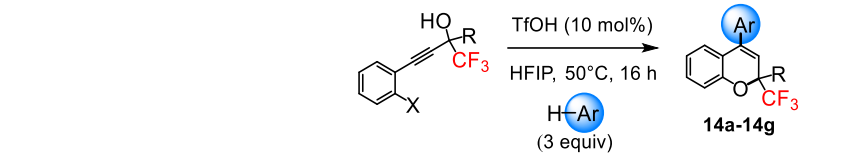
[182] (a) Korotaev V. Yu., Kutyashev I. B., Sosnovskikh V. Ya. *Heteroatom Chemistry*, **2005**, 16, 492-496; (b) Duda B., Tverdomed S. N., Röschenthaler G.-V. *J. Org. Chem*. **2011**, 76, 71-79; (c) Xu C., Yang G., Wang C., Fan S., Xie L., Gao Y. *Molecules*, **2013**, 18, 11964-11977; (d) Baryshnikova M. A., Volkonskii A. Yu., Gusev D. V., Labodneva N. O., Sigan A. L., Yakunina N. G., Chkanikov N. D. *Russ. Chem. Bull. Int. Ed*. **2014**, 63, 2551-2555; (e) Yan X., Shen D., Han J., Chen J., Deng H., Shao M., Zhang H., Cao W. *J. Fluor. Chem*. **2016**, 188, 58-64; (f) Li D., Zhou Y., Zhao Y., Zhang C., Li J., Zhao J., Qu J. *J. Fluor. Chem*. **2018**, 212, 122-129

[183] El Kharrat S., Laurent P., Blancou H., *J. Org. Chem*. **2006**, 71, 8637-8640

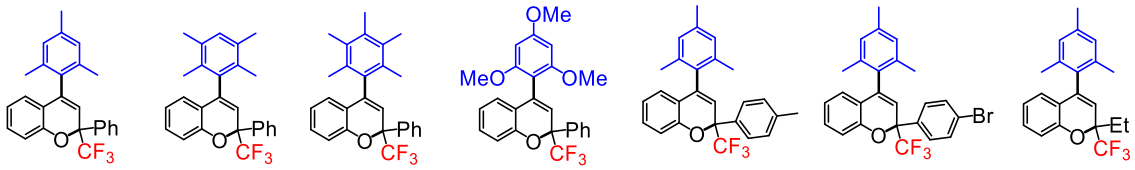
[184] Korotaev V. Yu., Sosnovskikh V. Ya., Kutyashev I. B., Barkov A. Yu., Matochkina E. G., Kodess M. I., *Tetrahedron*, **2008**, 64, 5055-5060

[185] Madabhushi S., Jillella R., Godala K. R., Mallu K. K. R., Beeram C. R., Chintala N., *Tetrahedron Lett*., **2012**, 53, 5275-5279

Table 4. Scope of chromenes bearing trifluoromethyl group



13a, X = OH, R = Ph
13e, X = OH, R = p-MeC_6H_4 **13e'**, X = OTBS, R = p-MeC_6H_4
13g, X = OH, R = Et **13f**, X = OTBS, R = p-BrC_6H_4



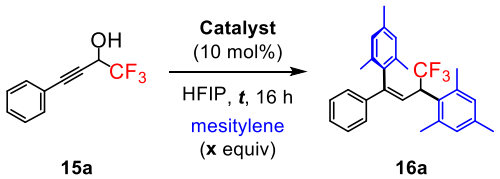
14a, quant. **14b**, 86% **14c**, quant. **14d**, 43% **14e**, 70% **14e'**, 71%[a] **14f**, 75% **14g**, 77%

[a]Run on 1 mmol scale.

3. 5. Reactivity of secondary α-CF_3 propargylic alcohols

After success in the activation of tertiary CF_3-propargylic alcohols towards nucleophilic substitution, the following step was to test the reactivity of secondary CF_3-propargylic alcohols

Table 3.4. Optimization of reactivity of α-trifluoromethyl secondary propargylic alcohols



15a **16a**

Entry	Catalyst	x	Temperature	Yield [%]
1	TfOH	1	rt	24
2	TfOH	2	rt	49
3	Tf_2NH	2	rt	56
4	$FeCl_3$	2	rt	31
5	TfOH	3	rt	59
6	Tf_2NH	3	rt	76
7	TfOH	3	50 °C	75
8	Tf_2NH	3	50 °C	88

in the same type of reaction (Table 3.4). Triflic acid (entries 1, 2, and 5), triflimide (entries 3 and 6) and iron(III) chloride (entry 4) were tested as catalysts at room temperature with 1–3 equiv of mesitylene. Surprisingly, in all cases, the bis-adduct with two nucleophile residues was observed (**16a**). The best result was achieved with triflimide, even at slightly higher temperature (entries 7-8). However, since it was still quite an efficient catalyst in this reaction, in further studies triflic acid was chosen as catalyst due to easier handling conditions, rather than triflimide.

A crystal structure of the product **16a** revealed the *Z*-geometry of the double bond, as well as the preferred parallel positions of two mesityl units (Figure 3.3).

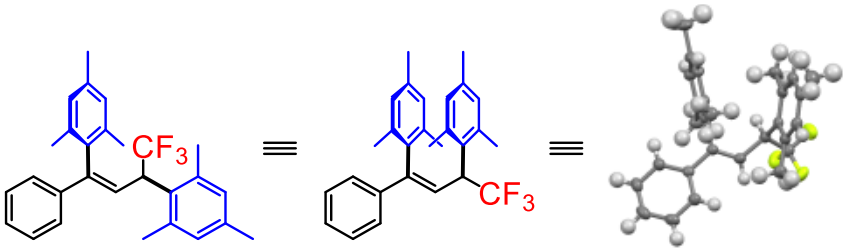
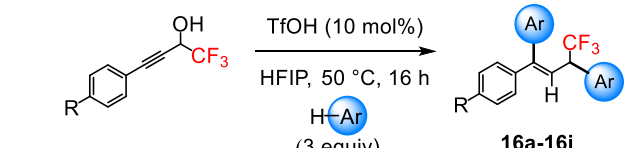


Figure 3.3. The crystal structure of the compound **17a**.

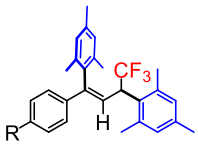
A series of *para*-substituted secondary α-trifluoromethyl propargylic alcohols was tested for Friedel-Crafts reactions with methyl- and methoxy-substituted benzenes as nucleophiles (Table 3.5). Methyl- (**15b**) and methoxy- (**15c**) substituted propargyl alcohols furnished products **16b** and **16c** in slightly higher yields than the parent alcohol **16a**. Substitution with a cyano-group led to significant loss in reactivity (**16d**), whereas the less electron-withdrawing bromine substituent lead to significantly minor loss in reactivity (**16e**). When 1,3,5-trimethoxybenzene is used as nucleophile, methoxy-substituted alcohol **15c** furnished the corresponding product **16f** in good yield. With other methyl-substituted benzenes, such as *p*-xylene (**16g**), pentamethylbenzene (**16h-i**) and durene (**16j**), as nucleophiles, reaction products were also obtained in good to excellent yields.

Table 3.5. Scope of the reactivity of secondary α-trifluoromethyl propargylic alcohols[a]

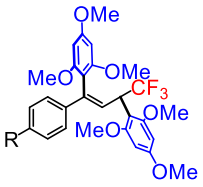


15a, R = H **15c**, R = OMe
15b, R = Me **15d**, R = CN
15e, R = Br

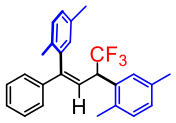
16a-16j



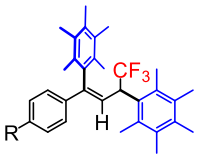
16a, R = H, 75%
16b, R = Me, 77% (92%[b])
16c, R = OMe, 81%
16d, R = CN, 22%[c]
16e, R = Br, 61%



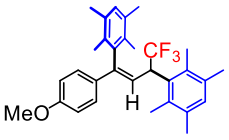
16f, R = OMe, 73%



16g, 49%[d]



16h, R = H, 95%
16i, R = Me, 88%

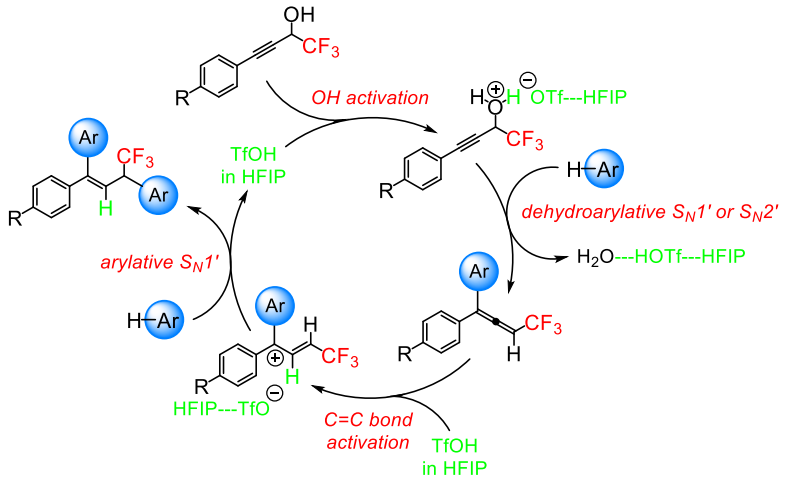


16j, 65%

[a]Isolated yields after column chromatography. [b]Run at 1 mmol scale.
[c]Reaction heated at 100 °C for 88 h. [d]Combined yield of isomers (*E*/*Z*).

The proposed mechanism is shown in Scheme 3.8. First, the hydroxyl group is activated by the TfOH/HFIP hydrogen-bond network, which is followed by nucleophilic substitution at the γ-carbon. Then, the C=C double bond that is more distant from the CF_3 group is protonated, forming a carbocation at the benzylic position. This carbocation is attacked by another molecule of the nucleophile in S_N1 process, furnishing the final bis-nucleophilic product.

Still, it was surprising that when more activated nucleophile (1,3,5-trimethoxybenzene) is employed, the reaction resulted in significantly lower yield of the product **16f**. In order to better understand this result, a ^{1}H-NMR titration of 1,3,5-trimethoxybenzene in HFIP with TfOH and C_6D_6 as internal standard was performed (Figure 3.4). The protonation of trimethoxybenzene (signals e, g, h and f that appeared) and significant downfield shift of signals of both protons of HFIP (c and d) was observed. It can be therefore concluded that 1,3,5-trimethoxybenzene acts like a buffer in HFIP, although in the same time the interaction with HFIP is observed, which explains why the yield decreased significantly, but still not totally.



Scheme 3.8. Plausible mechanistic scenario of secondary α-CF_3 propargylic alcohols in nucleophilic substitution in HFIP

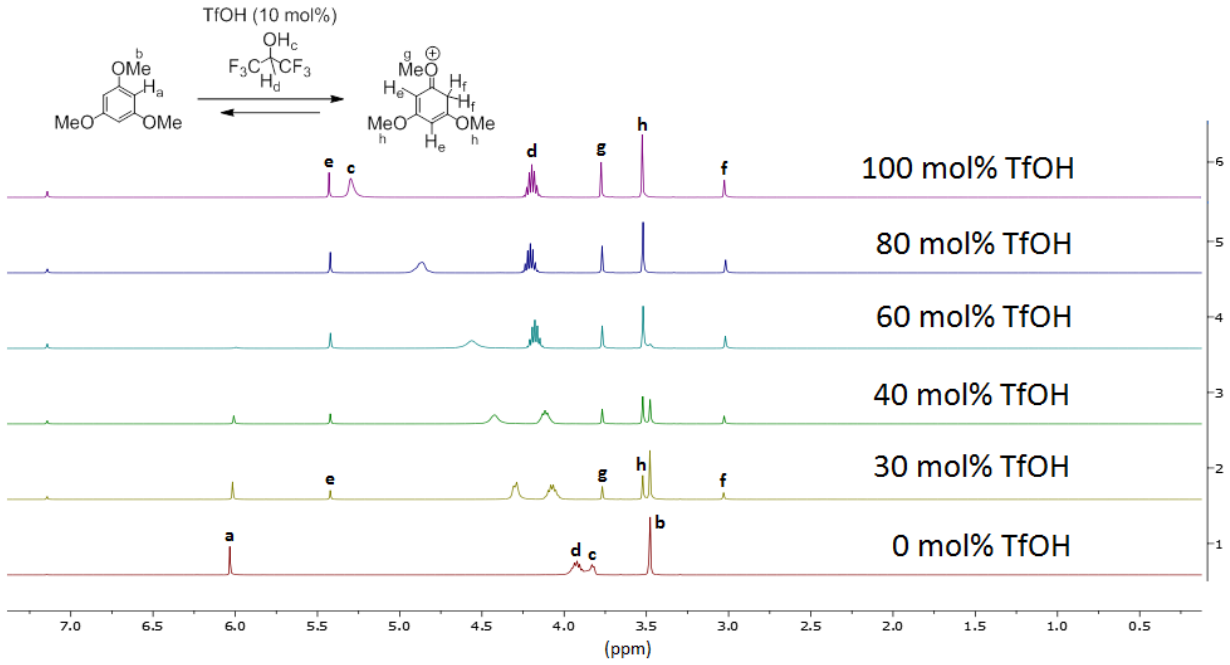
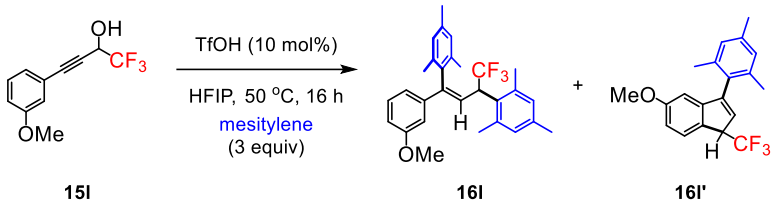


Figure 3.4. ^{1}H-NMR titration of 1,3,5-trimethoxybenzene (0.5 mmol) in HFIP (0.25 mL) and C_6D_6 (5 µL) with TfOH

Another interesting result was obtained when 4-(3-methoxyphenyl)-1,1,1-trifluorobut-3-yn-2-ol (**15l**) is employed as substrate. A mixture of a bis-nucleophile adduct **16l** and indene **16l'** was observed, suggesting that the electronic properties of the substrate play a significant role in

the determination of the selectivity of the reaction, and not exclusively the nature of the nucleophile, steric effects or the "ease" of the carbocation formation (Scheme 3.9).



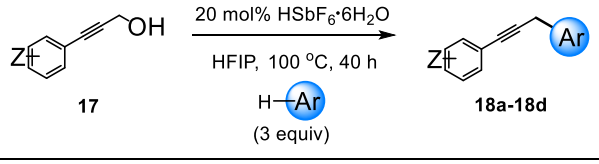
15l **16l** **16l'**

Scheme 3.9. Formation of an additional product - indene

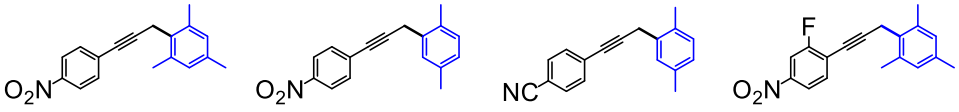
3. 6. Reactivity of primary propargylic alcohols

The biggest challenge in the field of propargylic alcohol activation is activation of primary propargylic alcohols in reactions of nucleophilic substitution, due to the high reactivity of the intermediate propargyl cation that leads to rapid polymerization. However, by use of $HSbF_6$/HFIP reaction conditions, it is possible, in a limited number of examples, to achieve the nucleophilic substitution of these substrates in good yields (Table 3.6).

Table 3.6. Scope of primary propargylic alcohols in nucleophilic substitution



17 **18a-18d**

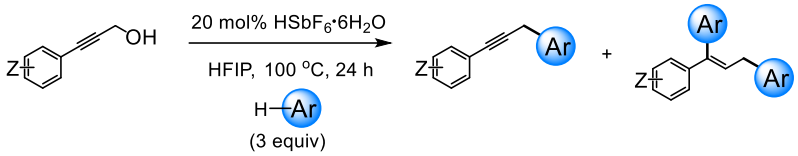


18a (60%)[a] **18b** (44%) **18c** (60%) **18d** (48%)

[a]Reaction time was 16 h.

Only substrates bearing electron-withdrawing groups successfully reacted with mesitylene and *p*-xylene as nucleophiles by employment of $HSbF_6 \cdot 6H_2O$ in HFIP. Substrates bearing slightly less deactivating groups gave bis-arylated products, whereas the substrates bearing electro-donating groups resulted in fast polymerization even at room temperature.

Therefore, the main problem that should still be overcome in these reactions is the addition of the second equivalent of the nucleophile at the benzylic position (Table 3.6).



Scheme 3.10. Formation of the second reaction product by addition of the second nucleophile equivalent

3. 7. Conclusion of Chapter 3 and perspectives

In the third chapter of this thesis, the reactivity of different types of propargylic alcohols towards nucleophilic arylative substitution in HFIP under strong Brønsted acid catalysts conditions was explored. From tertiary α-trifluoromethyl propargylic alcohols it was possible to obtain three different classes of products (trifluoromethyl substituted allenes, indenes and chromenes) by varying the reaction conditions. Secondary α-trifluoromethyl propargylic alcohols were suitable substrates for obtaining aryl-substituted β-trifluoromethyl alkenes. Finally, several examples of primary propargylic alcohols were successfully activated in nucleophilic monoarylative substitution reactions, although avoiding the bis-arylation still remains the significant challenge.

However, the following additional experiments are proposed:

- In order to confirm the proposed mechanism from the Scheme 3.8, several experiments can provide an insight in each step of the catalytic cycle. The first step can be investigated by measuring the kinetic solvent isotope effect, i. e. running the reaction in HFIP-d_2, to confirm the fast equilibrium protonation prior to the rate determining step. In this case, a higher value of KSIE is expected than it was measured in the Subchapter 2. 4. 3. of this thesis, because the hydrogen-bond network protonates the substrate in the third step as well. Therefore, the same experiment can give insight into the third step, since the product would be deuterated at the carbon β to the CF_3 group. Moreover, the first step can also be analyzed by the measurement of the kinetic effect of the α-CF_3 deuterated substrate. To confirm if the step 2 is S_N1' or S_N2', the

reaction order in nucleophile can be measured. Potentially, this experiment might also give insight into the reaction order of the third step of the cycle.

- The ^{1}H-NMR titration shown in the Figure 3.4 requires more attention than qualitative interpretation. By analysis of the integration of the peaks in the ^{1}H-NMR spectrum, it can be noticed that the 1,3,5-trimethoxybenzene is 100% protonated already when 80 mol% of TfOH is added. Furthermore, if this is indeed the case, and not result of the experimental error, then the downfield shift of the HFIP hydroxyl proton requires additional explanation.

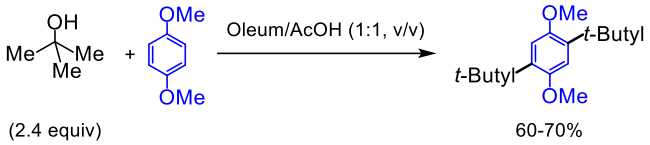
- Development or screening of chiral ligands that coordinate efficiently to iron(III) is proposed, in order to realize the allene synthesis in an stereoselective manner. However, this might be possible only if Fe^{3+} ions are involved in π-complexes.

CHAPTER 4

FRIEDEL-CRAFTS REACTIONS OF ALIPHATIC ALCOHOLS IN HFIP

4. 1. Friedel-Crafts reactions of tertiary and secondary aliphatic alcohols in HFIP

Tertiary aliphatic alcohols have been successfully employed in Friedel-Crafts reactions over the years. The first such attempts used strong Brønsted acids as solvent[4b] (Scheme 4.1). However, the research in this direction did not advance much in terms of lowering the catalyst loading, or rendering the reaction conditions milder. Despite numerous reports of tertiary aliphatic alcohol substitution published since then, almost all of them require either heterogenous activators at higher temperatures or strong acids in (super)stoichiometric quantities.[186]

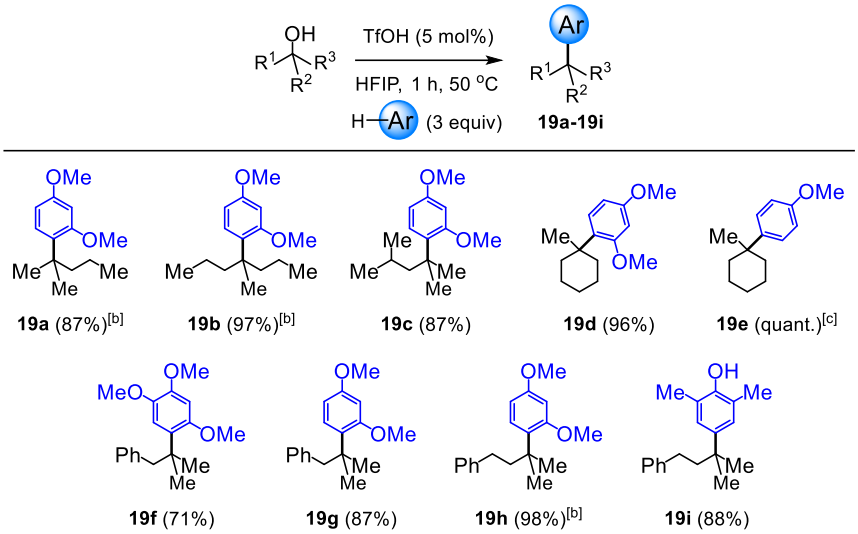


Scheme 4.1. One of the first examples of tertiary aliphatic alcohol activation (Kharasch, 1942)

As it has already been shown in the previous two chapters of this thesis, triflic acid and HFIP proved to be powerful catalytic system for Friedel-Crafts reactions of deactivated benzylic and propargylic alcohols. Therefore, we wondered if the same system would be also efficient for activation of tertiary aliphatic alcohols in dehydroarylative transformations. To test this hypothesis, 2-methyl-2-pentanol was subjected to 5 mol% TfOH in HFIP and pleasingly, it reacted within only 3 h at 50 ^{o}C with 1,3-dimethoxybenzene yielding the Friedel-Crafts product **19a** (Table 4.1). Other tertiary aliphatic alcohols, such as 4-methyl-4-heptanol and 2,4-dimethyl-2-pentanol, also furnished corresponding Friedel-Crafts products **19b** and **19c** in excellent yields. 1-methylcyclohexanol reacted in practically quantitative yields yielding **19d** and **19e**. 2-methyl-3-phenyl-2-propanol and 2-methyl-4-phenyl-2-butanol were suitable substrated as well, providing the corresponding products **19f-i** in high yields.

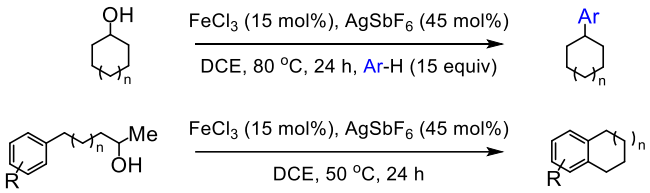
[186] Dryzhakov M., Richmond E., Moran J. *Synthesis*, **2016**, 48, 935-959

Table 4.1. Scope of tertiary aliphatic alcohols[a]



[a]Isolated yields after Kugelrohr distillation. [b]Reaction time was 3 h. [c]Reaction time was 16 h.

Unlike tertiary alcohols, there are only a few studies published so far for activation of secondary aliphatic alcohols for Friedel-Crafts reactions. The first such report from 2005 by Yi and Cai[187] contained only two lone examples of activation of isopropanol and cyclohexanol with anisole by use of Yb-based catalyst in a fluorous biphasic system. A more general method for activation of secondary aliphatic alcohols was published nine years later by Cook and Jefferies.[188] It comprised dehydroarylative substitution of several cyclic and phenyl-bearing (but not benzylic) secondary alcohols (Scheme 4.2). There is also one report based on the use of rare earth metal triflate salts and ionic liquids[189]. Isopropylation of benzene from isopropanol with zeolites was studied as well.[190]



Scheme 4.2. Study of secondary aliphatic alcohol activation by Cook (2014)

[187] Yi W.-B., Cai C. *J. Fluor. Chem.* **2005**, 126, 831-833
[188] Jefferies L. R., Cook S. P., *Org. Lett.* **2014**, 16, 2026-2029
[189] Mack R., Askins G., Lowry J., Hurley N., Reeves P. C. *Can. J. Chem.* **2013**, 91, 1262-1265
[190] (a) Vyawahare Y. K., Chumbhale V. R., Aswar A. S. *Rev. Roum. Chim.* **2012**, 57, 107-113; (b) Zou Y., Jiang H., Liu Y., Gao H., Xing W., Chen R. *Sep. and Purif. Technol.* **2016**, 170, 49-56

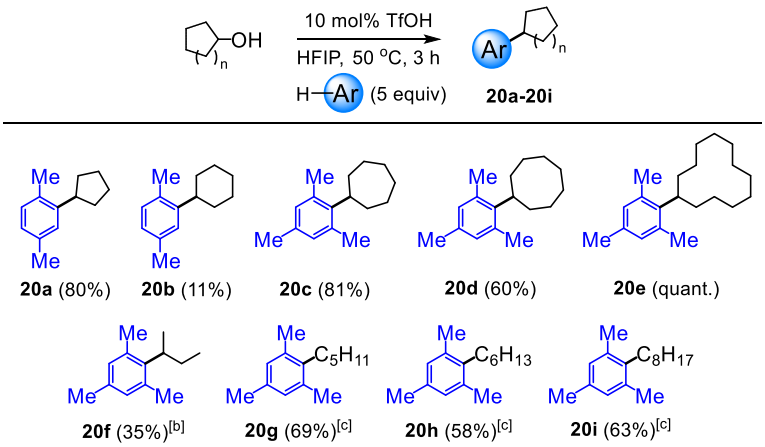
However, most of these strategies employ a high number of equivalents of the nucleophile (>15), temperatures mostly higher than 50 °C and reaction times greater than 24 h. This was therefore a good starting point for optimization of TfOH/HFIP conditions for Friedel-Crafts reactions of secondary aliphatic alcohols. Indeed, very quickly the optimal conditions were found and the scope of cyclic and acyclic secondary aliphatic alcohols was built (Table 4.2). Cyclopentanol, cycloheptanol, cyclooctanol and cyclododecanol yielded corresponding Friedel-Crafts products after only 3 h at 50 °C in excellent yields (**20a, 20c-e**). The only exception from this series was cyclohexanol, which reacted in poor yield (**20b**), most probably due to the shorter lifetime of the cyclohexyl cation compared to other cycloalkyl cations. This consideration is in accord with the trend of heats of hydrogenation for cyclohexenes (the highest value is for cyclohexene[191]). Mixture of products **20g** was obtained in similar ratios of regioisomers and yields from both 2-pentanol and 3-pentanol. Similarly, **20h** and **20i** were obtained as mixtures of regioisomers from 3-hexanol and 3-octanol, respectively. Activation of 2-butanol required higher temperature and prolonged reaction time, and resulted in lower yield of the product **20f**. It should also be mentioned that the great majority of the reactions presented in the scope of secondary alcohols also work at room temperature, only with prolonged reaction times (up to 24 h).

Isopropanol was also successfully activated at higher temperature (80 °C) with mesitylene as nucleophile, but this reaction resulted mostly in bis-alkylated product. Bis-alkylation was also observed with other nucleophiles, such as benzene and 1,4-dimethoxybenzene, and it represents a limitation of this method (in case that mono-alkylation is preferred reaction).

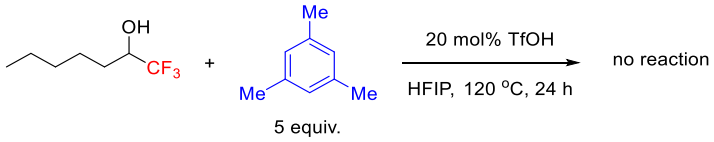
Also, it should be mentioned that α-trifluoromethyl aliphatic alcohols do not result in product formation, even at higher temperatures (Scheme 4.3).

[191] Allinger N. L., Hirsch J. A., Miller M. A., Tyminski I. J. *J. Am. Chem. Soc.* **1968**, 90, 5773-5780

Table 4.2. Scope of secondary aliphatic alcohols[a]



[a]Isolated yields after silica gel chromatography. [b]Performed at 80 °C for 24 h. [c]Reaction time was 6 h. Isolated as mixture of regioisomers.



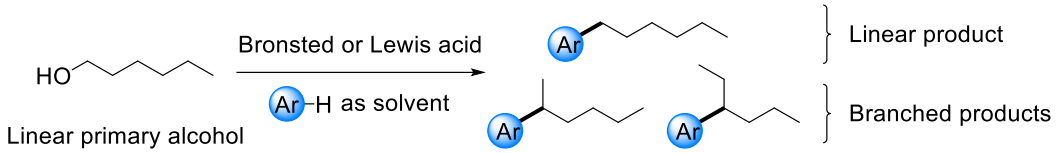
Scheme 4.3. Attempt of dehydroarylative transformation of 1,1,1-trifluoro-2-heptanol

4. 2. Friedel-Crafts reactions of primary aliphatic alcohols in HFIP

A typical (inherent) problem in Friedel-Crafts alkylations is the formation of complex mixtures of reaction products, due to carbocation migration and polyalkylation. Alternative ways to overcome these limitations have been proposed in past several years. General methods such as Friedel-Crafts acylation and pre-functionalization of alcohol hydroxyl groups into better leaving groups were established. Recently, new strategies based on silane assisted C-F bond activation have been developed, such as Siegel's method for Brønsted acid catalyzed Friedel-Crafts coupling of aryl fluorides[192] and Stephan's organofluorophosphonium catalyzed Friedel-Crafts reactions of alkyl fluorides.[193] Another method based on C-F bond activation, came from Paquin,[194] using activation of benzyl fluorides promoted by 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as co-solvent.

[192] Allemann O., Duttwyler S., Romanato P., Baldridge K. K., Siegel J. S. *Science*, **2011**, 332, 574-577
[193] Zhu J., Pérez M., Caputo C. B., Stephan D. W. *Angew. Chem. Int. Ed.* **2016**, 55, 1417-1421
[194] Champagne P. A., Benhassine Y., Desroches J., Paquin J.-F. *Angew. Chem. Int. Ed.* **2014**, 53, 13835-13839

However, the methods that provide access to Friedel-Crafts reactivity directly from primary alcohols as starting compounds have still remained rare. Those (more industrially-friendly) strategies rely upon use of solid catalysts, such as K10-montmorillonite[195] and zeolite-Y.[196] Although successful in activation of OH-functionality of alcohols, these approaches do not solve the problem of carbocation rearrangement, and result in complex mixtures of branched alkyl-chain regioisomers (Scheme 4.4).

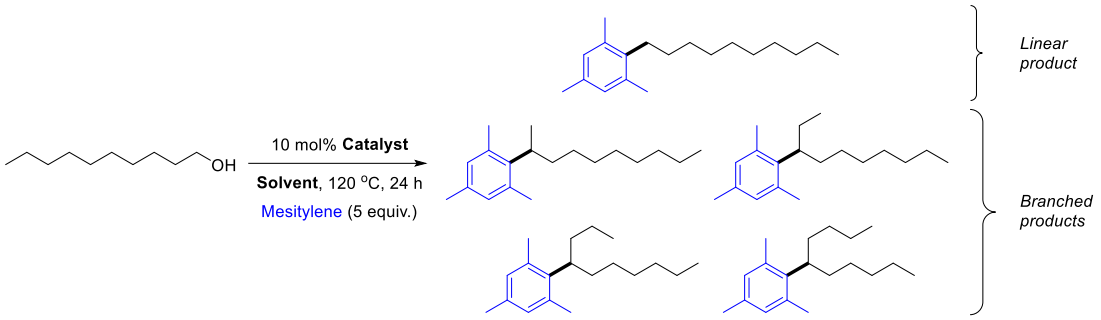


Scheme 4.4. General scheme of Friedel-Crafts reactions of primary aliphatic alcohols

Taking into account the results obtained so far in this thesis in regards to the activation of benzylic, propargylic and aliphatic alcohols, the only remained challenge is the ultimate challenge – catalytic activation of primary aliphatic alcohols. With increase of the temperature up to 120 ^{o}C and employment of 10 mol% TfOH and 5 equiv of nucleophile in HFIP, this was indeed achieved. After 24 h, the reaction was stopped, cooled down and analyzed by GC/MS. Very surprisingly, the formation of several regioisomers (branched Friedel-Crafts products) was not observed. Only one peak corresponding to the Friedel-Crafts product with linear alkyl chain ("linear product") was observed in the chromatogram (entry 1, Table 4.3). Therefore, a series of experiments with different catalysts and solvents was done and the ratio of liner and branched products was monitored. The percentage of the staring alcohol that reacted was also monitored and is given in Table 4.3 and Table 4.4 as consumption. In the absence of catalyst, no consumption of starting compound was observed (entry 2). In order to find out more about the observed phenomenon, other Brønsted and Lewis acids were tested. Triflimide was an efficient catalyst, but still gave traces of branched products (entry 3). Sodium triflate led to high consumption of the starting alcohol, but no linear or branched products were detected (entry 4). Calcium triflimide and iron(III) chloride left the starting alcohol intact (entries 5 and 6). With bismuth triflate high consumption of the starting alcohol was observed, with significant amount of branched products (entry 7). When the same reaction is run in the presence of 0.3 equiv

[195] Sieskind O., Albrecht P. *Tetrahedron Lett*, **1993**, 34, 1197-1200
[196] Deshmukh A. R. A. S., Gumaste V. K., Bhawal B. M. *Catalysis Letters*, **2000**, 64, 247-250

Proton sponge, the reactivity is completely lost (entry 8). Hydrofluoric acid as catalyst did not furnish the target compounds (entry 9), and other strong Brønsted acids yielded the mixtures of linear and branched products (entries 10-13).



Scheme 4.5. Friedel-Crafts reaction of *n*-decanol used for experiments in Table 4.3. and Table 4.4.

Table 4.3. Effect of different catalysts in HFIP as solvent on the ratio of linear and branched products in Friedel-Crafts reaction of *n*-decanol shown in Scheme 4.5.

Entry	Catalyst (10 mol%)	Consumption [%]	L/B ratio[a]
1	TfOH	>99	**100**:0
2	-	<5	-
3	Tf_2NH	>99	**95**:5
4	NaOTf	73	-
5	$Ca(NTf_2)_2$	<1	-
6	$FeCl_3$	<1	-
7	$Bi(OTf)_3$	>99	**89**:11
8	$Bi(OTf)_3$ + Proton sponge[b]	<1	-
9	HF(50% aq.)	56	-
10	*p*-TSA·H_2O	84	**35**:65[c]
11	TFA	80	**39**:61[c]
12	CSA	66	**46**:54
13	MsOH	44	**36**:64[c]

[a]Result is given as ratio of the GC chromatogram peak surface of Friedel-Crafts product with linear (L, in bold) alkyl chain and sum of surfaces of peaks of Friedel-Crafts products with branched (B) alkyl chains. All reactions were run in 0.25 M concentration. [b]Run with 0.3 equiv. of Proton Sponge. [c]Additional reaction products were detected.

Next, the solvent effect was investigated (Table 4.4). In other fluorinated solvents (entries 2-4), the reaction reached approximately the same consumption as in HFIP, though always preferentially forming branched products. A similar effect was noticed when mesitylene was used as solvent (entry 5), as well as in other apolar solvents such as 1,2-dichloroethane (entry 6)

and DCM (entry 7). To test the influence of the solvent fluorination, the reaction was run in perfluoro(methylcyclohexene). Although it resulted in high consumption, again, more branched products were formed than linear ones (entry 8). In other commonly used solvents, such as 1,4-dioxane, nitromethane, cyclohexane and acetonitrile, no Friedel-Crafts products were detected at all (entries 9-12).

Table 4.4. Effect of different solvents with 10 mol% TfOH as catalyst on the ratio of linear and branched products in Friedel-Crafts reaction of *n*-decanol shown in Scheme 4.5.

Entry	Solvent	Consumption [%]	L/B ratio[a]
1	HFIP	>99	**100**:0
2	HFIP-methyl ether	>99	**36**:64
3	2,2,2-trifluoroethanol	>80	**28**:72[b]
4	perfluoro-*tert*-butanol	>99	**37**:63
5	mesitylene	>99	**54**:46[b]
6	1,2-dichloroethane	>99	**65**:35[b]
7	DCM	>80	**42**:58[b]
8	Perfluoro(methylcyclohexane)	>99	**47**:53[b,c]
9	1,4-dioxane	72	-
10	$MeNO_2$	34	-
11	Cyclohexane	>99	-
12	MeCN	17	-

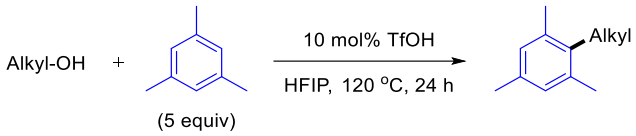
[a]Result is given as ratio of the GC chromatogram peak surface of Friedel-Crafts product with linear (L, in bold) alkyl chain and sum of surfaces of peaks of Friedel-Crafts products with branched (B) alkyl chains. All reactions were run in 0.25 M concentration. [b]Additional reaction products were detected. [c]Reaction mixture was heterogenous.

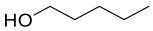
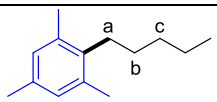
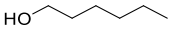
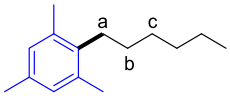
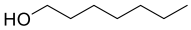
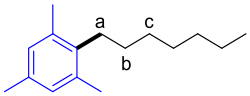
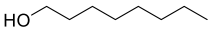
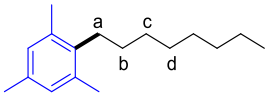
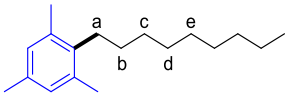
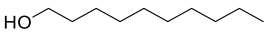
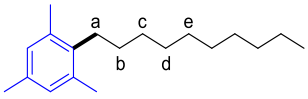
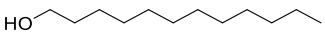
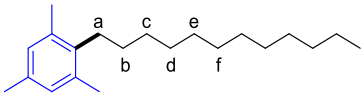
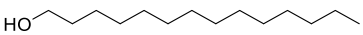
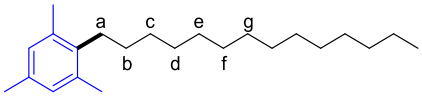
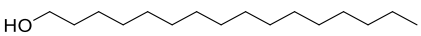
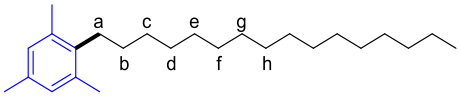
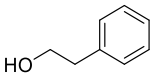
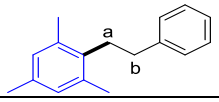
Although the experiments from Table 4.3 and Table 4.4 do not contain (isolated) yields of linear and branched products, or conversion, in this case it is actually not crucial. The goal of these experiments was to examinate L/B ratios under different reaction conditions regardless of the conversion, and this goual was accomplished - the 100:0 L/B ratio is observed only in the presence of TfOH in HFIP. This therefore certifies that the observed effect is unique to the TfOH/HFIP system at 120 ^{o}C.

A series of primary aliphatic alcohols was then examined under TfOH/HFIP/120 ^{o}C conditions (Table 4.5). In all cases, when reaction was conducted in 0.25 M concentration, only linear product was detected by GC. However, when reactions are conducted at 1.0 M concentration in HFIP with the respect to the *n*-decanol, instead of 0.25 M concentration (like it

was done for all control experiments), formation of linear and branched products was observed. This trend was observed across the whole range of linear primary aliphatic alcohols from *n*-pentanol to *n*-hexadecanol (Table 4.5, entries 1-9).

Table 4.5. Substrate scope of primary aliphatic alcohols



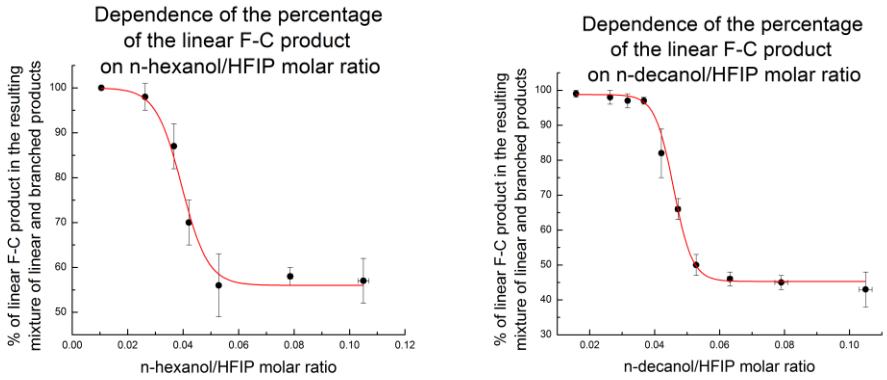
Entry	Starting compound	Structure of reaction product(s)	Distribution of products for starting alcohol concentration of: **1.0 mol L^{-1}** [a]	**0.25 mol L^{-1}**
1.			a b c **42**:42:16	only **a** detected
2.			a b c **50**:34:16	only **a** detected
3.			a b c **43**:30:26	only **a** detected
4.			a b c d **41**:27:13:11	only **a** detected
5.			a b c d e **50**:23:11:9:6	a 26%[b]
6.			a b c d e **38**:25:13:12:12	a 30%[b]
7.			a b c d e f **60**:14:6:5:6:7	a 24%[b]
8.			a b c d e f g **32**:22:11:9:9:9:8	a 57%[b]
9.			a b c d e f g+h **34**:18:9:8:7:8:15	a 49[b] (54%[c])
10.			a b 83%[d] -	a 94%[d]

[a]Ratios of peaks of Friedel-Crafts products in GC chromatogram. [b]Estimated GC yield of the linear product. [c]Yield based on calibration curve. [d]Isolated yield after column chromatography.

The yield of *n*-hexadecylmesitylene (Table 4.5, entry 9) was estimated using a calibration curve (GC response factors against *n*-hexadecylmesitylene concentration in the reaction

mixture). 54% yield of *n*-hexadecylmesitylene was observed when the reaction was run at 0.25 M concentration regime. Since there are many experimental difficulites to isolate pure linear Friedel-Crafts product from its mixture with the corresponding alkenes and mesitylene, the yields for lower homologs (Table 4.5, entries 5-8) were not calculated in the same manner. The response factors for mesitylene, 1-hexadecene and *n*-hexadecylmesitylene were calculated from relative peak areas in the gas chromatogram of their mixture of the known composition. The yield calculated for *n*-hexadecylmesitylene by this method (49%) agrees reasonably well with the more accurate yield obtained from the calibration curve (54%). Next, it was approximated that all homologous alkenes and linear products with mesitylene will have the same response factors to mesitylene, and the GC yields for products in entries 5 to 8 in Table 4.5 were estimated. The estimated yields range from modest (entries 5-7) to good (entries 8-9). Despite of the fact relatively low yields of linear Friedel-Crafts products are obtained with lower primary aliphatic alcohols, the author of this thesis considers that these results are encouraging enough to be used as the starting point for further optimizations.

Therefore, when Friedel-Crafts reactions of primary aliphatic alcohols (entries 1-9, Table 4.5) are conducted at 1.0 M concentration, linear and branched products were detected, whereas when the same reaction was conducted with four times more HFIP (0.25 M concentration), only the linear product was detected by GC after 24 h. For 2-phenylethanol, however, in both concentrations only "linear" product was observed (entry 10). To understand better this concentration dependence, the reaction with *n*-hexanol and *n*-decanol were run at different concentrations (in range from 0.1 to 1.0 mol L^{-1}), and the ratio of linear and branched products was monitored. The graphs plotted as percentage of the linear product in the reaction product mixture against *n*-alcanol/HFIP ratio (Figure 4.1) are sigmoidal curves with inflection points at about 0.04-0.045 alcohol/HFIP ratio, which corresponds to the concentration of alcohol about 0.4 M. The sigmoidal shape of the curve indicates presence of a cooperative effect. The fact that in both cases, for two different alcohols, the inflection point is at approximately the same value means that the observed effect is characteristic of the catalytic system (TfOH/HFIP/120 ^{o}C) independent on the substrate (linear alcohol).



a) b)

Figure 4.1. Percentage of the linear Friedel-Crafts product obtained in reactions at different alcohol/HFIP ratios (i. e. different alcohol concentrations) after 24 h at 120 °C in the presence of 10 mol% TfOH as catalyst and 5 equiv mesitylene as nucleophile

Next, reaction progress of *n*-hexadecanol with mesitylene in HFIP with TfOH as catalyst was monitored, and the results are shown in Figure 4.2. From the exponential fit, it was found that concentration of *n*-hexadecanol decays with first order kinetics and a corresponding rate constant $k = 7.4 \cdot 10^{-5}$ s^{-1}. The concentration of the linear Friedel-Crafts product constantly increases in the first 14-16 h. On the other hand, the concentration of branched products increases in the first two hours, and then starts to decrease. In the same time, the concentration of the hexadecenes increases, suggesting the decomposition of the branched products during the reaction.[197]

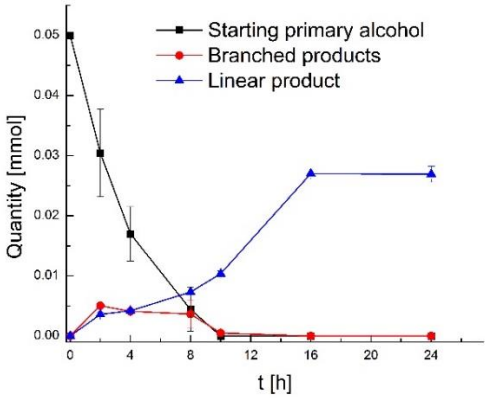


Figure 4.2. Progress of the reaction of *n*-hexadecanol with mesitylene (5 equiv) in the presence of 10 mol% TfOH in HFIP (concentration 0.25 M)

[197] Although the increase in the concentration of hexadecenes is observed, their exact concentration cannot be determined with certainty due to their low response factors in GC.

In order to test the stability of linear and branched products under the reaction conditions, the following three experiments were conducted. Linear products (in one reaction flask), branched products (in second reaction flask) and the mixture of linear and branched products (in third reaction flask) were subjected to 10 mol% TfOH in HFIP at concentration of 0.25 M. After 8 h, the linear product stayed intact, whereas branched products were completely degraded (Figure 4.3).

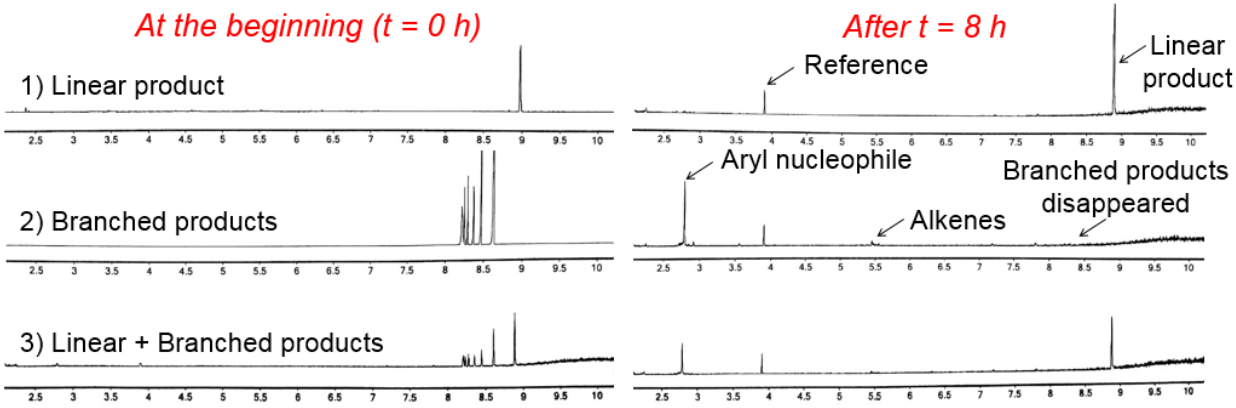
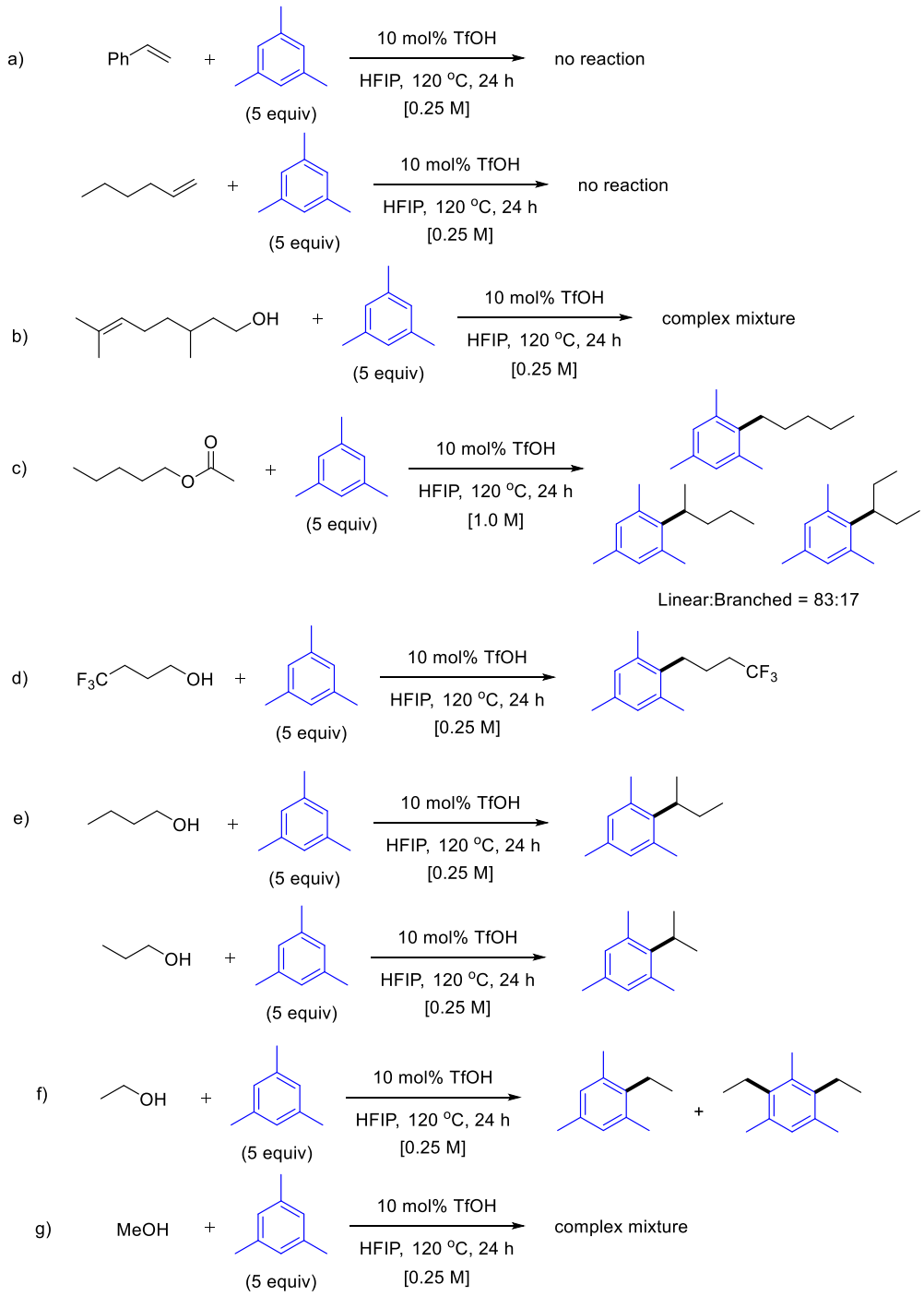


Figure 4.3. Test of the stability of linear and branched products under reaction conditions

At the end, another set of control experiments were performed. All experiments were conducted at 0.25 M concentration, 120 ^{o}C, during 24 h with 5 equiv of mesitylene. For the reaction of *n*-decanol, a decrease in catalyst loading led to a slight increase in the production of branched products (Table 4.6). When styrene and *n*-hexene are subjected to the reaction conditions with mesitylene as nucleophile, no corresponding Friedel-Crafts products were detected, confirming that alkenes do not react under these reaction conditions (Scheme 4.6.a). Still, β-citronellol failed to furnish only one Friedel-Crafts product with mesitylene, and complex mixture of products was observed (Scheme 4.6.b). *n*-Pentyl acetate yielded mixtures of linear and branched products in an 83:17 ratio, showing that esters do not stay intact under the reaction conditions (Scheme 4.6.c). Interestingly, 4,4,4-trifluoro-1-butanol furnished only the linear product at 1.0 M concentration (Scheme 4.6.d). *n*-Butanol and *n*-propanol react with formation of branched products (Scheme 4.6.e). Ethanol resulted in a mixture of mono- and bis-alkylated products in an 88:12 ratio (Scheme 4.6.f). Finally, methanol reacted as well, but resulted in mixture of products (Scheme 4.6.g).



Scheme 4.6. Miscellaneous experiments for probing the reactivity of primary alcohols

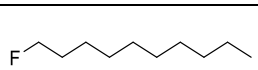
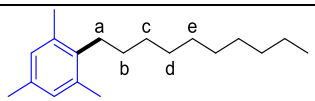
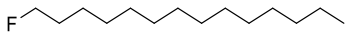
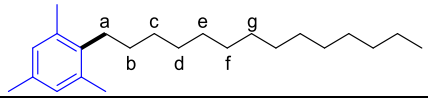
Table 4.6. Dependence of the ratio of linear and branched products on catalyst loading

TfOH loading [mol%]	L/B ratio[a]
10	**98**:2
5	**96**:4
2	**82**:18

[a]Result is given as ratio of the GC chromatogram peak surface of Friedel-Crafts product with linear (L, in bold) alkyl chain and sum of surfaces of peaks of Friedel-Crafts products with branched (B) alkyl chains. All reactions were run in 0.25 M concentration.

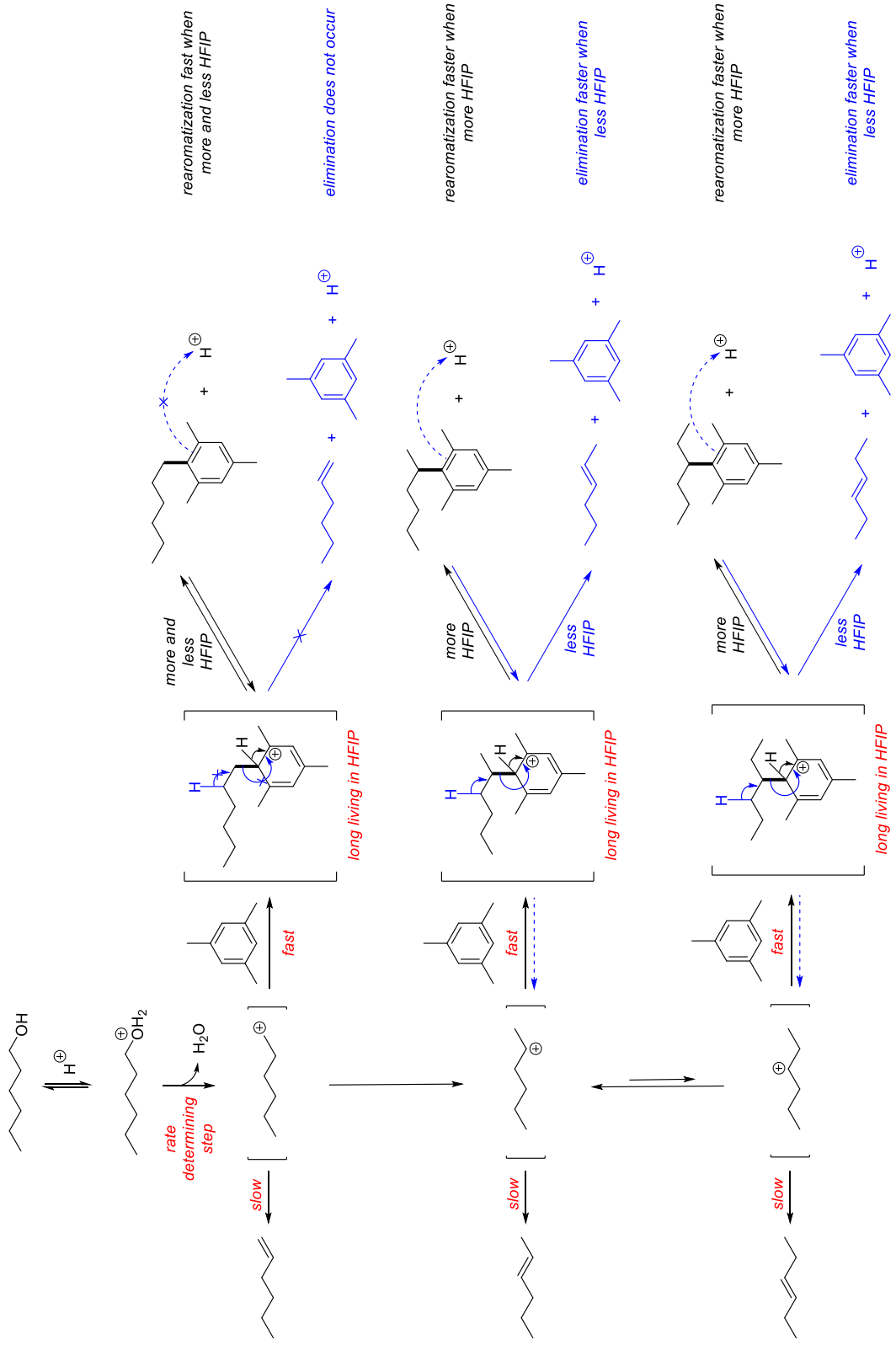
Interestingly, it was found that *n*-decyl fluoride and *n*-tetradecyl fluoride react in the same manner as corresponding alcohols (Table 4.7).

Table 4.7. Scope of alkyl fluorides

Entry	Starting compound	Structure of reaction product(s)	Distribution of products for starting fluoride concentration of:	
			1.0 mol L^{-1} [a]	**0.25 mol L^{-1}**
1.			a b c d e **42**:19:10:9:10	only **a** detected
2.			a b c d e f g **34**:17:10:8:9:7:8	only **a** detected

[a]Ratios of peaks of Friedel-Crafts products in GC chromatogram.

Based on all previous results, the following mechanism can be proposed (Scheme 4.7). After the initial protonation of the hydroxyl group of the starting alcohol, a primary carbocation is formed, that subsequently rearranges to more stable secondary carbocations. The proof that carbocation is formed is the existence of branched products themselves. If the carbocation had not been formed at the primary carbon in the first place, the formation of branched products would have not been observed. This, as well as first order kinetics consumption of the starting alcohol indicate the S_N1 mechanistic scenario. Next, the nucleophile (mesitylene) attacks the carbocation, forming another carbocation that is long living in HFIP. From this point, for each long living carbocation there are two possible pathways depending on the amount of HFIP present in the medium. "Black" pathway leads to the formation of the Friedel-Crafts products, whereas the "blue" pathway is leads to the elimination of the mesitylene and alkene formation.



Scheme 4.7. Plausible mechanism of Friedel-Crafts reactions of *n*-hexanol in HFIP

Therefore, in the case of branched products, rearomatization ("black pathway") is faster when more HFIP is in the medium (concentration of the starting alcohol 0.25 M). On the other hand, when there is less HFIP (1.0 M initial concentration of the alcohol), elimination ("blue pathway") is preferred. Although "blue" pathway as is shown resembles the E2 pathway, under these reaction conditions, E2 mechanism is not probable, because there is no strong base present that could sequester the "blue" proton. Therefore, an E1 mechanism is occurring, which means that the alkene is formed *via* an alkyl carbocation. This further means that the carbocation capture with mesitylene is reversible in case of branched products, but it is not reversible in case of linear products, due to the lower relative stability of the primary carbocation. Also, in more diluted reaction conditions, the nucleophile concentration is four times lower, therefore, the capture of alkyl carbocations by mesitylene will be four times slower, leaving more space for the carbocation deprotonation and alkene formation. However, all these considerations are valid regardless of the solvent that is used. What is therefore the unique role of HFIP in this scenario? First, let's consider the three irreversible "fates" of the primary alkyl carbocation. It can be captured by mesitylene, rearranged to secondary alkyl carbocation, or it can undergo a proton elimination to form a primary alkene. From these three processes, under given reaction conditions the first one is the fastest, and the last one is the slowest, which can be concluded from the product regioisomer ratios obtained from *n*-hexanol (Table 4.5, entry 2). In HFIP, the lifetimes of all carbocations are longer, therefore, all alkyl carbocations are susceptible to the easier nucleophile attack or rearrangement. The correct explanation thus probably lies elsewhere. If now we consider the effective concentration of protons that come from TfOH (i. e. proton-HFIP clusters), it will be four times more concentrated in "less HFIP" conditions compared to the "more HFIP" conditions. Therefore, the protonation of the final Friedel-Crafts products is four times more probable in concentrated solutions, and this would lead to the shift of the equilibria depicted in Scheme 4.7 towards "blue products". Still, if the cooperative effect observed in Figure 4.1 is only due to the increase in acidity of the solution, why is it observed exclusively in HFIP? It is plausible to suppose that HFIP stabilizes the transition state of the rearomatization step towards the linear product, favorizing in this way the formation of the linear product. This is in accord with the fact that in the case of *n*-hexadecanol, the linear product in "more HFIP" conditions is produced in higher quantity than in the "less HFIP" conditions.

4. 3. Conclusion of Chapter 4 and perspectives

TfOH in HFIP was successfully applied for activation of tertiary, secondary and primary aliphatic alcohols. An unexpected effect was discovered in the case of primary linear aliphatic alcohols. The ratio of linear and branched Friedel-Crafts products was found to be highly concentration-dependent. The reaction resulted in formation of more linear products when it was more diluted, i. e. when concentration of HFIP in the system was higher.

Further experiments are proposed to shade light on the discovered HFIP effect on the reactivity of primary aliphatic alcohols. To try to understand better the HFIP effect, ^{1}H NMR spectrum of *n*-decanol (or some other primary alkyl alcohol) at various temperatures could be recorded in both 0.25 M and 1.0 M concentration. Reaction with 2-phenylethanol could be run in other solvents in order to check if the result obtained in Table 4.5, entry 10 is HFIP-specific or substrate-specific. Also, reactions with other ω-phenyl-1-alcanols can be explored to widen the scope from the Table 4.5. Additional control experiment with *n*-hexadecyl triflate can be performed to verify if under reaction conditions formation of triflate esters from starting alcohols is possible and if it influences the results. Efforts can be made in order to estimate more accurately the conversion to the linear product for alcohols from Table 4.5 (entries 1-8). So far, there were experimental difficulties to isolate the pure linear product without significant losses. Therefore, there is space for advance on the isolation of the linear products. Finally, additional optimization could be done in order to increase the yield of the linear product, and decrease the formation of the branched products.

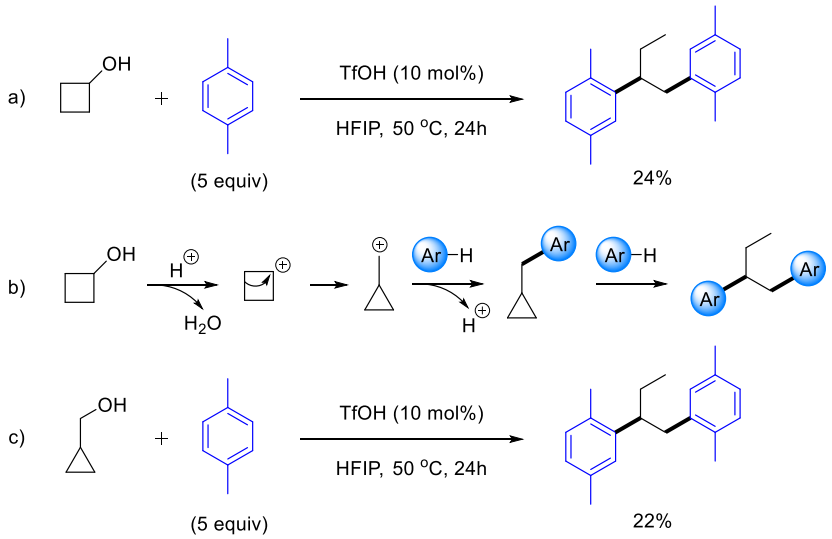
CHAPTER 5

FRIEDEL-CRAFTS REACTIONS OF CYCLOPROPANES IN HFIP[198]

[198] Parts of this chapter have been published: (a) Richmond E., Vuković V. D., Moran J. *Org. Lett.* **2018**, 20, 574-577; (b) Richmond E., Yi J., Vuković V. D., Sajadi F., Rowley C. N., Moran J. *Chem. Sci.* **2018**, 9, 6411-6416

5. 1. Scientific context

The idea for activation of substituted cyclopropanes in Friedel-Crafts reactions with TfOH in HFIP came from the previous chapter of this thesis. When the activation of cyclobutanol with *p*-xylene was tried, instead of 1-cyclobutyl-2,5,-dimethylbenzene, another reaction product was observed (Scheme 5.1.a). We reasoned that the formation of the bis-*p*-xylyl adduct could be explained by the contraction of the cyclobutyl cation to cyclopropanemethyl cation and subsequent nucleophilic attack, followed by ring-opening hydroarylation of the resulting cyclopropane (Scheme 5.1.b). To test this hypothesis, the reaction with cyclopropylmethanol was performed under identical reaction conditions, and the same product in roughly the same yield was isolated (Scheme 5.1.c). This encouraging result led to the development of a general method for nucleophilic ring-opening of activated and non-activated cyclopropanes using the TfOH/HFIP system.

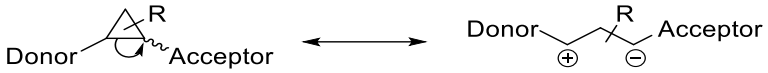


Scheme 5.1. Activation of cyclobutanol with TfOH/HFIP (a), the mechanistic hypothesis (b) and its confirmation (c)

5. 2. Nucleophilic ring-opening of donor-acceptor cyclopropanes in HFIP

Donor-acceptor (DA) cyclopropanes represent a class of substituted cyclopropanes that bear electron-donating ("donor") group(s) at one, and electron-withdrawing ("acceptor") group(s)

on the vicinal carbon of the cyclopropane ring. This specific distribution of electronic density in the cyclopropane ring (Scheme 5.2) brings them the specific reactivity that allows them to be involved in a number of chemically useful transformations,[199] such as 1,3-difunctionalizations,[200] [3+2] cycloadditions,[201] [3+3] cycloadditions[202] and homoconjugate additions.[203] On the other hand, only several studies have been published about catalytic arylative opening of cyclopropanes. The cyclopropane substrates in most of these studies always bear a geminal diester motif, and the catalysts employed are rare-earth metal triflate salts. The scope of cyclopropanes is therefore limited by the fact that only triflate salts can be employed as catalysts, since their mode of action depends on metal coordination to the diester moiety. Moreover, each of these methods is limited to a single class of nucleophiles (anisoles,[204] naphthols,[205] indoles[206] and anilines[207]). Finally, there are very few Brønsted acid catalyzed cyclopropane opening methods.[208]



Scheme 5.2. Resonance structures of vicinal DA cyclopropanes

[199] (a) Reissig H.-U., Zimmer, R. *Chem. Rev*. **2003**, 103, 1151-1196; (b) Yu M., Pagenkopf B. L. *Tetrahedron* **2005**, 61, 321-347; (c) Schneider T. F., Kaschel J., Werz D. B. *Angew. Chem. Int. Ed*. **2014**, 53, 5504-5523; (d) Cavitt M. A., Phun L. H., France, S. *Chem. Soc. Rev*. **2014**, 43, 804-818; (e) Grover H. K., Emmett M. R., Kerr M. A. *Org. Biomol. Chem.* **2015**, 13, 655-671; (f) Budynina E. M., Ivanov K. L., Sorokin I. D., Melnikov M. Y. *Synthesis*, **2017**, 49, 3035-3068

[200] For example: (a) Garve L. K. B., Barkawitz P., Jones P. G., Werz D. B. *Org. Lett*. **2014**, 16, 5804-5807; (b) Banik S. M., Mennie K. M., Jacobsen E. N. *J. Am. Chem. Soc*. **2017**, 139, 9152-9155; (c) Wallbaum J., Garve L. K. B., Jones P. G., Werz D. B. *Org. Lett*. **2017**, 19, 98-101

[201] For example: (a) Parsons A. T., Smith A. G., Neel A. J., Johnson J. S. *J. Am. Chem. Soc.* **2010**, 132, 9688-9692; (b) de Nanteuil F., Waser J. *Angew. Chem. Int. Ed.* **2011**, 50, 12075-12079; (c) Cui B., Ren J., Wang Z. *J. Org. Chem*. **2014**, 79, 790-796; (d) Garve L. K. B., Kreft A., Jones P. G., Werz D. B. *J. Org. Chem*. **2017**, 82, 9235-9242; (e) Augustin A. U., Sensse M., Jones P. G., Werz D. B. *Angew. Chem. Int. Ed*. **2017**, 56, 14293-14296

[202] For example: (a) Zhou Y., Li J., Ling L., Liao S., Sun X., Li Y., Wang L., Tang Y. *Angew. Chem. Int. Ed*. **2013**, 52, 1452-1456; (b) Zhang H., Luo Y., Wang H., Chen W., Xu P. *Org. Lett*. **2014**, 16, 4896-4899; (c) Chidley T., Vemula N., Carson C. A., Kerr M. A., Pagenkopf B. L. *Org. Lett*. **2016**, 18, 2922-2925

[203] Lambert J. B., Napoli J. J., Johnson K. K., Taba K. N., Packard B. S. *J. Org. Chem*. **1985**, 50, 1291-1295

[204] (a) Ivanova O. A., Budynina E. M., Grishin Y. K., Trushkov I. V., Verteletskii P. V. *Eur. J. Org. Chem*. **2008**, 2008, 5329-5335; (b) Jiang X., Lim Z., Yeung Y.-Y. *Tetrahedron Lett*. **2013**, 54, 1798-1801; (c) Talukdar R., Saha A., Tiwari D. P., Ghorai M. K. *Tetrahedron* **2016**, 72, 613-624

[205] Kaicharla T., Roy T., Thangaraj M., Gonnade R. G., Biju A. T. *Angew. Chem. Int. Ed.* **2016**, 55, 10061-10064

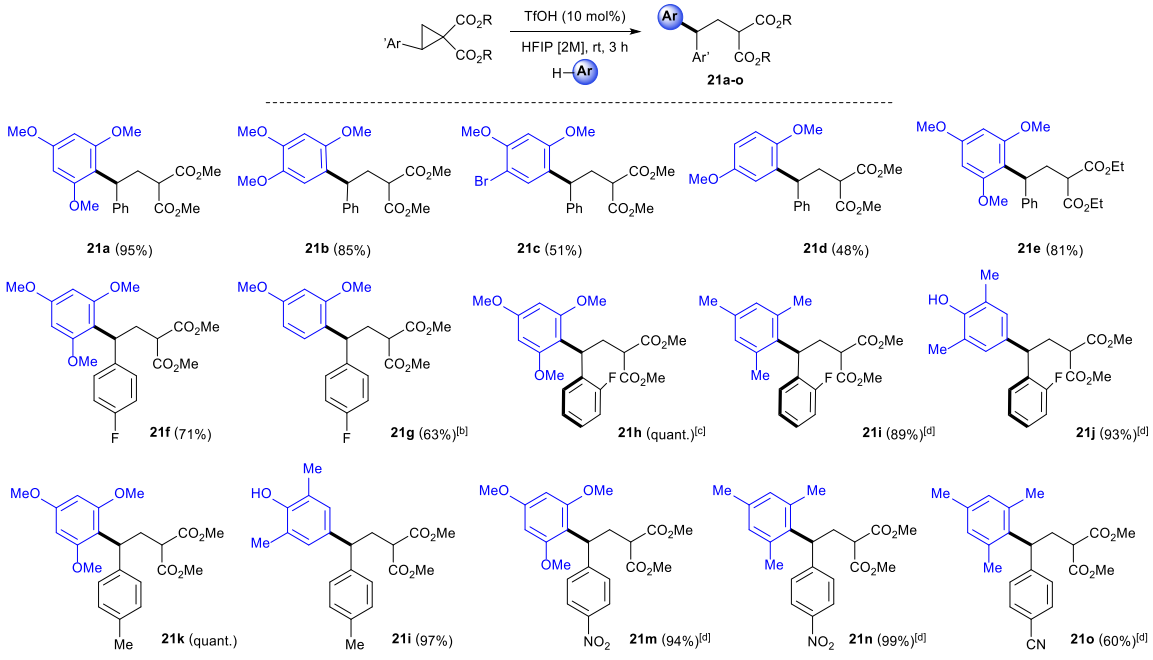
[206] (a) Harrington P., Kerr M. A. *Tetrahedron Lett*. **1997**, 38, 5949-5952; (b) Kerr M. A., Keddy R. G. *Tetrahedron Lett.* **1999**, 40, 5671-5675; (c) Grover H. K., Lebold T. P., Kerr M. A. *Org. Lett*. **2011**, 13, 220-223; (d) Wales S. M., Walker M. M., Johnson J. S. *Org. Lett*. **2013**, 15, 2558-2561; (e) de Nanteuil F., Loup J., Waser J. *Org. Lett*. **2013**, 15, 3738-3741.

[207] Kim A., Kim S.-G. *Eur. J. Org. Chem.* **2015**, 2015, 6419-6422.

[208] (a) Tsuge O., Kanemasa S., Otsuka T., Suzuki T. *Bull. Chem. Soc. Jpn*. **1988**, 61, 2897-2908; (b) Wilsdorf M., Leichnitz D., Reissig H.-U. *Org. Lett*. **2013**, 15, 2494-2497

Given the initial success with the activation of cyclopropanemethanol (Scheme 5.1.c), the optimal conditions for activation of cyclopropanes bearing a geminal diester motif were quickly established (Table 5.1). At room temperature, within only 3 h, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate furnished the corresponding Friedel-Crafts product **21a** in excellent yield. By using 1,2,4-trimethoxybenzene instead of 1,3,5-trimethoxybenzene the yield did not change significantly (**21b**), whereas when 1,3- or 1,4-dimethoxybenzene were engaged, the yield dropped significantly (**21c-d**). The exchange of methyl groups of the ester moiety with ethyl groups did not influence the reactivity significantly either (**21e**). Introduction of fluorine in the *p*-position of the initial substrate's phenyl ring led to a slight decrease in yield for both 1,3,5-trimethoxy- and 1,4-dimethoxybenzene as nucleophiles (**21f-g**). However, the *o*-substitution with fluorine required increased reaction time at moderately elevated temperature (**21h-j**). *p*-Toluyl bearing cyclopropanes reacted in excellent yields at room temperature (**21k-l**), whereas reactions with strong deactivating groups, such as nitro and cyano, at *para* position were possible only at 50 °C (**21m-o**).

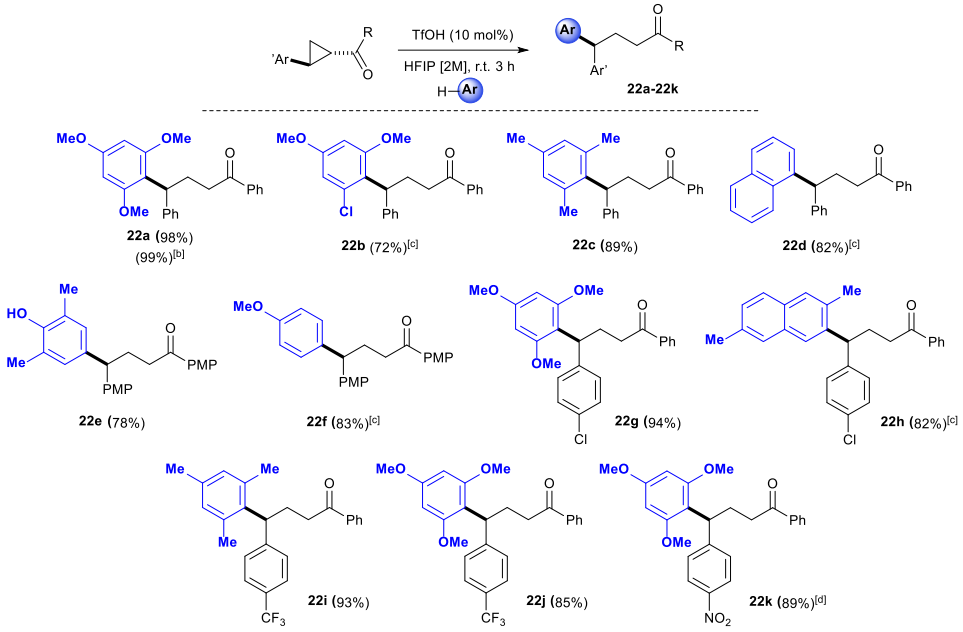
Table 5.1. Scope of arylative ring opening of DA cyclopropanes with a geminal diester motif[a]



[a]Isolated yields after column chromatography. [b]Isolated as a mixture of regioisomers. [c]Reaction performed at 40 °C for 4 h. [d]Reaction performed at 50 °C for 24 h.

The reactivity of keto-substituted cyclopropanes was explored as well (Table 5.2). Phenyl(2-phenylcyclopropyl) ketone gave **22a** in almost quantitative yield, even at larger scale. With slightly less activated nucleophiles, the reaction consequently proceeded with slightly decreased yield (**22b-d**). The use of a more activated *p*-methoxyphenylcyclopropyl substrate allowed reaction with 2,6-dimethylphenol and anisole (**22e-f**). Exchange of the methoxy group on the phenyl ring with chlorine did not influence the reactivity much (**22g-h**), which was also the case with the trifluoromethyl analog (**22i-j**). However, the *p*-nitrophenylcyclopropyl substrate reacted only at higher temperature (**22k**).

Table 5.2. Scope of arylative ring opening of DA cyclopropanes bearing a keto-acceptor group[a]

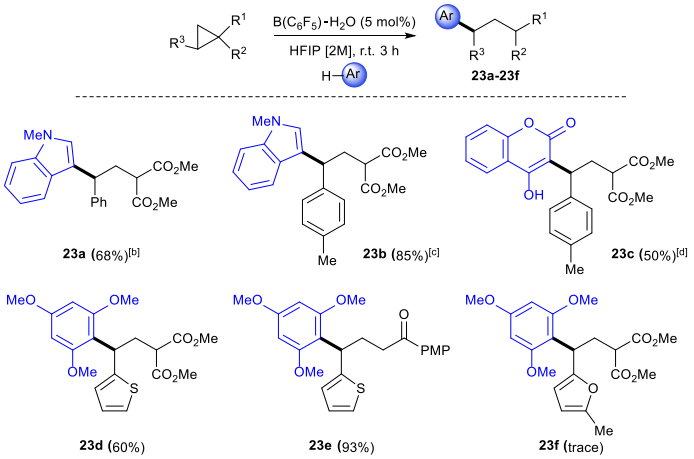


[a]Isolated yields after column chromatography. PMP = *p*-methoxyphenyl. [b]Run at 2.5 mmol scale with 5 mol% TfOH. [c]Isolated as a mixture of regioisomers.
[d]Reaction performed at 80 °C.

Heteroaromatic nucleophiles and heteroromatic cyclopropanes were not compatible with TfOH and resulted mostly in degradation of the starting materials. However, by using milder $B(C_6F_5)_3 \cdot H_2O$ catalyst, this problem was overcome (Table 5.3). Although higher temperatures and prolonged reaction times were necessary, *N*-methylindole was successfully employed as nucleophile with geminal diester-bearing cyclopropanes (**23a-b**). 4-Hydrohy-*2H*-chromen-2-one as nucleophile also yielded the corresponding product **23c** in moderate yield even with TfOH as

catalyst. 2-Thiophene-substituted cyclopropanes reacted with 1,3,5-trimethoxybenzene as nucleophile in good to excellent yields at room temperature within only 3 h (**23d-e**). However, methyl-furan bearing product **23f** decomposed during the purification, and it was therefore isolated only in traces.

Table 5.3. Scope of heteroaromatic nucleophiles and heteroaromatic DA cyclopropanes[a]



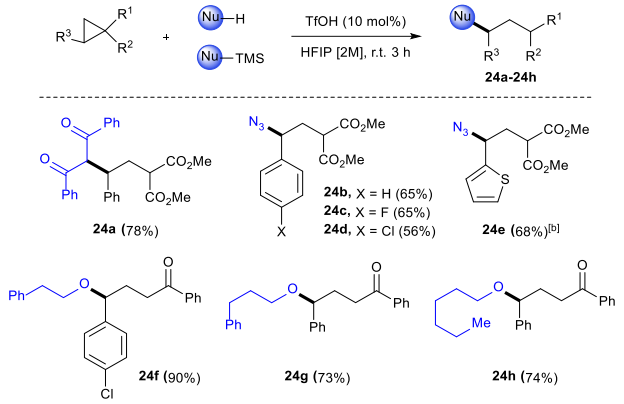
[a]Isolated yields after column chromatography. PMP = *p*-methoxyphenyl. [b]Reaction performed with 10 mol% of the catalyst at 80 ºC for 24 h. [c]Reaction performed at 80 ºC for 24 h in $MeNO_2$ as solvent. [d]Reaction performed with 10 mol% of TfOH as catalyst.

Finally, other nucleophiles but aromatic were tested as well (Table 5.4). A 1,3-diketone reacted efficiently as nucleophile to yield the product **24a**. With TMS-azide, corresponding products **24b-e** were obtained in good yields. To obtain product **24e** from the parent 2-thiophene substituted cyclopropane, $B(C_6F_5)_3 \cdot H_2O$ was used as catalyst. Primary aliphatic alcohols were employed as nucleophiles with success as well, yielding the products **24f-h**.

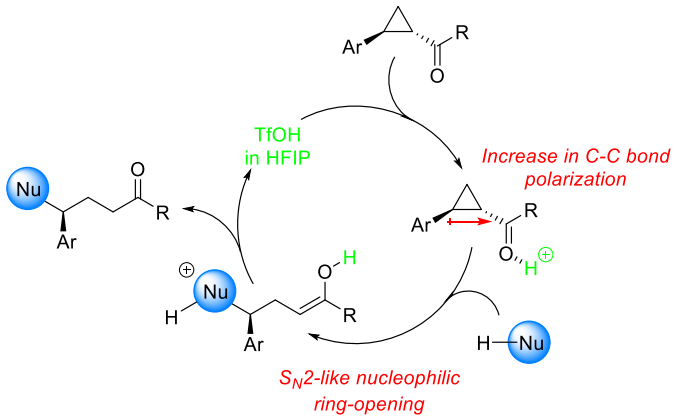
In order to understand the mechanism of the substitution of DA cyclopropanes under the TfOH/HFIP catalytic conditions, enantiopure dimethyl (2*S*)-phenylcyclopropane-1,1-dicarboxylate was subjected to the same reaction conditions from Table 5.1 with 1,3,5-trimethoxybenzene as nucleophile. Formation of (*R*)-**21a** in high yield indicated the S_N2-like mechanistic scenario, depicted in Scheme 5.3. First, the protonation of the acceptor-motif of the cyclopropane occurs, leading to the C–C bond polarization and thus activation of the benzylic position. Next, the nucleophile attacks the activated benzylic position in an S_N2 manner. Finally,

after the keto-enol tautomerization, the Brønsted acid is regenerated, enabling the turnover of the catalytic cycle, and the ring-opened reaction product is formed.

Table 5.4. Scope of nucleophilic ring-opening of DA cyclopropanes[a]



[a]Isolated yields after column chromatography. [b]Reaction performed with 5 mol% of $B(C_6F_5)_3 \cdot H_2O$ as catalyst.



Scheme 5.3. Plausible mechanistic scenario for TfOH catalyzed nucleophilic ring-opening of DA cyclopropanes in HFIP

5. 3. Nucleophilic ring-opening of monosubstituted cyclopropanes in HFIP

Unlike the vicinally substituted donor-acceptor cyclopropanes, the field of mono-substituted or geminally substituted cyclopropanes has not been as much developed. Oxidative ring-opening reactions of this subclass of cyclopropanes are limited to transition metal mediated

oxidative additions into C–C bonds[209] and oxidative 1,3-difunctionalizations.[200b] Other types of transformations include ring-opening by frustrated Lewis acid-base pairs,[210] strong nucleophiles[211] or mineral acids.[203,212] However, ring-opening hydroarylation of cyclopropanes substituted with two geminal acceptor groups was reported only under extremely high pressures[206a] or by using superstoichiometric quantities triflic acid.[213] Finally, catalytic hydroarylative ring-opening of monosubstituted cyclopropanes has not been reported so far.

Since we have already successfully demonstrated the use of the TfOH/HFIP system for ring-opening of DA cyclopropanes, we decided to test the same system for the analogous reactions of more challenging mono-substituted cyclopropanes. The first subclass of these compounds that was tested were cyclopropyl ketones (**Table 5.5**). Cyclopropyl methyl ketone furnished the Friedel-Crafts product **25a** with 1,3,5-trimethoxybenzene in good yield, which was also the case with cyclopropyl phenyl ketone (**25b**). Interestingly, employment of less activated nucleophiles, such as 1,3-dimethoxybenzene and halogenated derivatives thereof led to a slight increase in reactivity (**25c-e**). An activating methoxy group on the phenyl ring decreased the yield (**25f**), whereas the halogen-substituted analogs reacted in excellent yields (**25g-i**). Finally, less activated nucleophiles successfully reacted with chlorophenyl cyclopropane (**25j**).

Next, a series of cyclopropanes bearing a geminal diester motif was tested with previously established TfOH/HFIP conditions (Table 5.6, entries **26a-d**). With 1,3,5-trimethoxybenzene as a nucleophile, dimethyl-dicarboxylate substrate gave **26a** in excellent yield. However, when methyl groups are exchanged with ethyl groups, the yield dropped (**26b**). Employment of weaker nucleophiles (**26c-d**) led to a decrease in yield as well. Substrate bearing a monocarboxylate motif reacted poorly under harsh conditions, suggesting the importance of the diester motif for the reactivity of this subclass of cyclopropanes (**26e**).

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[209] (a) Souillart L., Cramer N. *Chem. Rev.* **2015**, 115, 9410-9464; (b) Fumagalli G., Stanton S., Bower J. F. *Chem. Rev.* **2017**, 117, 9404-9432

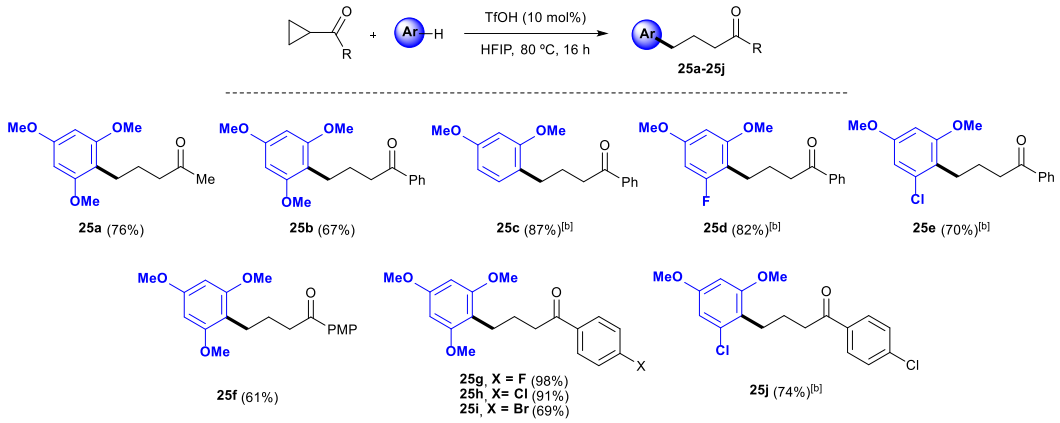
[210] (a) Morton J. G., Dureen M. A., Stephan D. W. *Chem. Comm.* **2010**, 46, 8947-8949; (b) Zhang Z.-Y., Liu Z.-Y., Guo R.-T., Zhao Y.-Q., Li X., Wang X.-C. *Angew. Chem. Int. Ed.* **2017**, 56, 4028-4032

[211] (a) Bone W. A., Perkin W. H. *J. Chem. Soc. Trans.* **1895**, 67, 108-119; (b) Truce W. E., Lindy L. B. *J. Org. Chem.* **1961**, 26, 1463-1467; (c) Smith A. B., Scarborough R. B. Jr. *Tetrahedron Lett.* **1978**, 19, 1649-1652; (d) Dieter R. K., Pounds S. *J. Org. Chem.* **1982**, 47, 3174-3177

[212] (a) Perkin W. H., Marshall T. R. *J. Chem. Soc. Trans.* **1891**, 59, 853-894; (b) W. Xu, W. R. Dolbier Jr, J. Salazar, *J. Org. Chem.* **2008**, 73, 3535-3538

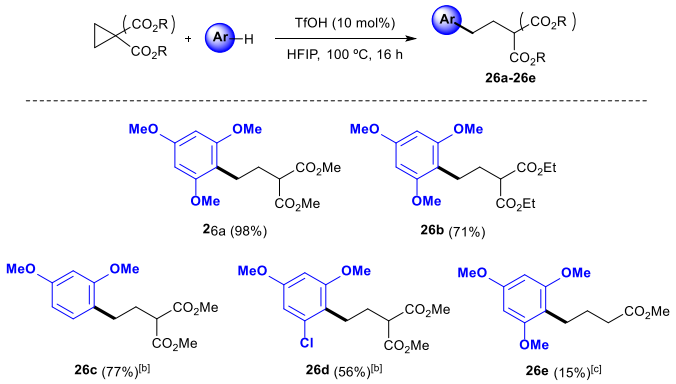
[213] Chen G.-Q., Tang X.-Y., Shi M. *Chem. Commun.* **2012**, 48, 2340-2342

Table 5.5. Scope of cyclopropyl ketones[a]



[a]Isolated yields after column chromatography. [b]Isolated as mixture of regioisomers.

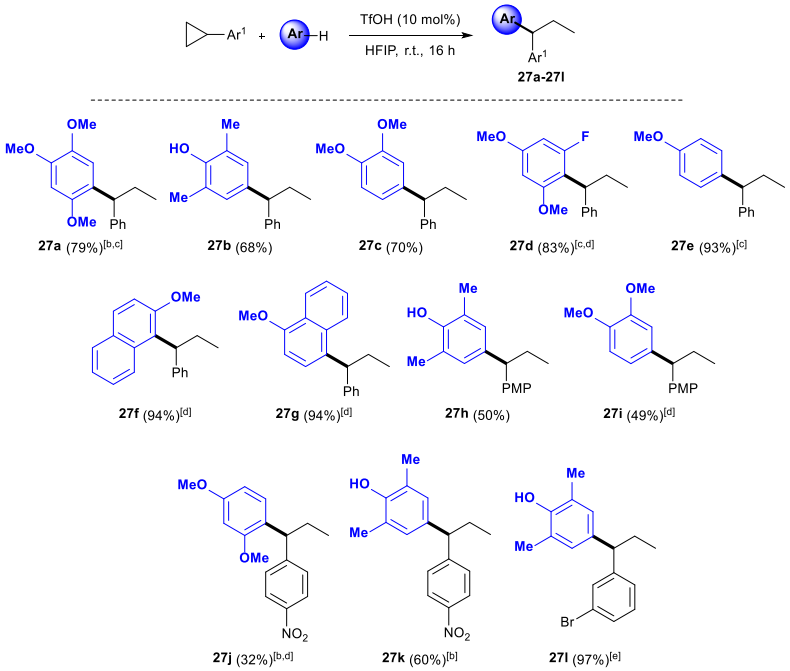
Table 5.6. Scope of cyclopropanes bearing geminal diester motif[a]



[a]Isolated yields after column chromatography. [b]Isolated as mixture of regioisomers. [c]Reaction performed at 100 °C in 1,2-dichloroethane.

However, we wondered if the keto- and carboxylate-bearing cyclopropanes are the only ones to react under TfOH/HFIP conditions. Therefore, the reactivity of cyclopropylbenzene with various nucleophiles was explored (Table 5.7), and pleasingly, it reacted even at room temperature in good to excellent yields (**27a-g**). In these cases, weaker nucleophiles also reacted better (**27e-g**). When phenyl ring of the initial cyclopropane substrate was substituted with either methoxy, either nitro group, the drop of reactivity was observed (**27h-k**). Only in the case of *m*-bromo substrate, the yield of **27l** was significantly higher.

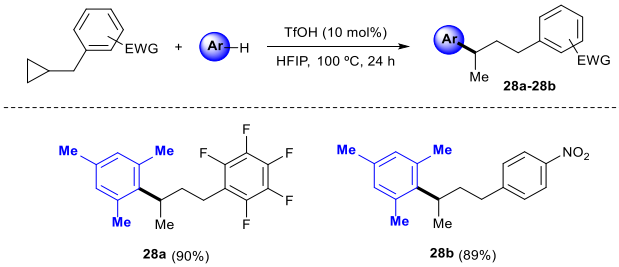
Table 5.7. Scope of monoaryl substituted cyclopropanes[a]



[a]Isolated yields after column chromatography. PMP = 4-methoxyphenyl. [b]Reaction heated at 80 °C. [c]NMR yield. [d]Combined yield of regioisomeric products. [e]1.1 equiv of nucleophile was used.

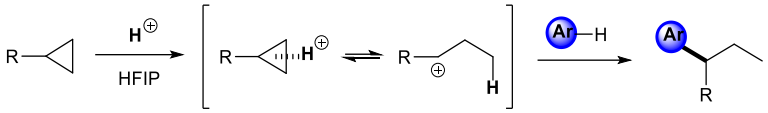
Finally, 2,3,4,5,6-pentafluorobenzyl- and *p*-nitrobenzylcyclopropane were successfully ring-opened with mesitylene in excellent yields (Table 5.8). *p*-Methoxybenzyl and benzyl analogs furnished mixtures of reaction products, indicating that the transformation occurs *via* acid-mediated ring-opening, and a subsequent 1,2-hydride shift to provide less inductively destabilized carbocation, and finally, nucleophile attack.

Table 5.8. Scope of benzylic cyclopropanes[a]



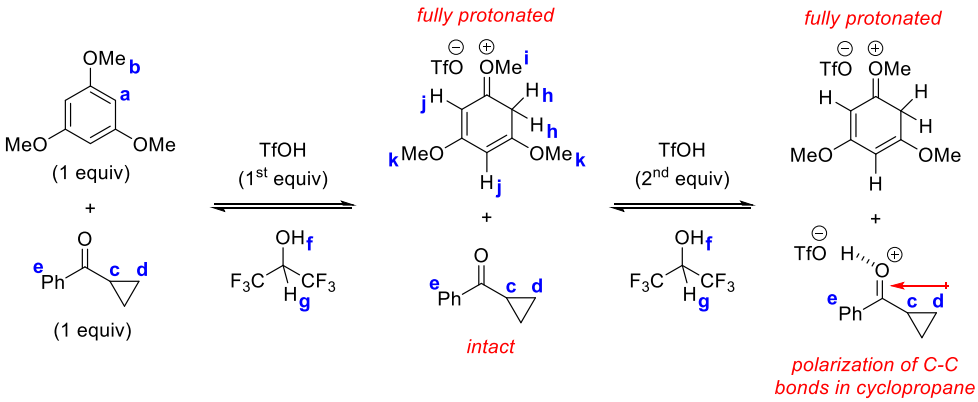
[a]Isolated yields after column chromatography.

In order to get mechanistic insight into the reactivity of the cyclopropyl ketones, a series of different experiments and calculations was performed. Treatment of cyclopropylbenzene with 10 mol% TfOH in HFIP in the absence of the nucleophile resulted in a highly exothermic reaction followed by the orange coloring of the solution, and decomposition of the starting material. These findings, as well as the wide nucleophile scope for these substrates are indicators of an S_N1 mechanistic pathway (Scheme 5.4).



Scheme 5.4. Proposed S_N1 mechanism of the ring-opening of aryl cyclopropanes

On the other hand, treatment of cyclopropyl phenyl ketone with TfOH in HFIP without nucleophile did not lead to any spontaneous reactivity. Moreover, in the presence of the nucleophile such as 1,3,5-trimethoxybenzene, the preferential interaction with the nucleophile over the cyclopropane is observed (Scheme 5.5). Upon addition of 1 equiv TfOH to the equimolar mixture of 1,3,5-trimethoxybenzene and cyclopropyl phenyl ketone (Figure 5.1, spectra 1-5), protonation of trimethoxybenzene is observed. Also, a downfield shift of the OH proton of HFIP was observed, suggesting fast exchange with TfOH and slow exchange with protonated trimethoxybenzene. Only after addition of the excess TfOH (spectra 6-9), a downfield shift of both cyclopropane and phenyl ring protons of the ketone is observed. Upon addition of additional equivalents of TfOH, no further changes in the spectra were observed (spectra 10-13).



Scheme 5.5. Mechanistic explanation of the titration of 1,3,5-trimethoxybenzene with TfOH in the presence of cyclopropyl phenyl ketone in HFIP. Titration is shown in Figure 5.1.

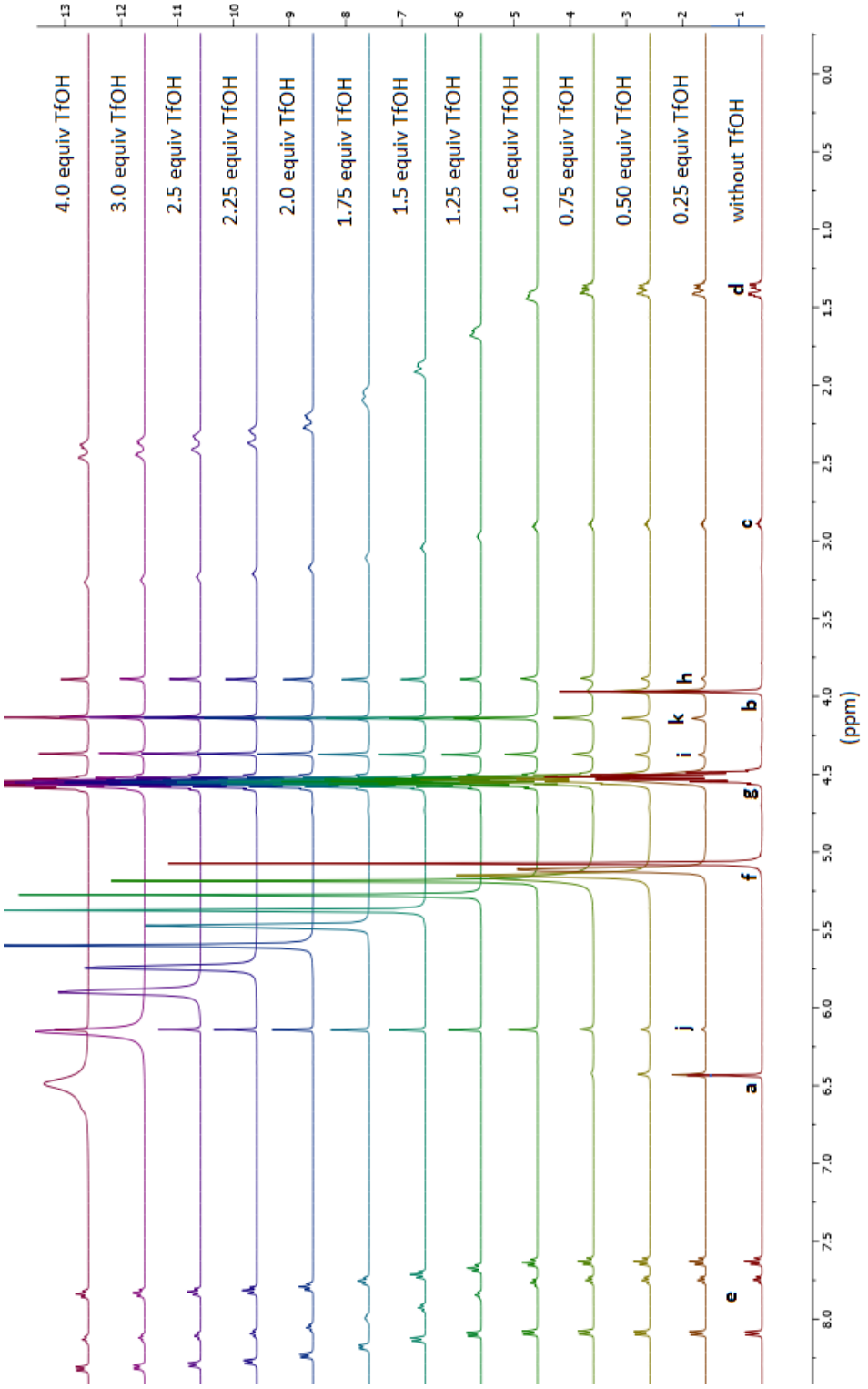


Figure 5.1. ^{1}H NMR titration of 1,3,5-trimethoxybenzene and cyclopropyl phenyl ketone (1:1) with TfOH in HFIP. Explanation given in Scheme 5.5.

To further assess the mechanism proposed in Scheme 5.5, the reaction system was studied by density function theory calculations (ωB97XD/def2-TZVP). The results suggested the reaction profile depicted in Figure 5.2. For most substrates, protonation of the oxygen atom of the keto group was predicted, forming therefore an activated species with partial enol character. Then, the formed activated species is captured by the nucleophile, which is at the same time the rate determining step. Next, an arenium intermediate is formed, deprotonated, and after the keto-enol tautomerization finally, the target product is formed. Similar kinetic barriers for nucleophilic attack of cyclopropyl methyl ketone and cyclopropyl dicarboxylate were calculated, which is in accord with high yields obtained for the reactions of these substrates with 1,3,5-trimethoxybenzene (cf. yields for **25a** and **26a**). Also, high kinetic barrier for the reaction with monocarboxylate correlates well with the poor yield obtained for **26e**. Moreover, the barriers for the attacks of 1,2-, 1,2,3- and 1,2,4-substituted di- and trimethoxybenzenes are higher than for 1,3,5-trimethoxybenzene, which is also consistent with the reactivity observed in Table 5.5 and Table 5.6.

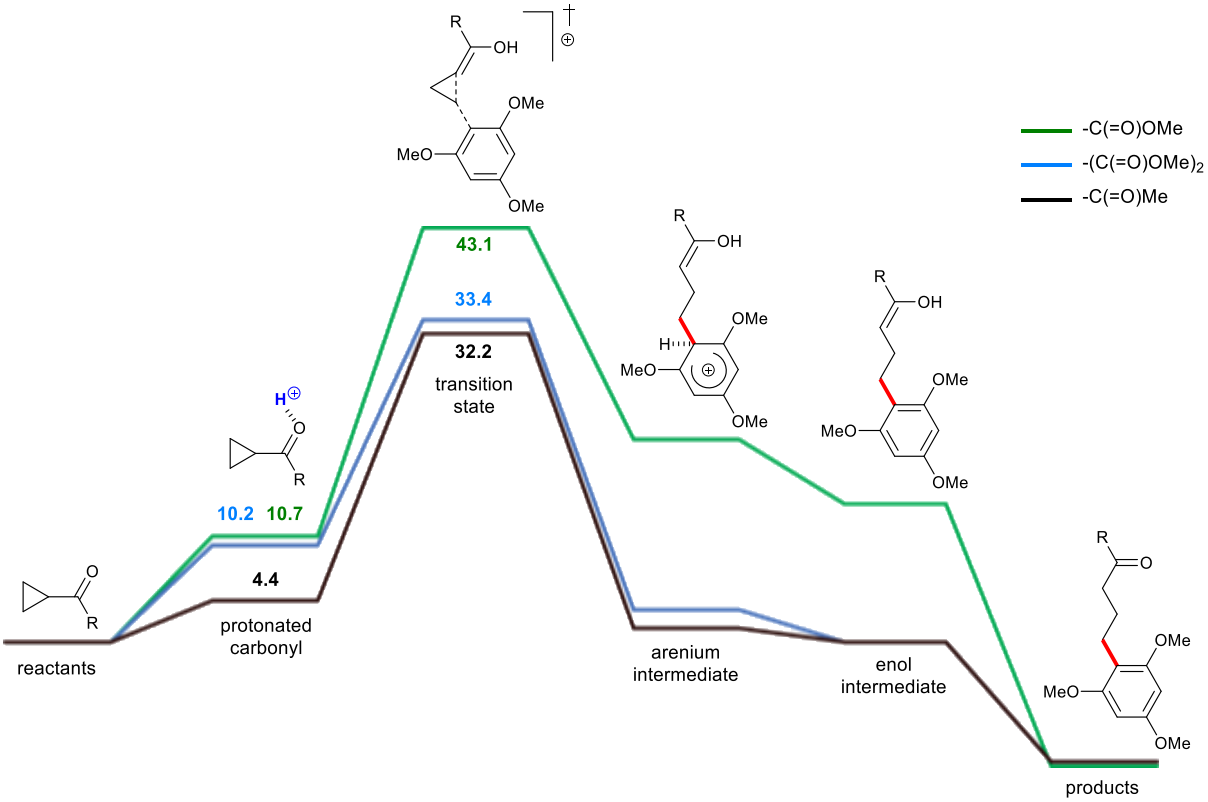


Figure 5.2. Reaction profile of Brønsted acid-catalyzed arylative ring-opening of cyclopropyl ketones calculated by DFT. Energy values are in kcal mol^{-1}.

Furthermore, a Hammett analysis of several *p*-substituted phenyl cyclopropanes was performed (Figure 5.3). A linear correlation was found for reaction rates' logarithms of *p*-methyl-, *p*-chloro- and *p*-fluorophenyl cyclopropane, together with cyclopropyl benzene, against Hammett σ-parameters for these substituents. The value of the obtained ρ parameter is negative and close to zero (–0.41), which suggests S_N2 mechanism rather than development of the positive charge in the course of the reaction. However, the *p*-methoxy substrate did not fit into this linear trend, most probably due to the high stability of the protonated cyclopropane intermediate, which leads to the highest activation energy (calculated from the protonated intermediate to the activated complex, Figure 5.4).

Based on previous experiments and calculations, the following mechanism can be proposed (Scheme 5.6). The cyclopropyl ketone is protonated, and subsequently attacked by the nucleophile in a homo-conjugate manner. Then, after the dearomatization and enol/keto tautomerization the corresponding product is formed, releasing the proton and enabling the catalytic turnover. In the same time, the protonated nucleophile serves as a proton reservoir, and buffers the system.

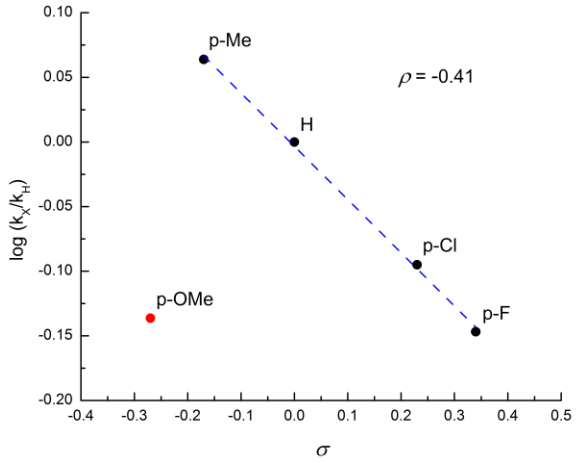


Figure 5.3. Hammett plot for the ring-opening of *p*-substituted phenyl cyclopropanes

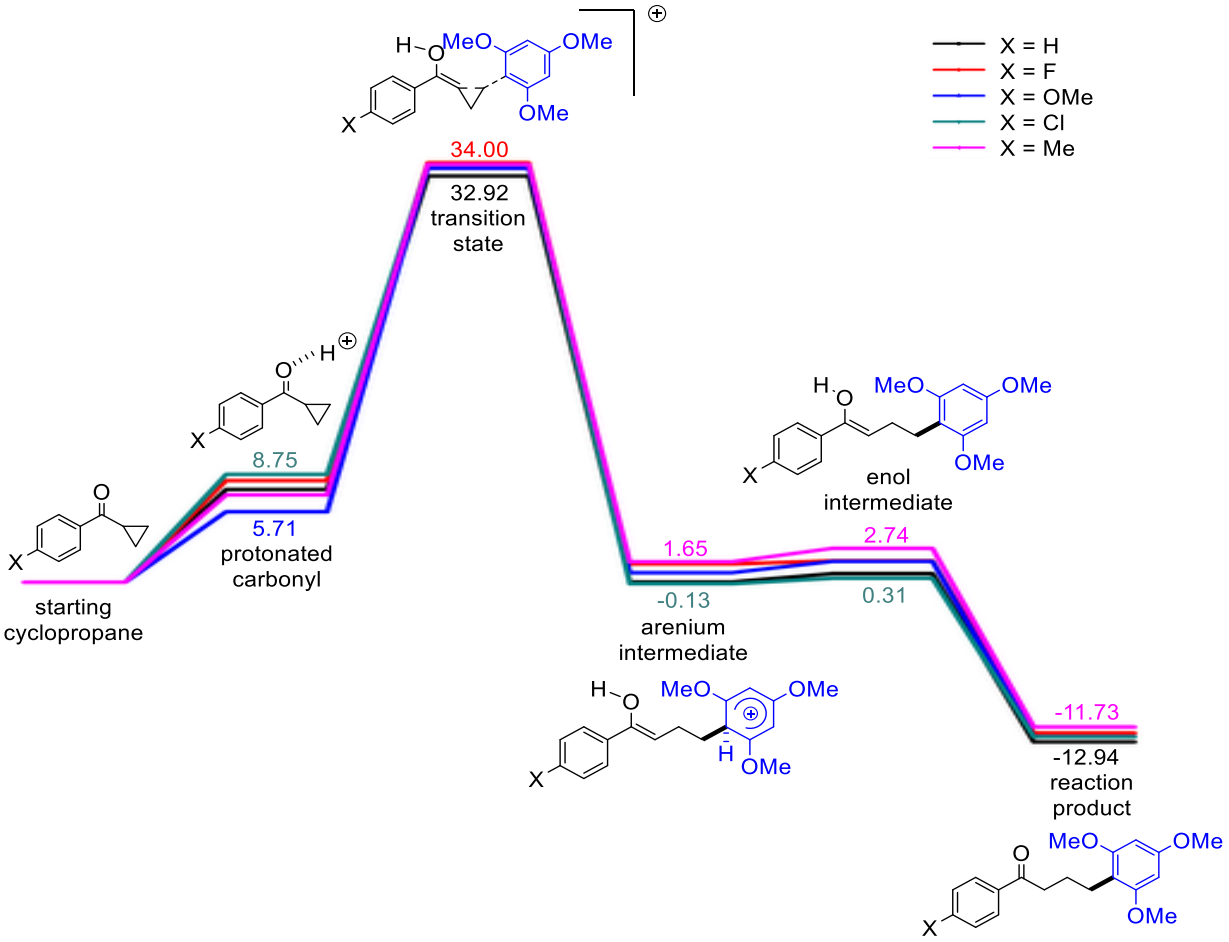
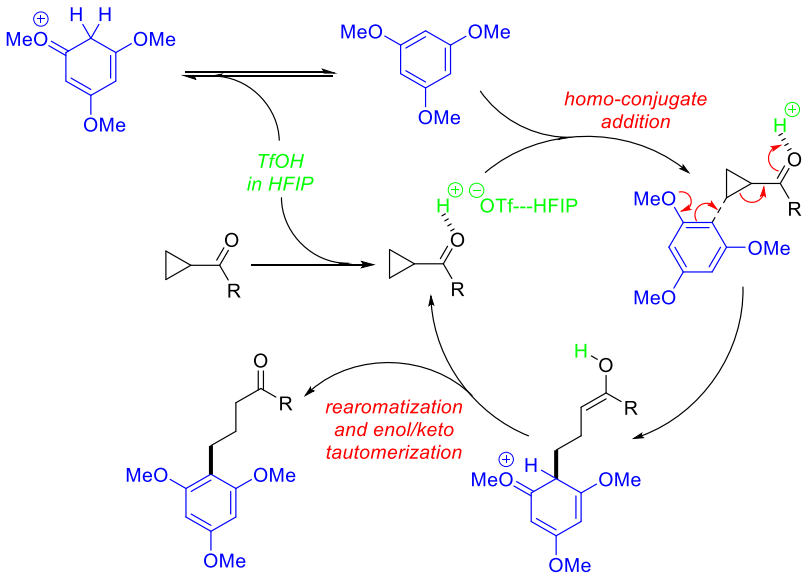


Figure 5.4. Reaction profile of Brønsted acid-catalyzed ring-opening of cyclopropyl phenyl ketones with 1,3,5-trimethoxybenzene calculated by DFT. Energy values are in kcal mol^{-1}.



Scheme 5.6. Proposed mechanistic scenario

5. 4. Conclusion of Chapter 5 and perspectives

In this chapter, a general method for arylative ring-opening of vicinally and geminally substituted cyclopropanes has been developed. TfOH is used as catalyst in HFIP as solvent, and a wide variety of Friedel-Crafts nucleophiles is compatible with the reaction conditions. The regioselectivity of the nucleophilic attack depends on the substituents that the cyclopropane substrates are bearing, as well as the type of mechanism. Experimental mechanistic studies are supported with DFT calculations and show good correlation.

CHAPTER 6.
GENERAL CONCLUSION

This doctoral thesis is dedicated to the exploration of the use of Brønsted acids in hexafluoroisopropanol for catalysis of Friedel-Crafts alkylations. The substrates that were successfully employed comprise highly electronically deactivated benzylic and propargylic alcohols. Access to a number of fluorinated diarylmethanes, allenes, chromenes, indenes and alkenes was provided by the employment of catalytic quantities of triflic acid and 3-5 equiv of aryl nucleophile in hexafluoropropanol solvent. A method for direct catalytic activation of primary, secondary and tertiary aliphatic alcohols in Friedel-Crafts reactions was developed. Furthermore, a general method for catalytic arylative ring-opening of donor-accceptor and monosubstituted cyclopropanes was established. Each type of transformation that is described was followed by detailed mechanistic studies. Triflic acid in hexafluoroisopropanol proved to be a powerful and versatile system for catalysis of those Friedel-Crafts reactions that normally required use of superacids in superstoichiometric quantities in the past. Therefore, the boundaries of the Friedel-Crafts reactivity have been moved - extremely deactivated or non-activated substrates, that were practically impossible to activate otherwise, reacted under TfOH/HFIP reaction conditions with ease.

Still, a lot of space remained for improvment and further development. Heteroaromatic nucleophiles, ecpecially nitrogen and oxygen containing heteroaromatics, were mostly not compatible with TfOH/HFIP reaction conditions, therefore an alternative to engage these nucleophiles is necessary. Determination of the transition state thermodynamic parameters would significantly enrich already existing mechanistic studies. Additional physico-chemical studies can shed light on the missing details about the TfOH/HFIP system. For example, it could be described with Hammett acidity functions. It would also be interesting to explore the reactivity of the carbocations formed with laser flash photolysis.

A concise summary of the key synthetic contributions that this doctoral thesis brings to science is depicted in Figure 6.1. Despite these contributions being modest, the author of this thesis hopes that work described herein will serve as a source of inspiration for further development of chemistry.

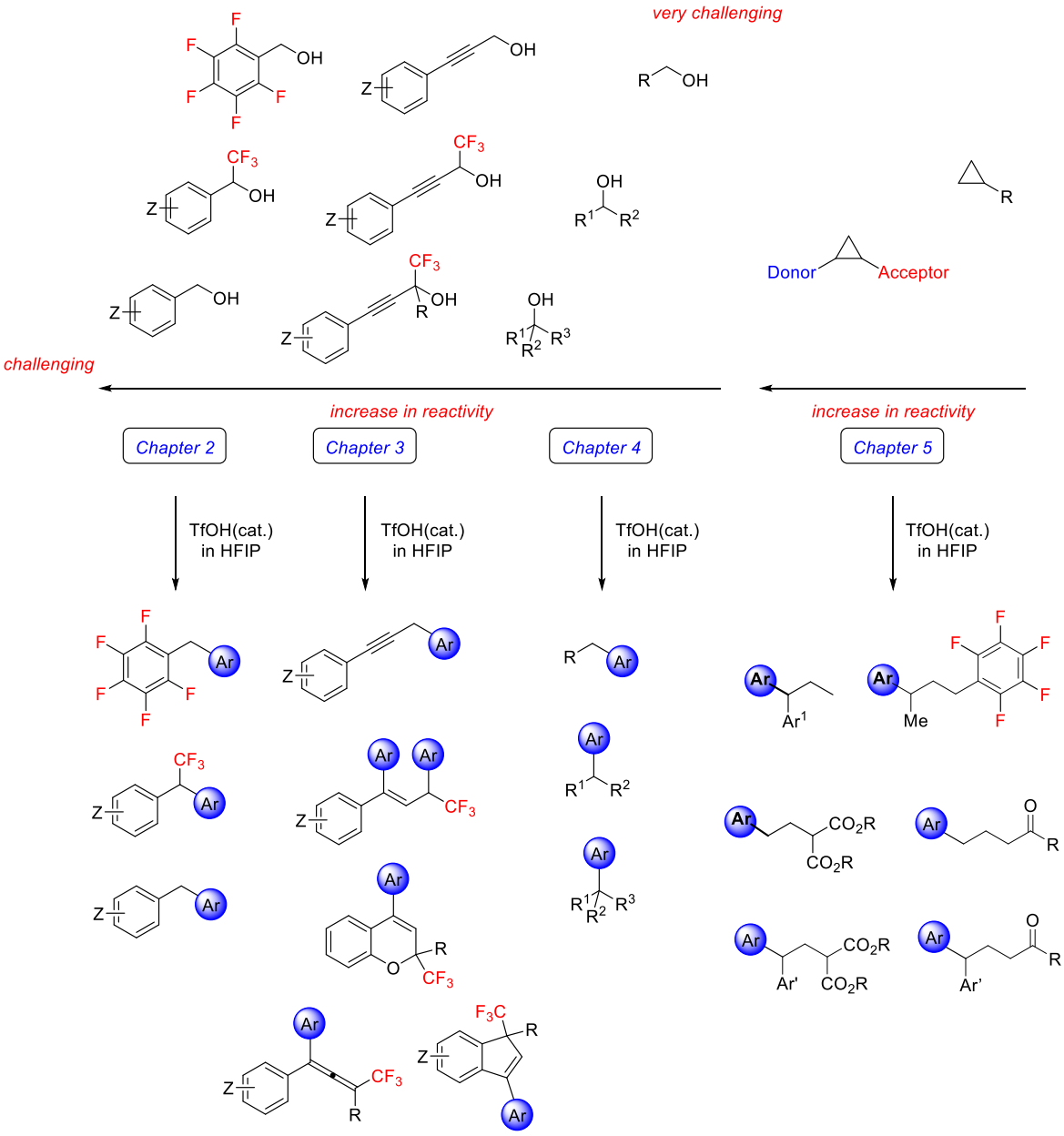


Figure 6.1. Substrates activated for Friedel-Crafts reactions with catalytic TfOH in HFIP within this thesis. Summary of the overall work done.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION – CHAPTER 2
CATALYTIC DEHYDROARYLATIVE REACTIONS OF DEACTIVATED BENZYLIC ALCOHOLS

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4. Characterization data for Friedel-Crafts benzylation products	120
5. Kinetic experiments	131

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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.

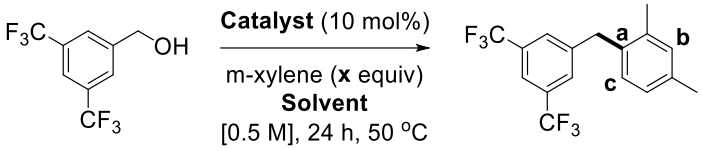
^{1}H-NMR spectra were recorded on a Bruker UltraShield 400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard ($CDCl_3$ at 7.26 ppm). **^{13}C-NMR** spectra were recorded on a Bruker UltraShield Plus 400 (100 MHz) spectrometer at ambient temperature 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 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) and MicroTOF-Q Bruker (ESI).

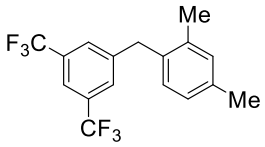
Materials: All commercial materials were purchased from Sigma-Aldrich, Alfa Aesar and FluoroChem, and were used as received, without further purification. Triflic acid (TfOH) *ReagentPlus*®, ≥99% (CAS: 1493-13-6) was purchased from Sigma Aldrich, and HFIP (CAS: 920-66-1) from FluoroChem. 2,2,2-Trifluoro-1-phenylethanol (CAS: 340-04-5) was purchased from Sigma-Aldrich. Other trifluoromethylbenzyl alcohols were prepared according to a literature procedure with analytical data in agreement with those reported.[211]

2. Optimization of reaction conditions



6 **7**

General procedure for optimization experiments

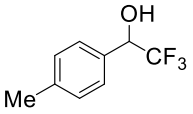


1-(3,5-bis(trifluoromethyl)benzyl)-2,4-dimethylbenzene (**7**) was prepared from 3,5-bis(trifluoromethyl)benzyl alcohol (61.1 mg, 0.25 mmol) and *m*-xylene (3 or 5 equiv.), in 0.5 mL of the solvent (24 h, 100 °C) in a 10 mL glass pressure tube equipped with a stirring bar, so that the concentration of the benzylic alcohol equals ~ 0.5 M. Then the catalyst (10 mol%, 0.025 mmol) was added, and the reaction mixture was heated for 24 h at 100ºC. The product **7** was purified by flash column chromatography over silica (petroleum ether/EtOAc 99.5:0.5). R_f = 0.80 (petroleum ether/EtOAc 9:1). Appearance of the product: colorless oil. The yields refer to combined yields of three regioisomers (regioisomer ratio: 73:18:9). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.75 (s, 1.3H), 7.67 (s, 0.2H), 7.60 (s, 2H), 7.48 (s, 0.5H), 7.22–7.09 (m, 0.7H), 7.09–6.96 (m, 3H), 6.93 (s, 0.1H), 6.82 (s, 0.2H), 4.20 (s, 0.5H), 4.09 (s, 2H), 4.04 (s, 0.2H), 2.35 (s, 3H), 2.32 (s, 0.8H), 2.26 (s, 1.5H), 2.22 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 144.0, 143.5, 142.9, 138.9, 138.7, 137.1, 137.1, 136.4, 134.7, 133.7, 132.0, 131.8 (q, *J* = 33.0 Hz), 131.7, 130.0, 129.1 (d, *J* = 2.5 Hz), 128.9 (d, *J* = 2.4 Hz), 128.8 (m), 128.0 (d, *J* = 2.4 Hz), 127.4, 127.3, 126.9, 123.6 (q, *J* = 270.7 Hz), 120.3 (ap. quint, *J* = 3.6 Hz), 41.6, 38.9, 34.9, 21.4, 21.1, 20.3, 19.7. Signals corresponding to all three regioisomers are reported. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H -

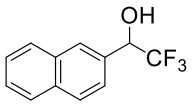
[211] *J. Org. Chem.* **2012**, *77*, 8131

ext. std.) δ (ppm): –62.8 (s, minor), –62.8 (s, 6F, major), –62.9 (s, minor). **HRMS** (ESI): *m/z* for $C_{17}H_{14}F_6Na$ ($[M+Na]^+$): calculated 355.0892; found 355.0882.

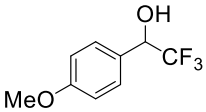
3. Starting material preparation



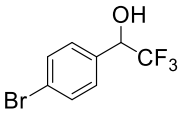
2,2,2-Trifluoro-1-(*p*-tolyl)ethanol[211] was isolated as a pale yellow liquid. Yield = 68%. R_f = 0.56 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.37 (d, *J* = 2.0 Hz, 2H), 7.21 (d, *J* = 2.0 Hz, 2H), 4.99 (m, 1H), 2.53 (d, *J* = 1.1 Hz, 1H), 2.38 (s, 3H). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –78.43 (d, *J* = 6.8 Hz).



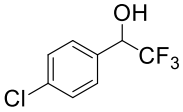
2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanol[212] was isolated as an off-white solid. Yield = 49%. R_f = 0.26 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.85-7.97 (m, 4H), 7.51-7.60 (m, 3H), 5.20 (q, *J* = 1.7 Hz, 1H), 2.68 (s, 1H). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –76.8 (d, *J* = 6.4 Hz).



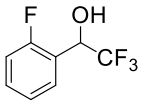
2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol[211] was isolated as a pale yellow liquid. Yield = 73%. R_f = 0.35 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.40 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.97 (q, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 2.59 (br s, 1H). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –77.3 (d, *J* = 6.7 Hz).



1-(4-Bromophenyl)-2,2,2-trifluoroethanol[213] was isolated as a pale yellow liquid. Yield = 93%. R_f = 0.51 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.57-7.55 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 5.04-4.98 (m, 1H), 2.71-2.67 (m, 1H). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –78.4 (d, *J* = 6.6 Hz).



1-(4-Chlorophenyl)-2,2,2-trifluoroethanol[212] was isolated as a yellow liquid. Yield = 52%. R_f = 0.40 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.45-7.37 (m, 4H), 5.05-4.97 (m, 1H), 2.81 (d, *J* = 1.1 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –77.3 (d, *J* = 6.8 Hz).



2,2,2-Trifluoro-1-(2-fluorophenyl)ethanol[211] was isolated as a pale yellow liquid. Yield = 92%. R_f = 0.56 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.61 (t, *J* = 7.4 Hz, 1H), 7.43-7.37 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.13-

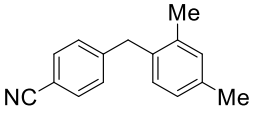
[212] *J. Org. Chem.* **2013**, *78*, 3300.
[213] *J. Org. Chem*. **2013**, *78*, 7749.

7.08 (m, 1H), 5.42 (q, J = 6.3 Hz, 1H), 2.76 (dd, J = 5.6, 1.0 Hz, 1H). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –77.5 (ap. t, J = 6.1 Hz), from –116.8 to –116.9 (m).

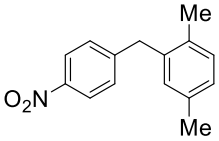
4. Characterization data for Friedel-Crafts benzylation products

General procedure A: To a solution of the requisite benzyl alcohol (0.25 mmol) in HFIP (0.500 mL, [0.5 M]) was added the requisite arene nucleophile (0.75 mmol), followed by TfOH (10 mol%, 2.21 µL). The reaction vessel was sealed, and heated at 100 °C for 24 h. Upon completion, the crude reaction mixture was purified by flash column chromatography over silica according to the given conditions to yield the desired bisarylmethanes. Regioisomeric ratios were calculated from ^{1}H NMR spectra and corroborated with GC/MS chromatogram peak ratios.

General Procedure B: To a solution of the requisite trifluoromethylbenzylalcohol (0.25 mmol) in HFIP (0.500 mL, [0.5 M]) was added the requisite arene nucleophile (0.75 mmol), followed by TfOH (10 or 20 mol%, 2.21 µL or 4.42 µL respectively). The reaction vessel was then sealed and heated at 100 °C for 24 h. The crude reaction mixture was then purified by flash column chromatography over silica according to the given conditions to yield the desired diaryl(trifluoro)methanes. Regioisomer ratios were calculated from ^{1}H NMR spectra or ^{19}F NMR spectra and corroborated with GC/MS chromatogram peak ratios.



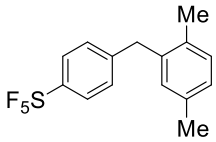
1-(4-Cyanobenzyl)-2,4-dimethylbenzene (8a) was prepared according to <u>*General Procedure A*</u> from 4-cyanobenzyl alcohol (33.3 mg, 0.250 mmol) and *m*-xylene (91.7 µL, 0.750 mmol), with 4.42 µL (0.050 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 95:5) gave 31.5 mg (60% yield, regioisomer ratio: 73:21:6) of colorless oil. R_f = 0.61 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.60–7.51 (m, 2.6H), 7.31 (d, J = 8.0 Hz, 0.2H), 7.23 (d, J = 8.6 Hz, 2H), 7.19–7.08 (m, 1.4H), 7.04 (s, 1H), 7.01 (s, 1.7H), 6.99 (s, 0.1H), 6.90 (s, 0.1H), 6.81 (s, 0.2H), 4.13 (s, 0.6H), 4.02 (s, 2H), 3.97 (s, 0.2H), 2.34 (s, 3H), 2.31 (s, 0.5H), 2.24 (s, 1.7H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 147.1, 146.6, 145.8, 139.3, 138.3, 137.1, 136.7, 136.4, 135.3, 134.2, 132.3, 132.2, 131.5, 130.1, 129.7, 129.4, 128.7, 128.4, 128.3, 127.0, 126.9, 126.8, 119.1, 109.8, 109.8, 41.9, 40.9, 39.2, 35.3, 23.9, 21.3, 21.0, 20.2, 19.6. Signals corresponding to all three regioisomers are reported. Spectral data are in agreement with the literature.[214]



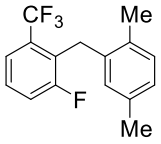
1-(4-Nitrobenzyl)-2,5-dimethylbenzene (8b) was prepared according to <u>*General Procedure A*</u> from 4-nitrobenzyl alcohol (38.7 mg, 0.253 mmol) and *p*-xylene (92.7 µL, 0.752 mmol), with 2.23 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (48 h, 100 °C). Purification by flash column chromatography

[214] *J. Am. Chem. Soc.* **2015**, *137*, 9694.

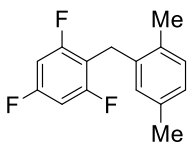
over silica (with petroleum ether/EtOAc 98:2) gave 55.4 mg (91% yield) of pale yellow oil. R_f = 0.69 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 4.07 (s, 2H), 2.33 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 148.7, 146.5, 137.0, 135.9, 133.4, 130.9, 130.6, 129.5, 127.9, 123.7, 39.4, 21.0, 19.2. Spectral data are in agreement with the literature.[214]



1-(4-(Pentafluorothio)benzyl)-2,5-dimethylbenzene (8c) was prepared according to modified *General Procedure A* from 4-(pentafluorothio)benzyl alcohol (63.8 mg, 0.272 mmol) and *p*-xylene (168 µL, 1.36 mmol, 5 equiv.), with 9.4 mg (0.027 mmol) of $HSbF_6{\cdot}6H_2O$, in 0.54 mL of HFIP. The reaction mixture was heated at 80 °C during 48 h. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 67.7 mg (77% yield) of colorless oil. R_f = 0.82 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 4.01 (s, 2H), 2.34 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 152.0 (t, *J* = 17.1 Hz), 144.8, 137.4, 135.9, 133.5, 130.9, 130.6, 128.9, 127.8, 126.1 (quint, *J* = 4.2 Hz), 39.1, 21.1, 19.3. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): +86.4 (quint, *J* = 150.0 Hz, 1F), +64.4 (d, *J* = 149.8 Hz, 4F). **HRMS** (CI): *m/z* for $C_{15}H_{15}SF_5$ [M^+]: calculated 322.0815; found 322.0806 (ppm –2.8).

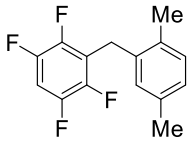


1-(6-Fluoro-2-(trifluoromethyl)benzyl)-2,5-dimethylbenzene (8d) was prepared according to *General Procedure A* from 6-fluoro-2-(trifluoromethyl)benzyl alcohol (55.8 mg, 0.287 mmol) and *p*-xylene (106 µL, 0.860 mmol), with 2.54 µL (0.029 mmol) of triflic acid, in 0.57 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 99.5:0.5) gave 61.3 mg (76% yield) of colorless oil. R_f = 0.81 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 7.8 Hz, 1H), 7.43 (ap. q, *J* = 13.3, 7.9 Hz, 1H), 7.33 (t, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.17 (s, 2H), 2.44 (s, 3H), 2.22 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 162.2 (d, *J* = 246.0 Hz), 137.2, 135.5, 132.6, 131.6 (qd, *J* = 30.0, 4.1 Hz), 129.9, 128.3 (d, *J* = 8.9 Hz), 127.5, 126.9, 126.7 (d, *J* = 18.3 Hz), 123.9 (qd, *J* = 272.4, 3.5 Hz), 122.0 (m), 119.3 (d, *J* = 22.9 Hz), 28.5, 21.2, 19.4. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –59.5 (s, 3F), –113.0 (t, *J* = 6.8 Hz, 1F). **HRMS** (ESI): *m/z* for $C_{16}H_{15}F_4$ ($[M+H]^+$): calculated 283.1104; found 283.1107.

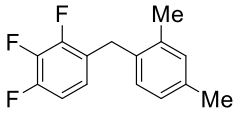


1-(2,4,6-Trifluorobenzyl)-2,5-dimethylbenzene (8e) was prepared according to modified *General Procedure A* from 2,4,6-trifluorobenzyl alcohol (55.7 mg, 0.344 mmol) and *p*-xylene (127 µL, 1.03 mmol), with 3.04 µL (0.034 mmol) of triflic acid, in 0.69 mL of HFIP. Reaction mixture was heated at 50 °C for 30 min. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 76.4 mg (89% yield) of colorless oil. R_f = 0.86 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.11 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.72 (t, *J* = 8.2

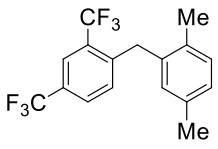
Hz, 2H), 3.96 (s, 2H), 2.40 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 161.6 (dm, *J* = 247.1 Hz, 2C), 136.6, 135.6, 133.0, 130.3, 128.9, 127.3, 112.5 (td, *J* = 20.5, 4.6 Hz), 100.7–99.6 (m), 25.2, 21.1, 19.2. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –110.8 (m, 1F), –111.0 (t, *J* = 6.4 Hz, 2F). **HRMS** (ESI): *m/z* for $C_{15}H_{14}F_3$ ($[M+H]^+$): calculated 251.1042; found 251.1008.



1-(2,3,5,6-Tetrafluorobenzyl)-2,5-dimethylbenzene (8f) was prepared according to the *General Procedure A* from 2,3,5,6-tetrafluorobenzyl alcohol (45.0 mg, 0.250 mmol) and *p*-xylene (91.7 µL, 0.744 mmol), with 2.21 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 60.3 mg (90% yield) of colorless oil. R_f = 0.85 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.11 (d, *J* = 6.2 Hz, 1H), 7.06–6.94 (m, 2H), 6.84 (s, 1H), 4.06 (s, 2H), 2.40 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 146.1 (dddd, *J* = 245.9, 14.8, 10.2, 3.7 Hz), 145.1 (dddd, *J* = 244.0, 13.6, 6.0, 4.0 Hz), 135.83, 135.44, 133.06, 130.44, 129.13, 127.72, 119.99 (t, *J* = 18.1 Hz), 104.27 (t, *J* = 22.6 Hz), 26.13, 21.08, 19.21. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –139.52 (ddd, *J* = 22.6, 12.8, 9.6 Hz, 2F), –142.79 (ddd, *J* = 20.7, 12.8, 7.5 Hz, 2F). **HRMS** (CI): *m/z* for $C_{15}H_{12}F_4$ [M^+]: calculated 268.0875; found 268.0876 (ppm 0.4).

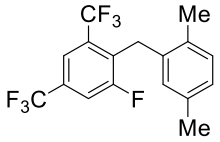


1-(2,3,4-Trifluorobenzyl)-2,4-dimethylbenzene (8g) was prepared according to modified *General Procedure A* from 2,3,4-trifluorobenzyl alcohol (40.2 mg, 0.248 mmol) and *m*-xylene (91.0 µL, 0.744 mmol), with 2.19 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP. Reaction mixture was heated at 50 °C for 1 h. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 99.5:0.5) gave 50.1 mg (81% yield, regioisomer ratio: 71:21:8) of colorless oil. R_f = 0.85 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.21–7.09 (m, 0.9H), 7.08–6.97 (m, 2.9H), 6.94–6.72 (m, 1.6H), 6.72–6.62 (m, 1H), 6.39–6.28 (m, 0.3H), 4.05 (s, 0.6H), 3.96 (s, 2H), 3.93 (s, 0.2H), 2.36 (s, 3.2H), 2.33 (s, 0.6H), 2.25 (s, 4.7H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 149.8 (dm, *J* = 245.6 Hz), 140.0 (dm, *J* = 249.0 Hz), 138.4, 137.9, 137.4, 136.7, 136.5, 134.4, 133.5, 131.5, 129.8, 128.5, 128.4, 127.1, 127.0, 126.7, 126.2, 125.3 (dd, *J* = 13.3, 3.4 Hz), 123.8–123.3 (m), 122.0–121.6 (m), 111.7 (dd, *J* = 17.0, 3.9 Hz), 111.7 (dd, *J* = 16.8, 5.0 Hz), 34.2, 31.3, 27.2, 21.4, 21.3, 21.0, 20.0, 19.4. Signals corresponding to all three regioisomers are reported. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): from –123.7 to –124.7 (m, 1F), from –124.7 to –125.3 (m, 1F), from –147.2 to –148.3 (m, 1F). Spectral data are in agreement with the literature.[214]

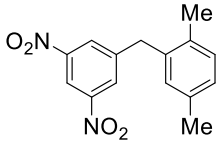


1-(2,4-Bis(trifluoromethyl)benzyl)-2,5-dimethylbenzene (8h) was prepared according to *General Procedure A* from 2,4-bis(trifluoromethyl)benzyl alcohol (61.1 mg, 0.250 mmol) and *p*-xylene (92.5 µL, 0.750 mmol), with 2.21 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by

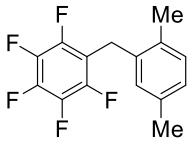
flash column chromatography over silica (with petroleum ether/EtOAc 99.5:0.5) gave 49.0 mg (59% yield) of colorless oil. R_f = 0.87 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.94 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.06 (m, 2H), 6.86 (s, 1H), 4.19 (s, 2H), 2.31 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 144.0, 136.3, 136.0, 133.7, 131.4, 131.0, 130.7, 129.5 (q, *J* = 30.6 Hz), 128.9 (q, *J* = 33.2 Hz), 128.7, 128.1, 124.0 (q, *J* = 272.5 Hz), 123.7 (q, *J* = 270.3 Hz), 123.2 (m), 35.6, 21.1, 19.1. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –61.2 (s, 3F), –62.7 (s, 3F). **HRMS** (CI): *m/z* for $C_{17}H_{15}F_6$ ($[M+H]^+$): calculated 333.1078; found 333.1081 (ppm 0.9).



1-(6-Fluoro-2,4-bis(trifluoromethyl)benzyl)-2,5-dimethylbenzene (8i) was prepared according to *General Procedure A* from 6-fluoro-2,4-bis(trifluoromethyl)benzyl alcohol (67.7 mg, 0.258 mmol) and *p*-xylene (95.0 µL, 0.770 mmol), with 4.57 µL (0.052 mmol) of triflic acid, in 0.5 mL of HFIP (48 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 99.5:0.5) gave 66.5 mg (74% yield) of colorless oil. R_f = 0.85 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.86 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.32 (s, 1H), 4.17 (s, 2H), 2.41 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 162.0 (d, *J* = 249.3 Hz), 136.1, 135.7, 132.7, 132.7 (qd, *J* = 32.8, 4.9 Hz), 131.4 (d, 17.6 Hz), 131.1 (qd, *J* = 34.6, 8.6 Hz), 130.1, 127.3, 127.3, 123.1 (qd, *J* = 272.8, 3.2 Hz), 122.9 (qd, *J* = 270.4, 1.7 Hz), 119.2, 116.6 (dd, *J* = 26.1, 3.2 Hz), 28.7, 21.2, 19.5. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –58.9 (s, 3F), –61.8 (s, 3F), –108.1 (d, *J* = 8.7 Hz, 1F). **HRMS** (CI): *m/z* for $C_{17}H_{14}F_7$ ($[M+H]^+$): calculated 351.0984; found 351.0986 (ppm 0.6).

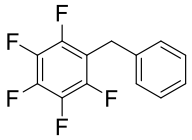


1-(3,5-Dinitrobenzyl)-2,5-dimethylbenzene (8j) was prepared according to *General Procedure A* from 3,5-dinitrobenzyl alcohol (49.8 mg, 0.251 mmol) and *p*-xylene (92.0 µL, 0.746 mmol), with 4.42 µL (0.050 mmol) of triflic acid, in 0.5 mL of HFIP (48 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 42.0 mg (58% yield) of yellow solid. R_f = 0.45 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.88 (s, 1H), 8.31 (s, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 4.17 (s, 2H), 2.33 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 148.7, 145.6, 136.4, 135.5, 133.2, 131.1, 130.9, 128.8, 128.7, 116.9, 39.1, 21.1, 19.3. **HRMS** (CI): *m/z* for $C_{15}H_{15}N_2O_4$ ($[M+H]^+$): calculated 287.1032; found 287.1042 (ppm 3.5).

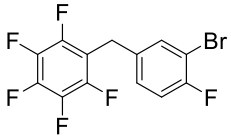


1-(2,3,4,5,6-Pentafluorobenzyl)-2,5-dimethylbenzene (8k) was prepared according to *General Procedure A* from 2,3,4,5,6-pentafluorobenzyl alcohol (49.3 mg, 0.249 mmol) and *p*-xylene (92.1 µL, 0.747 mmol), with 2.20 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 67.3 mg (94% yield)

of white solid. R_f = 0.85 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.10 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.01 (s, 2H), 2.39 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 145.4 (dm, *J* = 244.0 Hz), 140.1 (dm, *J* = 241.6 Hz), 137.7 (dm, *J* = 243.7 Hz), 136.9, 136.2, 133.0, 130.5, 129.0, 127.8, 114.0 (td, *J* = 18.4, 3.5 Hz), 25.5, 21.1, 19.2. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –141.1 (dd, *J* = 22.2, 8.3 Hz, 2F), –155.9 (t, *J* = 20.7 Hz, 1F), –161.3 (td, *J* = 21.6, 7.8 Hz, 2F). **HRMS** (CI): *m/z* for $C_{15}H_{12}F_5$ ($[M+H]^+$): calculated 287.0859; found 287.0856 (ppm –1.0).



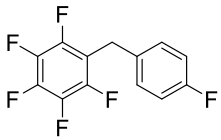
1-(2,3,4,5,6-Pentafluorobenzyl)-benzene (8l) was prepared according to <u>*General Procedure A*</u> from 2,3,4,5,6-pentafluorobenzyl alcohol (49.0 mg, 0.247 mmol) and benzene (67.0 µL, 0.750 mmol), with 2.21 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 45.8 mg (72% yield) of colorless liquid. R_f = 0.83 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.26-7.36 (m, 5H), 4.07 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 145.0 (dm, *J* = 244.1 Hz), 139.9 (dm, *J* = 250.2 Hz), 137.5, 137.6 (dm, *J* = 249.7 Hz), 128.8, 128.4, 127.0, 114.5 (td, *J* = 18.7, 3.4 Hz), 28.1. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –142.2 (dd, *J* = 22.6, 8.1 Hz, 2F), –156.0 (t, *J* = 20.7 Hz, 1F), –161.3 (td, *J* = 21.6, 7.9 Hz, 2F). Spectral data are consistent with previous report.[215]



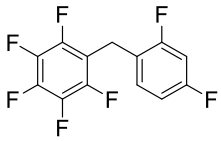
1-(2,3,4,5,6-Pentafluorobenzyl)-3-bromo-4-fluorobenzene (8m) was prepared according to <u>*General Procedure A*</u> from 2,3,4,5,6-pentafluorobenzyl alcohol (48.6 mg, 0.245 mmol) and 1-bromo-2-fluorobenzene (134 µL, 1.226 mmol), with 2.17 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with 100% petroleum ether) gave 45.9 mg (53% yield, regioisomer ratio: 78:12:9:1) of colorless oil. R_f = 0.79 (petroleum ether/EtOAc 9:1). The major regioisomer was tentatively assigned based on analogy to similar nucleophiles[216] and on expected chemical shifts of the aromatic protons. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.58-7.51 (m, 0.1H), 7.50-7.38 (m, 0.5H), 7.32-7.27 (m, 0.1H), 7.24-7.08 (m, 0.9H), 7.07-6.87 (m, 0.9H), 6.82-6.74 (m, 0.1H), 4.19 (s, 0.1H), 4.08 (s, 0.2H), 4.03 (s, 0.02H), 3.98 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.5 (d, *J* = 245.5 Hz), 159.2 (d, *J* = 241.5 Hz), 158.3 (d, *J* = 245.5 Hz), 157.2 (d, *J* = 246.1 Hz), 145.1 (dm, *J* = 244.6 Hz), 142.0-141.3 (m), 139.5-138.7 (m), 136.8-136.2 (m), 134.9 (d, *J* = 3.1 Hz), 133.9, 133.7, 133.4, 132.7, 132.1, 130.2, 129.6 (d, *J* = 2.5 Hz), 129.1 (d, *J* = 7.1 Hz), 128.6 (d, *J* = 8.3 Hz), 126.0 (d, *J* = 16.4 Hz), 125.4, 125.3, 124.8 (d, *J* = 1.1 Hz), 116.9 (d, *J* = 22.3 Hz), 116.7 (d, *J* = 22.1 Hz), 115.1 (d, *J* = 22.7 Hz), 113.9-113.1 (m), 111.5 (d, *J* = 21.1 Hz), 109.6 (d, *J* = 20.9 Hz), 109.4 (d, *J* = 21.0 Hz), 109.3-109.0 (m), 107.7 (d, *J* = 20.7 Hz), 32.1, 29.9, 29.5, 28.6, 27.6, 27.2, 22.9, 22.1, 14.3. Signals corresponding to all four regioisomers are reported. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H -

[215] *Angew. Chem. Int. Ed.* **2016**, *55*, 8448
[216] *Angew. Chem. Int. Ed.* **2011**, *50*, 10913

ext. std.) δ (ppm): –102.6 (dd, *J* = 7.9, 6.0 Hz, 0.1F), –105.4 (t, *J* = 8.3 Hz, 0.4F), –106.0 to –106.1 (m, 0.1F), –108.5 (m, 0.5F), –109.3 (quint, *J* = 7.2 Hz, 0.1F), –140.3 (dd, *J* = 21.5, 7.9 Hz, 0.4F), –141.2 (dt, *J* = 22.2, 8.3 Hz, 0.4F), –142.0 (dd, *J* = 13.9, 8.3 Hz, 1.1F), –142.1 (dd, *J* = 22.2, 8.3 Hz, 1.6F), –154.4 (t, *J* = 21.1 Hz, 0.2F), –154.7 (t, *J* = 21.1 Hz, 0.6F), –154.8 (t, *J* = 21.1 Hz, 1F), –155.3 (t, *J* = 20.7 Hz, 0.02F), –160.4 to –160.6 (m, 2.6F), –160.9 (quintd, *J* = 21.3, 7.9 Hz, 0.8F). **HRMS** (CI): *m/z* for $C_{13}H_6F_6{}^{79}Br$ ($[M+H]^+$): calculated 354.9557; found 354.9594 (ppm –2.3).

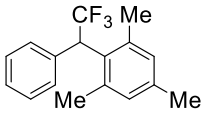


1-(2,3,4,5,6-Pentafluorobenzyl)-4-fluorobenzene (8n) was prepared according to *General Procedure A* from 2,3,4,5,6-pentafluorobenzyl alcohol (50.0 mg, 0.252 mmol) and fluorobenzene (70.4 µL, 0.750 mmol), with 2.21 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 36.1 mg (52% yield, regioisomer ratio: 56:36:8) of colorless liquid. R_f = 0.79 (petroleum ether/EtOAc 9:1). Identity of the major regioisomer assigned by analogy to the results of Hall and co-workers.[214] **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.96-7.32 (m, 6.9H), 4.09 (s, 1.3H), 4.05 (s, 0.3H), 4.02 (2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm):163.1 (d, *J* = 245.2 Hz), 162.0 (d, *J* = 243.9), 160.9 (d, *J* = 245.2), 145.4 (dm, *J* = 245.2 Hz), 145.1 (dm, *J* = 244.7 Hz), 140.2 (dm, *J* = 248.4 Hz), 137.7 (dm, *J* = 250.0 Hz), 133.3, 130.4 (d, *J* = 3.7 Hz), 130.1 (d, *J* = 8.0 Hz), 129.0 (d, *J* = 8.1 Hz), 124.4 (d, *J* = 3.5 Hz), 124.3, 124.1 (d, *J* = 1.9 Hz), 115.8 (d, *J* = 21.3 Hz), 115.7 (d, *J* = 21.5 Hz), 115.6-115.4 (m), 114.7-114.2 (m), 114.2 (d, *J* = 20.9 Hz), 113.1 (td, *J* = 18.4, 3.3 Hz), 29.9, 28.0, 27.5, 21.6. Signals corresponding to all three regioisomers are reported. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –111.5 to –111.4 (m, 0.1F), –114.5 (m, 0.6F), –116.2 to –116.1 (m, 0.5F), –141.5 to –141.4 (m, 1.2), –142.0 (dd, *J* = 22.2, 8.3 Hz, 0.3F), –142.4 (dd, *J* = 22.2, 8.3 Hz, 2F), –155.3 (t, *J* = 20.7 Hz, 0.1F), –155.7 to –155.5 (m, 1.7F), –160.9 (m, 0.2F), –161.0 (m, 2F), –161.3 (m, 1.2F). **HRMS** (CI): *m/z* for $C_{13}H_7F_6$ ($[M+H]^+$): calculated 277.0452; found 277.0452 (ppm 0.0).

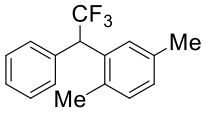


1-(2,3,4,5,6-Pentafluorobenzyl)-2,4-difluorobenzene (8o) was prepared according to *General Procedure A* from 2,3,4,5,6-pentafluorobenzyl alcohol (49.7 mg, 0.251 mmol) and 1,3-difluorobenzene (124 µL, 1.257 mmol), with 2.22 µL (0.025 mmol) of triflic acid, in 0.5 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (with 100% petroleum ether) gave 21.0 mg (28% yield, regioisomer ratio: 88:12) of colorless oil. R_f = 0.77 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.20-7.24 (m, 0.1H), 7.10-7.16 (m, 0.9H), 6.85-6.89 (m, 0.2H), 6.77-6.84 (m, 1.8H), 4.07 (s, 0.3H), 4.02 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 162.3 (dd, *J* = 246.9, 11.8 Hz), 161.5 (dd, *J* = 274.4, 7.4 Hz), 160.8 (dd, *J* = 248.0, 11.8 Hz), 145.3 (dm, *J* = 245.7 Hz), 140.4 (dm, *J* = 251.2 Hz), 137.7 (dm, *J* = 250.9 Hz), 131.2 (dd, *J* = 9.2, 5.5 Hz), 129.1 (t, *J* = 10.2 Hz), 120.3 (dd, *J* = 16.0, 3.3 Hz), 113.1-112.7 (m), 111.6 (dd, *J* = 21.1, 3.6 Hz), 104.2 (t, *J* = 25.4 Hz), 21.2, 15.7. Signals corresponding to both regioisomers are reported. **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –110.2 (m, 0.6F), –111.7 (m, 0.7F),

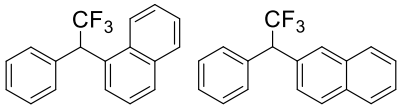
–113.2 to –113.1 (m, 0.2F), –141.5 to –141.3 (m, 0.3F), –141.6 to –141.5 (m, 2F), –155.1 (t, *J* = 20.9 Hz, 1F), –155.6 (t, *J* = 20.9 Hz, 0.2F), –161.0 (td, *J* = 21.3, 7.9 Hz, 1.9F), –161.6 (td, *J* = 21.3, 7.8 Hz, 0.3F). **HRMS** (CI): *m/z* for $C_{13}H_6F_7$ ($[M+H]^+$): calculated 295.0358; found 295.0357 (ppm –0.3).



1,3,5-Trimethyl-2-(2,2,2-trifluoro-1-phenylethyl)benzene (9a) was prepared according to *General Procedure B* from 2,2,2-trifluoro-1-phenylethanol (0.035 mL, 0.25 mmol), mesitylene (0.104 mL, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9a** as a colorless liquid. Yield = 0.052 g, 75%. R_f = 0.59 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.32-7.24 (m, 5H), 6.96 (s, 1H), 6.80 (s, 1H), 5.37 (q, *J* = 10.7 Hz, 1H), 2.48 (s, 3H), 2.28 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 138.7 (d, *J* = 9.3 Hz), 137.9, 136.2, 131.8, 130.0, 129.4, 128.6, 127.7, 127.3 (q, *J* = 281.3 Hz), 126.8, 49.2 (q, *J* = 27.5 Hz), 21.9, 21.1, 20.9. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –61.3 (d, *J* = 10.7 Hz, 3F). **HRMS** (CI): *m/z* for $C_{17}H_{18}F_3$ ($[M+H]^+$): calculated 279.1361; found 279.1358 (–1.1 ppm).



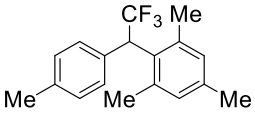
1,4-Dimethyl-2-(2,2,2-trifluoro-1-phenylethyl)benzene (9b) was prepared according to *General Procedure B* from 2,2,2-trifluoro-1-phenylethanol (0.035 mL, 0.25 mmol), *p*-xylene (0.092 mL, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9b** as a colorless liquid. Yield = 0.044 g, 67%. R_f = 0.48 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.33-7.26 (m, 6H), 7.07-7.02 (m, 2H), 4.87 (q, *J* = 10.0 Hz, 1H), 2.35 (s, 3H), 2.23 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 135.9, 135.1, 133.8, 133.6, 130.9, 129.7, 128.7 (3C), 127.9, 126.6 (q, *J* = 280.7 Hz), 51.3 (q, *J* = 27.2 Hz), 21.4, 19.6. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.8 (d, *J* = 10.0 Hz, 3F). **HRMS** (CI): *m/z* for $C_{16}H_{16}F_3$ ($[M+H]^+$): calculated 265.1204; found 265.1194 (–3.8 ppm).



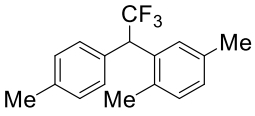
1-(2,2,2-Trifluoro-1-phenylethyl)naphthalene (9c) and **2-(2,2,2-Trifluoro-1-phenylethyl)naphthalene (9c')** were prepared according to *General Procedure B* from 2,2,2-trifluoro-1-phenylethanol (0.035 mL, 0.25 mmol), naphthalene (0.096 g, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9c** and **9c'** (1.4:1 **9c** to **9c'**) as a white solid. Combined yield = 0.061 g, 85%. R_f = 0.33 (100% petroleum ether). Analytical data are in agreement with the literature.[217] **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.99-7.83 (m, 4H), 7.59-7.31 (m, 8H), 5.58 (q, *J* = 9.7 Hz, 0.59H) (**9c**, 1-isomer), 4.91 (q, *J* = 9.9 Hz, 0.41H) (**9c'** 2-isomer). **^{13}C NMR** (100 MHz, $CDCl_3$) (only characteristic peaks are reported) δ (ppm): 55.7 (q, *J* = 27.5 Hz) (**9c',** 2-isomer), 50.9 (q, *J* = 27.4 Hz) (**9c**, 1-isomer).

[217] *Russ. Chem. Bull.* **1998**, *47*, 1820

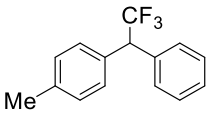
^{19}F NMR (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.5 (d, *J* = 9.8 Hz, 3F) (**9c**, 1-isomer) and –64.3 (d, *J* = 9.8 Hz, 2F) (**9c'**, 2-isomer).



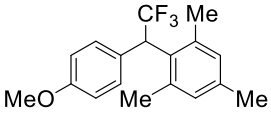
1,3,5-Trimethyl-2-(2,2,2-trifluoro-1-(*p*-tolyl)ethyl)benzene (9d) was prepared according to *General Procedure B* from 1-(4-methylphenyl)-2,2,2-trifluoroethanol. Purification by flash column chromatography over silica (100% petroleum ether) gave **9d** as a colorless liquid. Yield = 94%. R_f = 0.79 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.23-7.17 (m, 4H), 7.02 (s, 1H), 6.87 (s, 1H), 5.41 (q, *J* = 10.8 Hz, 1H), 2.54 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 1.93 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 138.7, 137.8, 136.5, 133.0, 131.8, 130.2, 129.4, 129.3, 127.6, 127.4 (q, *J* = 279.6 Hz), 127.1, 48.9 (q, *J* = 27.3 Hz), 21.8, 21.2, 21.1, 20.9. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –61.3 (d, *J* = 10.5 Hz, 3F). **HRMS** (CI): *m/z* for $C_{18}H_{19}F_3$ [M^+]: calculated 292.1439; found 292.1437 (ppm –0.7).



1,4-Dimethyl-2-(2,2,2-trifluoro-1-(*p*-tolyl)ethyl)benzene (9e) was prepared according to *General Procedure B* from 1-(4-methylphenyl)-2,2,2-trifluoroethanol. Purification by flash column chromatography over silica (100% petroleum ether) gave **9e** as a colorless liquid. Yield = 94%. R_f = 0.75 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.25 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.98-6.88 (m, 2H), 4.74 (q, *J* = 10 Hz, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 137.7, 135.8, 134.0, 133.6, 132.1, 130.9, 129.5, 129.4, 128.6 (2C), 126.7 (q, *J* = 278.8 Hz), 50.9 (q, *J* = 27.0 Hz), 21.4, 21.2, 19.6. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.9 (d, *J* = 9.4 Hz, 3F). **HRMS** (CI): *m/z* for $C_{17}H_{17}F_3$ [M^+]: calculated 278.1282; found 278.1276 (ppm –2.2).

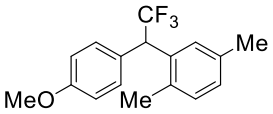


1-Methyl-4-(2,2,2-trifluoro-1-phenylethyl)benzene (9f) was prepared according to *General Procedure B* from 1-(4-methylphenyl)-2,2,2-trifluoroethanol. Purification by flash column chromatography over silica (100% petroleum ether) gave **9f** as a colorless liquid. Yield = 71%. R_f = 0.75 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.31-7.08 (m, 7H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.53 (q, *J* = 12.0 Hz, 1H), 2.20 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 137.8, 135.8, 132.6, 129.6, 129.2, 129.1, 128.8, 128.0, 126.4 (q, *J* = 278.6 Hz), 55.3 (q, *J* = 27.3 Hz), 21.2. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –64.7 (d, *J* = 10.2 Hz, 3F). **HRMS** (CI): *m/z* for $C_{15}H_{14}F_3$ ([M+H]$^+$): calculated 251.1048; found 251.1046 (ppm –0.8).

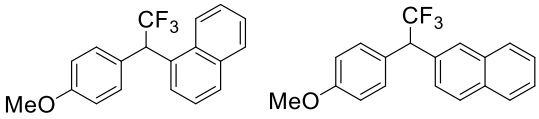


1,3,5-Trimethyl-2-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)benzene (9g) was prepared according to *General Procedure B* from 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (0.051 g, 0.25 mmol), mesitylene (0.104 mL, 0.75 mmol) and TfOH (2.2 µL, 10 mol%). Purification by flash column chromatography over silica (petroleum ether/EtOAc 99:1) gave **9g** as a colorless liquid. Yield = 0.056 g, 73%. R_f = 0.13

(100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.15 (d, *J* = 8.1 Hz, 2H), 6.94 (s, 1H), 6.92-6.78 (m, 3H), 5.30 (q, *J* = 10.7 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 3H), 2.27 (s, 3H), 1.85 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 158.3, 138.7, 137.8, 131.8, 130.2, 129.4, 128.8, 128.0, 127.4 (q, *J* = 281.2 Hz), 127.0, 113.9, 55.3, 48.5 (q, *J* = 27.6 Hz), 21.8, 21.2, 20.9. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –61.4 (d, *J* = 10.8 Hz, 3F). **HRMS** (CI): *m/z* for $C_{18}H_{20}OF_3$ ($[M+H]^+$): calculated 309.1466; found 309.1461 (–1.6 ppm).

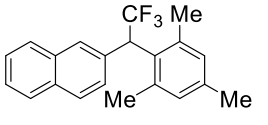


1,4-Dimethyl-2-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)benzene (9h) was prepared according to <u>*General Procedure B*</u> from 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (0.051 g, 0.25 mmol), *p*-xylene (0.092 mL, 0.75 mmol) and TfOH (2.2 µL, 10 mol%). Purification by flash column chromatography over silica (petroleum ether/EtOAc 99:1) gave **9h** as a colorless liquid. Yield = 0.059 g, 95%. R_f = 0.13 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.41 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.13-7.07 (m, 2H), 6.93-6.89 (m, 2H), 4.88 (q, *J* = 10.1 Hz, 1H), 3.83 (s, 3H), 2.41 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.2, 135.8, 134.0, 133.5, 130.9, 130.8, 128.5, 128.4, 127.0, 126.7 (q, *J* = 280.6 Hz), 114.1, 55.3, 50.5 (q, *J* = 27.2 Hz), 21.4, 19.6. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –64.1 (d, *J* = 10.0 Hz, 3F). **HRMS** (CI): *m/z* for $C_{17}H_{18}OF_3$ ($[M+H]^+$): calculated 295.1310; found 295.1305 (–1.7 ppm).

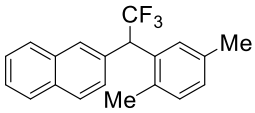


1-(2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl)-naphthalene (9i) and 2-(2,2,2-Trifluoro-1-(4-methoxyphenyl) ethyl)naphthalene (9i') were prepared according to <u>*General Procedure B*</u> from 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (0.051 g, 0.25 mmol), naphthalene (0.096 g, 0.75 mmol) and TfOH (2.2 µL, 10 mol%). Purification by flash column chromatography over silica (petroleum ether/EtOAc 99:1) gave **9i** and **9i'** (4:1 **9i** to **9i'**) as a colorless liquid. Combined yield = 95%. R_f = 0.14 (100% petroleum ether). Analytical data for **9i'** (2-isomer) is in agreement with the literature.[218] **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.97-7.83 (m, 4H), 7.58-7.46 (m, 3H), 7.38-7.34 (m, 2H), 6.92 (d, *J* = 8.7 Hz, 0.42H) (**9i'**, 2-isomer), 6.87 (d, *J* = 8.7 Hz, 1.52H), 5.52 (q, *J* = 9.7 Hz, 0.79H) (**9i,** 1-isomer), 4.86 (q, *J* = 9.9 Hz, 0.21H) (**9i'**, 2-isomer), 3.81 (s, 0.66H) (**9i'**, 2-isomer), 3.77 (s, 2.35H) (**9i**, 1-isomer). **^{13}C NMR** (100 MHz, $CDCl_3$) (only characteristic peaks are reported) δ (ppm): 55.33 (**9i'**, 2-isomer), 55.28 (**9i**, 1-isomer), 54.9 (q, *J* = 27.5 Hz) (**9i'**, 2-isomer), 50.1 (q, *J* = 27.4 Hz) (**9i**, 1-isomer). **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.8 (d, *J* = 9.7 Hz, 3F) (**9i**, 1-isomer) and –64.6 (d, *J* = 10.0 Hz, 0.8F) (**9i'**, 2-isomer). **HRMS** (CI): *m/z* for $C_{19}H_{16}OF_3$ ($[M+H]^+$): calculated 317.1153; found 317.1148 (–1.6 ppm).

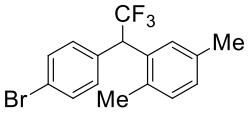
[218] *Chem. Eur. J.* **2016**, *22*, 120



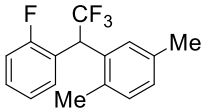
2-(1-(2-Naphthyl)-2,2,2-trifluoroethyl)-1,3,5-trimethylbenzene (9j) was prepared according to *General Procedure B* from 1-(2-naphthyl)-2,2,2-trifluoroethanol (57.6 mg, 0.255 mmol), *p*-xylene (94,2 µL, 0.764 mmol) and TfOH (4.51 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9j** as a colorless liquid. Yield = 38.8 mg, 49%. R_f = 0.78 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H), 7.91-7.84 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.50-7.59 (m, 2H), 7.24-7.32 (m, 1H), 7.08 (s, 1H), 6.88 (s, 1H), 5.60 (q, 10.4 Hz, 1H), 2.61 (s, 3H), 2.37 (s, 3H), 1.91 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$ - one C_q not observed) δ (ppm): 138.8, 137.9, 133.4, 133.2, 132.1, 131.8, 129.7, 129.4, 128.3, 128.2, 127.6, 127.3 (q, *J* = 279.0 Hz), 126.4, 126.2, 126.2, 125.9, 49.4 (q, *J* = 27.4 Hz), 21.8, 21.1, 20.9. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –61.2 (d, *J* = 10.5 Hz, 3F). **HRMS** (CI): *m/z* for $C_{21}H_{19}F_3$ [M^+]: calculated 328.1439; found 328.1434 (ppm –1.5).



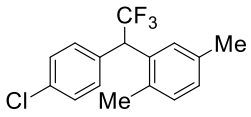
2-(1-(2-Naphthyl)-2,2,2-trifluoroethyl)-1,4-dimethylbenzene (9k) was prepared according to *General Procedure B* from 1-(2-naphthyl)-2,2,2-trifluoroethanol (55.9 mg, 0.247 mmol), mesitylene (103 µL, 0.740 mmol) and TfOH (4.37 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9k** as a colorless liquid. Yield = 55.0 mg, 68%. R_f = 0.75 (petroleum ether/EtOAc 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.80-7.87 (m, 4H), 7.56-7.48 (m, 2H), 7.47-7.40 (m, 2H), 7.14-7.06 (m, 2H), 5.11 (q, *J* = 10.0 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$ - one C_q not observed) δ (ppm): 136.0, 133.7, 133.3, 132.8, 132.7, 131.0, 128.9, 128.8, 128.7, 128.4, 128.2, 127.7, 127.3, 126.7 (q, *J* = 279.0 Hz), 126.5, 126.5, 51.4 (q, *J* = 27.0 Hz), 21.4, 19.7. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.6 (d, *J* = 9.8 Hz, 3F). **HRMS** (CI): *m/z* for $C_{20}H_{17}F_3$ [M^+]: calculated 314.1282; found 314.1276 (ppm –1.9).



2-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-1,4-dimethylbenzene (9l) was prepared according to *General Procedure B* from 1-(4-bromophenyl)-2,2,2-trifluoroethanol (0.064 g, 0.25 mmol), *p*-xylene (0.092 mL, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9l** as a colorless liquid. Yield = 0.051 g, 59%. R_f = 0.58 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.46-7.44 (m, 2H), 7.27 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.08-7.03 (m, 2H), 4.82 (q, *J* = 9.8 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 136.1, 134.2, 133.5, 133.2, 131.9, 131.3, 131.1, 128.9, 128.5, 126.3 (q, *J* = 280.7 Hz), 122.2, 50.8 (q, *J* = 27.5 Hz), 21.4, 19.6. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –63.9 (d, *J* = 9.9 Hz, 3F). **HRMS** (CI): *m/z* for $C_{16}H_{14}F_3{}^{79}Br$ ([M+H]$^+$): calculated 342.0231; found 342.0224 (–2.0 ppm).

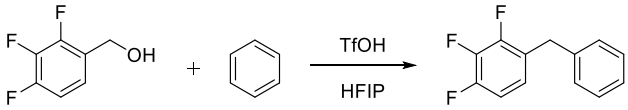


1,4-Dimethyl-2-(2,2,2-trifluoro-1-(2-fluorophenyl)ethyl)benzene (9m) was prepared according to *General Procedure B* from 2,2,2-trifluoro-1-(2-fluorophenyl)ethanol (0.049 g, 0.25 mmol), *p*-xylene (0.092 mL, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9m** as a colorless liquid. Yield = 0.0090 g, 13%. R_f = 0.63 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.45 (t, *J* = 7.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.08-7.02 (m, 3H), 5.30 (q, *J* = 9.8 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 160.9 (d, *J* = 247.6 Hz), 135.8, 134.0, 132.8, 130.9, 130.1, 129.7 (d, *J* = 8.6 Hz), 128.9 (2C), 126.4 (q, *J* = 280.6 Hz), 124.5 (d, *J* = 3.4 Hz), 122.9 (d, *J* = 13.6 Hz), 115.6 (d, *J* = 22.5 Hz), 43.2 (qd, *J* = 28.4, 3.6 Hz), 21.4, 19.3. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –64.2 (d, *J* = 3.4 Hz, 3F), –115.8 (q, *J* = 3.0 Hz, 1F). **HRMS** (CI): *m/z* for $C_{16}H_{15}F_4$ ($[M+H]^+$): calculated 283.1104; found 283.1110 (–2.1 ppm).

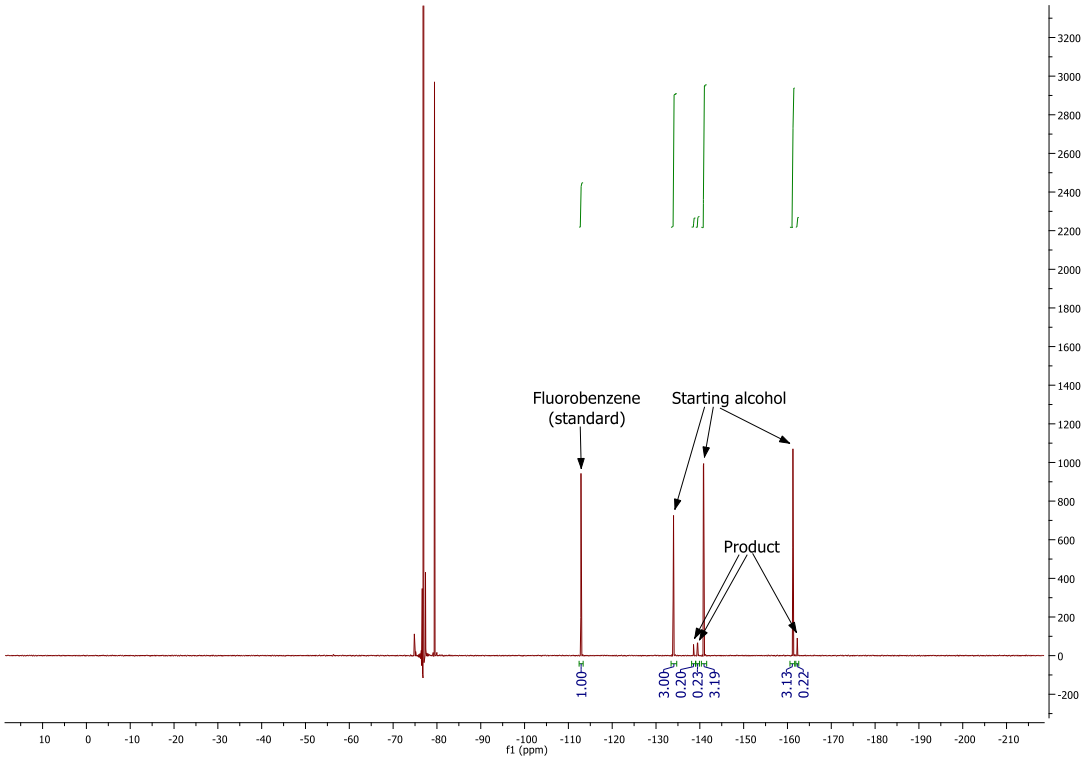


2-(1-(4-Chlorophenyl)-2,2,2-trifluoroethyl)-1,4-dimethylbenzene (9n) was prepared according to *General Procedure B* from 1-(4-chlorophenyl)-2,2,2-trifluoroethanol (0.053 g, 0.25 mmol), *p*-xylene (0.092 mL, 0.75 mmol) and TfOH (4.4 µL, 20 mol%). Purification by flash column chromatography over silica (100% petroleum ether) gave **9n** as a colorless liquid. Yield = 0.041 g, 59%. R_f = 0.87 (100% petroleum ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.32 (m, 3H), 7.29-7.27 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.89 (q, *J* = 9.9 Hz, 1H), 2.39 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 136.1, 134.0, 133.7, 133.5, 133.3, 131.1, 131.0, 128.9 (2C), 128.5, 126.4 (q, *J* = 280.7 Hz), 50.7 (q, *J* = 27.5 Hz), 21.4, 19.6. **^{19}F NMR** (376.5 MHz, $CDCl_3$; CF_3CO_2H - ext. std.) δ (ppm): –64.0 (d, *J* = 9.8 Hz, 3F). **HRMS** (CI): *m/z* for $C_{16}H_{14}F_3{}^{35}Cl$ ($[M+H]^+$): calculated 298.0736; found 298.0736 (0.0 ppm).

5. Kinetic Experiments



Representative ^{19}F NMR spectrum for data analysis

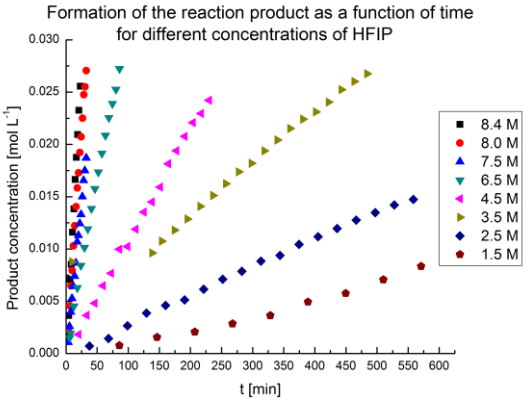


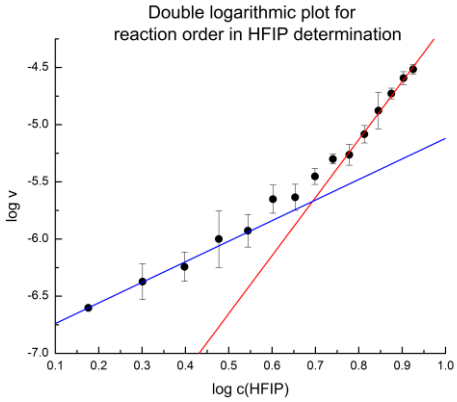
Reaction order in HFIP

Approximately 0.125 mmol (1 equiv) of 2,3,4-trifluorobenzyl alcohol was weighed in an NMR tube, and benzene (5 equiv) and pentane (HPLC grade) were added. Pentane was added as an inert co-solvent to maintain a constant volume. A sealed capillary filled with C_6D_6 and fluorobenzene was placed in the NMR tube and a solution of TfOH in HFIP was added, such that the concentration of starting benzylic alcohol equals 0.250 mol L^{-1}. The NMR tube was immediatelly introduced into the NMR spectrometer, and the reaction progress was followed by ^{19}F NMR at ambient temperature. The time after which the first spectrum was acquired varied from experiment to experiment, as well as the time between two subsequent spectrum acquisitions. The concentration of product in a given moment of time was calculated according to the equation:

$$c = c_0 \frac{P_1 + P_2 + P_3}{S_1 + S_2 + S_3 + P_1 + P_2 + P_3}$$

where c_0 is the initial concentration of 2,3,4-benzylic alcohol, S_1, S_2 and S_3 are the intensities of the peaks in the ^{19}F NMR spectrum corresponding to the unreacted starting alcohol, and P_1, P_2 and P_3 are the intensities of the peaks in the ^{19}F NMR spectrum of the reaction product.





The double logarithmic plot shows that the concentration dependence in HFIP changes as a function of concentration. For higher concentrations of HFIP [6.5 mol L^{-1} - 8.4 mol L^{-1} (pure solvent)] the reaction order in HFIP equals:

5.1 ± 0.3,

(R^2 = 0.9903, red line on the double logarithmic plot).

For lower concentrations of HFIP [1.5 mol L^{-1} - 3.5 mol L^{-1}] the reaction order in HFIP is:

1.80 ± 0.07,

(R^2 = 0.9942, blue line on the double logarithmic plot).

Experimental data:

c_{HFIP} = 8.4 mol L^{-1} (1)	
t [min]	c (product) [mol L^{-1}]
2.8	0.0049
3.6	0.0067
5.7	0.0111
7.8	0.0146
9.9	0.0184
11.9	0.0202
14.0	0.0250
$v_0 = 3.0 \cdot 10^{-5}$ mol L^{-1} s^{-1}	

c_{HFIP} = 8.4 mol L^{-1} (2)	
t [min]	c (product) [mol L^{-1}]
2.8	0.0026
3.5	0.0039
5.5	0.0087
7.6	0.0130
9.6	0.0165
11.7	0.0202
13.8	0.0236
$v_0 = 3.1 \cdot 10^{-5}$ mol L^{-1} s^{-1}	

c_{HFIP} = 8.0 mol L^{-1} (1)	
t [min]	c (product) [mol L^{-1}]
2.4	0.0021
3.2	0.0041
5.3	0.0072
7.4	0.0112
9.4	0.0145
11.5	0.0175
13.6	0.0204
15.6	0.0235
$v_0 = 2.67 \cdot 10^{-5}$ mol L^{-1} s^{-1}	

c_{HFIP} = 8.0 mol L^{-1} (2)	
t [min]	c (product) [mol L^{-1}]
3.1	0.0024
4.3	0.0040
6.3	0.0079
8.4	0.0115
10.5	0.0141
12.5	0.0168
14.6	0.0198
16.7	0.0225
18.7	0.0239
$v_0 = 2.4 \cdot 10^{-5}$ mol L^{-1} s^{-1}	

c_{HFIP} = 7.5 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
6.0	0.0030
8.1	0.0057
10.2	0.0079
12.2	0.0094
14.3	0.0130
16.4	0.0142
18.4	0.0162
20.5	0.0194
22.5	0.0209
24.6	0.0233
26.7	0.0250

$v_0 = 1.75 \cdot 10^{-5}$ mol L^{-1} s^{-1}

c_{HFIP} = 7.5 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
2.4	0.0015
3.1	0.0025
5.2	0.0052
7.3	0.0082
9.3	0.0110
11.4	0.0129
13.4	0.0158
15.5	0.0183
17.6	0.0206
19.6	0.0224
21.7	0.0246

$v_0 = 1.99 \cdot 10^{-5}$ mol L^{-1} s^{-1}

c_{HFIP} = 7.0 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
3.7	0.0006
5.8	0.0022
7.8	0.0031
9.9	0.0050
12.0	0.0064
14.0	0.0074
16.1	0.0086
18.2	0.0099
20.2	0.0109
22.3	0.0120
24.4	0.0132
26.4	0.0144
28.5	0.0155
30.5	0.0167
32.6	0.0176

$v_0 = 9.8 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 7.0 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
5.4	0.0011
7.5	0.0035
9.6	0.0050
11.6	0.0065
13.7	0.0090
15.8	0.0103
17.8	0.0121
19.9	0.0137
22.0	0.0155
24.0	0.0169
26.1	0.0183
28.2	0.0199
30.2	0.0214
32.3	0.0226
34.4	0.0242
36.4	0.0258
38.5	0.0272

$v_0 = 1.30 \cdot 10^{-5}$ mol L^{-1} s^{-1}

c_{HFIP} = 7.0 mol L^{-1} (3)

t [min]	c (product) [mol L^{-1}]
2.5	0.0012
3.3	0.0018
5.4	0.0046
7.4	0.0065
9.5	0.0097
11.6	0.0107
13.6	0.0137
15.7	0.0159
17.7	0.0177
19.8	0.0197
21.9	0.0216
23.9	0.0237
26.0	0.0252

$v_0 = 1.71 \cdot 10^{-5}$ mol L^{-1} s^{-1}

c_{HFIP} = 6.5 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
4.8	0.0022
7.5	0.0031
13.2	0.0061
18.8	0.0092
24.4	0.0115
30.1	0.0141
35.7	0.0164
41.4	0.0187
47.0	0.0209
52.6	0.0228
58.3	0.0249
63.9	0.0269

$v_0 = 7.0 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 6.5 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
5.1	0.0027
5.9	0.0036
9.7	0.0052
13.5	0.0087
17.2	0.0107
21.0	0.0129
24.9	0.0153
28.7	0.0175
32.4	0.0194
36.2	0.0214
40.0	0.0233
43.8	0.0251

$v_0 = 9.5 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 6.0 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
4.9	0.0011
6.3	0.0020
12.0	0.0044
17.6	0.0069
23.2	0.0095
28.9	0.0117
34.5	0.0139
40.1	0.0159
45.8	0.0182
51.4	0.0198
57.0	0.0220
62.7	0.0238
68.3	0.0258

$v_0 = 6.5 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 6.0 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
15.2	0.0031
20.7	0.0042
26.1	0.0060
31.6	0.0081
37.0	0.0095
42.5	0.0106
47.9	0.0126
53.4	0.0128
58.9	0.0154
64.3	0.0166
69.8	0.0178
75.2	0.0180
80.7	0.0204

$v_0 = 4.4 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 6.0 mol L^{-1} (3)

t [min]	c (product) [mol L^{-1}]
6.3	0.0016
10.1	0.0030
13.9	0.0044
17.6	0.0056
21.4	0.0070
25.2	0.0089
29.0	0.0101
32.8	0.0109
36.6	0.0128
40.4	0.0136
44.2	0.0150
48.0	0.0160
51.8	0.0172
55.6	0.0182
59.3	0.0195
63.1	0.0208
66.9	0.0215
70.7	0.0225

$v_0 = 5.5 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 5.5 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
5.3	0.0017
6.6	0.0019
17.2	0.0061
27.8	0.0098
38.5	0.0134
49.1	0.0168
59.7	0.0200
70.4	0.0233
81.0	0.0265

$v_0 = 5.5 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 5.5 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
9.6	0.0020
12.5	0.0027
15.5	0.0038
18.4	0.0049
21.4	0.0055
24.4	0.0064
27.3	0.0071
30.3	0.0080
33.2	0.0089
36.2	0.0098
39.2	0.0102
42.1	0.0109
45.1	0.0116

$v_0 = 4.5 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 5.0 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
7.9	0.0010
9.1	0.0010
19.7	0.0034
30.5	0.0063
41.2	0.0078
51.8	0.0107
62.4	0.0128
73.1	0.0150
83.7	0.0168
94.3	0.0186
105.0	0.0206
115.6	0.0228
126.3	0.0243
136.9	0.0260

$v_0 = 3.3 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 4.5 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
21.1	0.0035
34.2	0.0065
47.3	0.0094
60.5	0.0117
73.6	0.0138
86.7	0.0159
99.9	0.0181
113.0	0.0199
126.1	0.0223
139.3	0.0244
152.4	0.0258

$v_0 = 2.75 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 4.5 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
20.0	0.0018
33.2	0.0037
46.3	0.0048
59.4	0.0065
72.6	0.0077
85.7	0.0100
98.8	0.0102
112.0	0.0119
125.1	0.0135
138.2	0.0145
151.4	0.0159
164.5	0.0181
177.6	0.0194
190.8	0.0208
203.9	0.0221

$v_0 = 1.79 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 5.0 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
16.2	0.0042
26.8	0.0064
37.5	0.0091
48.1	0.0119
58.7	0.0149
69.4	0.0164
80.0	0.0195
90.6	0.0214
101.3	0.0236
111.9	0.0257

$v_0 = 3.8 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 4.5 mol L^{-1} (3)

t [min]	c (product) [mol L^{-1}]
18.5	0.0024
31.7	0.0049
44.8	0.0068
57.9	0.0093
71.1	0.0118
84.2	0.0134
97.3	0.0153
110.5	0.0172
123.6	0.0189
136.7	0.0206
149.9	0.0228
163.0	0.0242
176.1	0.0256

$v_0 = 2.41 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 4.0 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
8.9	0.0008
22.0	0.0025
35.2	0.0045
48.3	0.0061
61.4	0.0074
74.6	0.0092
87.7	0.0112
100.8	0.0127
114.0	0.0141
127.1	0.0154
140.2	0.0169
153.4	0.0184
166.5	0.0197
179.6	0.0210
192.8	0.0224
205.9	0.0238
219.0	0.0248

$v_0 = 1.91 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 4.0 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
25.0	0.0041
40.7	0.0067
56.3	0.0102
72.0	0.0128
87.6	0.0155
103.2	0.0176
118.9	0.0205
134.5	0.0223
150.1	0.0243

$v_0 = 2.56 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 3.5 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
25.4	0.0039
46.1	0.0070
66.7	0.0099
87.3	0.0128
108.0	0.0152
128.6	0.0176
149.2	0.0198
169.9	0.0221
190.5	0.0245

$v_0 = 9.33 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 3.5 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
26.1	0.0025
46.7	0.0045
67.4	0.0065
88.0	0.0088
108.7	0.0106
129.3	0.0124
149.9	0.0146
170.6	0.0162
191.2	0.0176
211.8	0.0195
232.5	0.0212
253.1	0.0226
273.7	0.0242

$v_0 = 1.43 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 3.0 mol L^{-1} (1)

t [min]	c (product) [mol L^{-1}]
38.0	0.0024
68.6	0.0048
99.2	0.0067
129.9	0.0086
160.5	0.0107
191.1	0.0124
221.8	0.0141
252.4	0.0159
283.0	0.0176
313.7	0.0189
344.3	0.0204
374.9	0.0219
405.6	0.0236
436.2	0.0252

$v_0 = 9.3 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 3.0 mol L^{-1} (2)

t [min]	c (product) [mol L^{-1}]
36.0	0.0036
66.6	0.0071
97.3	0.0102
127.9	0.0132
158.6	0.0156
189.2	0.0183
219.8	0.0208
250.5	0.0232
281.1	0.0254

$v_0 = 1.44 \cdot 10^{-6}$ mol L^{-1} s^{-1}

c_{HFIP} = 3.0 mol L^{-1} (3)

t [min]	c (product) [mol L^{-1}]
37.1	0.0012
67.8	0.0021
98.4	0.0036
129.0	0.0051
159.7	0.0061
190.3	0.0071
220.9	0.0081
251.6	0.0094
282.2	0.0101

$v_0 = 6.2 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 2.5 mol L^{-1} (1)

t [min]	*c* (product) [mol L^{-1}]
37.6	0.0007
68.2	0.0014
98.9	0.0027
129.5	0.0039
160.1	0.0046
190.8	0.0051
221.4	0.0062
252.0	0.0071
282.7	0.0079
313.3	0.0088
343.9	0.0094
374.6	0.0104
405.2	0.0112
435.9	0.0120
466.5	0.0128
497.1	0.0135
527.8	0.0142
558.4	0.0147
589.0	0.0158
619.7	0.0163
650.3	0.0173
680.9	0.0179
711.6	0.0188
742.2	0.0192

$v_0 = 4.36 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 2.5 mol L^{-1} (2)

t [min]	*c* (product) [mol L^{-1}]
97.2	0.0045
127.8	0.0061
158.5	0.0072
189.1	0.0081
219.7	0.0089
250.4	0.0102
281.0	0.0110
311.6	0.0121
342.3	0.0130
372.9	0.0138
403.5	0.0149
434.2	0.0162
464.8	0.0171
495.5	0.0179
526.1	0.0190
556.7	0.0198
587.4	0.0206
618.0	0.0222
648.6	0.0241

$v_0 = 5.65 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 2.5 mol L^{-1} (3)

t [min]	*c* (product) [mol L^{-1}]
40.1	0.0016
70.8	0.0032
101.4	0.0043
132.1	0.0064
162.7	0.0074
193.3	0.0095
224.0	0.0108
254.6	0.0122
285.2	0.0135
315.9	0.0146
346.5	0.0163
377.1	0.0171
407.8	0.0189
438.4	0.0199
469.0	0.0211
499.7	0.0224
530.3	0.0230
560.9	0.0243
591.6	0.0260
622.2	0.0265
652.8	0.0280

$v_0 = 7.1 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 1.5 mol L^{-1}

t [min]	*c* (product) [mol L^{-1}]
85.7	0.0008
146.4	0.0016
207.0	0.0021
267.6	0.0029
328.3	0.0036
388.9	0.0049
449.6	0.0058
510.2	0.0071
570.8	0.0084
631.5	0.0092
692.1	0.0102
752.7	0.0113
813.4	0.0122
1174.8	0.0171
1442.0	0.0199

$v_0 = 2.50 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 2.0 mol L^{-1} (1)

t [min]	*c* (product) [mol L^{-1}]
127.7	0.0037
188.3	0.0049
249.0	0.0066
309.7	0.0084
370.3	0.0096
430.9	0.0119
491.6	0.0133
552.2	0.0154
612.8	0.0166
673.5	0.0181
836.9	0.0258

$v_0 = 4.5 \cdot 10^{-7}$ mol L^{-1} s^{-1}

c_{HFIP} = 2.0 mol L^{-1} (2)

t [min]	*c* (product) [mol L^{-1}]
65.9	0.0026
126.6	0.0037
187.2	0.0048
247.8	0.0059
308.5	0.0072
369.1	0.0083
429.7	0.0097
490.4	0.0108
551.0	0.0125
611.6	0.0149
672.3	0.0178

$v_0 = 3.5 \cdot 10^{-7}$ mol L^{-1} s^{-1}

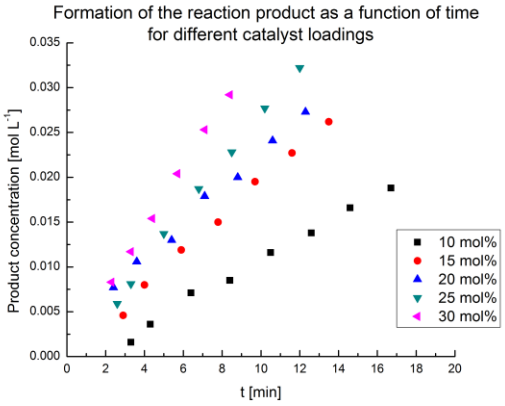
c_{HFIP} = 2.0 mol L^{-1} (3)

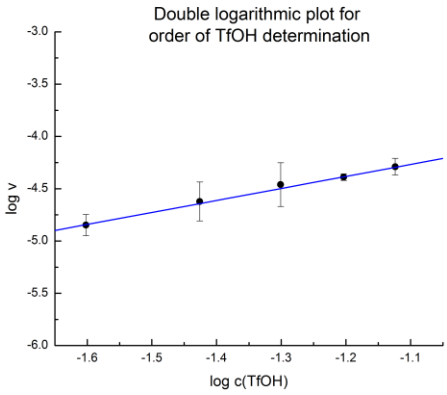
t [min]	*c* (product) [mol L^{-1}]
66.0	0.0018
126.7	0.0033
187.3	0.0049
247.9	0.0075
308.6	0.0091
369.2	0.0105
429.8	0.0121
490.5	0.0137
551.1	0.0157
611.7	0.0169
672.4	0.0187

$v_0 = 4.7 \cdot 10^{-7}$ mol L^{-1} s^{-1}

Reaction order in TfOH

Approximately 0.125 mmol (1 equiv) of 2,3,4-trifluorobenzyl alcohol was weighed in an NMR tube, and benzene (5 equiv) was added. A sealed capillary filled with C_6D_6 and fluorobenzene was then placed in the NMR tube and a solution of TfOH in HFIP was added, such that the total volume of the solution equals 0.5 mL, i. e. that the concentration of starting benzylic alcohol equals 0.250 mol L^{-1}. The NMR tube was immediately introduced into the NMR spectrometer, and the reaction progress was followed by ^{19}F NMR at ambient temperature. The time after which the first spectrum was acquired varied from experiment to experiment, as well as the time between two subsequent spectrum acquisitions. The concentration of product in a given moment of time was calculated according to the same equation used for the calculation of the order in HFIP. The reported values are average values of two or three experiments.





The calculated reaction order in catalyst (TfOH) is:

1.15 ± 0.04,

(R^2 = 0.9966, blue line on the double logarithmic plot).

Experimental data:

10 mol% TfOH (1)

t [min]	*c* (product) [mol L^{-1}]
3.4	0.0030
4.1	0.0041
6.2	0.0069
8.3	0.0091
10.3	0.0107
12.4	0.0128
14.0	0.0150
16.5	0.0171
18.6	0.0193
20.7	0.0209
22.7	0.0233
24.8	0.0248
26.9	0.0264

$v_0 = 1.66 \cdot 10^{-5}$ mol L^{-1} s^{-1}

10 mol% TfOH (2)

t [min]	*c* (product) [mol L^{-1}]
4.8	0.0037
7.2	0.0058
9.6	0.0080
12.0	0.0101
14.4	0.0135
16.8	0.0138
19.2	0.0166
21.6	0.0183
24.0	0.0195
26.4	0.0216
28.8	0.0237
31.2	0.0257

$v_0 = 1.37 \cdot 10^{-5}$ mol L^{-1} s^{-1}

10 mol% TfOH (3)

t [min]	*c* (product) [mol L^{-1}]
3.8	0.0008
5.9	0.0021
8.0	0.0039
10.0	0.0060
12.1	0.0074
14.1	0.0090
16.2	0.0110
18.3	0.0123
22.4	0.0155
26.5	0.0181
28.6	0.0194
30.7	0.0204
32.7	0.0219

$v_0 = 1.23 \cdot 10^{-5}$ mol L^{-1} s^{-1}

15 mol% TfOH (1)

t [min]	*c* (product) [mol L^{-1}]
2.9	0.0046
4.0	0.0080
5.9	0.0119
7.8	0.0150
9.7	0.0195
11.6	0.0227
13.5	0.0262

$v_0 = 3.31 \cdot 10^{-5}$ mol L^{-1} s^{-1}

15 mol% TfOH (2)

t [min]	*c* (product) [mol L^{-1}]
2.6	0.0035
3.6	0.0048
5.6	0.0074
7.5	0.0098
9.4	0.0122
11.3	0.0147
13.2	0.0169
15.1	0.0191
17.0	0.0212
18.9	0.0231
20.8	0.0255

$v_0 = 2.01 \cdot 10^{-5}$ mol L^{-1} s^{-1}

15 mol% TfOH (3)

t [min]	*c* (product) [mol L^{-1}]
2.4	0.0019
4.1	0.0042
6.0	0.0064
7.9	0.0087
9.8	0.0110
11.7	0.0135
13.6	0.0154
15.5	0.0176
17.4	0.0194
19.3	0.0213
21.2	0.0231
23.1	0.0250

$v_0 = 1.86 \cdot 10^{-5}$ mol L^{-1} s^{-1}

20 mol% TfOH (1)

t [min]	*c* (product) [mol L^{-1}]
2.4	0.0077
3.6	0.0106
5.4	0.0130
7.1	0.0179
8.8	0.0200
10.6	0.0241
12.3	0.0273

$v_0 = 3.26 \cdot 10^{-5}$ mol L^{-1} s^{-1}

20 mol% TfOH (2)

t [min]	*c* (product) [mol L^{-1}]
3.0	0.0066
4.0	0.0087
5.7	0.0149
7.5	0.0196
9.2	0.0245

$v_0 = 4.95 \cdot 10^{-5}$ mol L^{-1} s^{-1}

20 mol% TfOH (3)

t [min]	*c* (product) [mol L^{-1}]
3.0	0.0014
4.0	0.0034
5.9	0.0057
7.8	0.0098
9.8	0.0104
11.7	0.0136
13.6	0.0165
15.5	0.0186
17.4	0.0211
19.3	0.0226
21.2	0.0256

$v_0 = 2.17 \cdot 10^{-5}$ mol L^{-1} s^{-1}

25 mol% TfOH (1)

t [min]	*c* (product) [mol L^{-1}]
2.6	0.0059
3.3	0.0081
5.0	0.0137
6.8	0.0187
8.5	0.0228
10.2	0.0277
12.0	0.0322
13.7	0.0353

$v_0 = 4.25 \cdot 10^{-5}$ mol L^{-1} s^{-1}

25 mol% TfOH (2)

t [min]	*c* (product) [mol L^{-1}]
2.6	0.0046
3.9	0.0086
5.6	0.0127
7.3	0.0170
9.1	0.0204
10.8	0.0240

$v_0 = 3.90 \cdot 10^{-5}$ mol L^{-1} s^{-1}

30 mol% TfOH (1)

t [min]	*c* (product) [mol L^{-1}]
2.9	0.0076
4.6	0.0108
5.9	0.0135
7.3	0.0190
8.6	0.0225
10.0	0.0256

$v_0 = 4.50 \cdot 10^{-5}$ mol L^{-1} s^{-1}

30 mol% TfOH (2)

t [min]	*c* (product) [mol L^{-1}]
2.3	0.0083
3.3	0.0117
4.4	0.0154
5.7	0.0204
7.1	0.0253
8.4	0.0292

$v_0 = 5.76 \cdot 10^{-5}$ mol L^{-1} s^{-1}

EXPERIMENTAL SECTION – CHAPTER 3
PROPARGYLIC ALCOHOLS AS VERSATILE SUBSTRATES IN FRIEDEL-CRAFTS REACTIONS

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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 400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard ($CDCl_3$ at 7.26 ppm). **^{13}C-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 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.

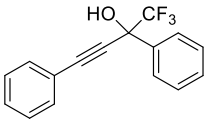
GC/MS analysis was conducted on a GC System 7820A (G4320) connected to a MSD block 5977E (G7036A) using Agilent High Resolution Gas Chromatography Column HP-5MS UI, 30 m×0.250 mm×0.25 µm.

High resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and CI) and MicroTOF-Q Bruker (ESI).

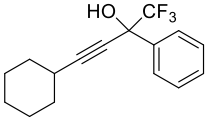
Materials: All commercial materials were purchased from Sigma-Aldrich, Alfa Aesar and FluoroChem, and were used as received, without further purification.

2. Preparation of tertiary propargylic alcohols

***General procedure C for tertiary propargylic alcohols synthesis*:** Trifluoromethyl phenyl ketone (5-10 mmol, 1 equiv) and phenyl acetylene (1.5 equiv) were diluted in 10-15 mL DMSO. CuI (0.1 equiv) and K_2CO_3 (0.2 equiv) were added and the reaction mixture was heated at 50-70 ^oC for 24 h. The reaction mixture was then treated with brine, extracted with DCM, dried with anhidrous sodium sulfate and concentrated at reduced pressure. The product was then purified by silica gel column chromatography.

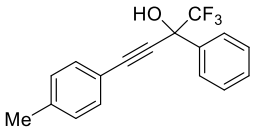


1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. Spectral data are in agreement with the literature[219]. Yield = 85%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.86–7.79 (m, 2H), 7.57–7.52 (m, 2H), 7.48–7.42 (m, 3H), 7.42–7.32 (m, 3H), 3.10 (s, 1H).

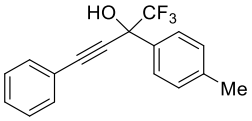


4-cyclohexyl-1,1,1-trifluoro-2-phenylbut-3yn-2-ol was prepared according to *General procedure C* and isolated as yellow oil. Yield = 44%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.82-7.68 (m, 2H), 7.43-7.39 (m, 3H), 2.92 (s, 1H), 2.54 (sept. *J* = 4 Hz, 1H), 2.13-2.00 (m, 1H), 1.91-1.80 (m, 1H), 1.80-1.65 (m, 3H), 1.65-1.46 (m, 3H), 1.45-1.29 (m, 2H).

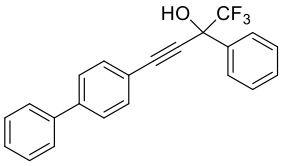
[219] Geri J. B., Wade Wolfe M. M., Szymczak N. K. *Angew. Chem. Int. Ed.* **2018**, 57, 1381-1385



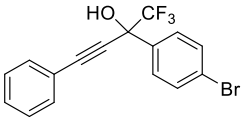
1,1,1-trifluoro-2-phenyl-4-(*p*-toluyl)but-3-yn-2-ol was prepared according to *General procedure C* and isolated as a pale yellow oil. Spectral data are in agreement with the literature[220] Yield = 85%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.82 (m, 2H), 7.52–7.36 (m, 5H), 7.17 (d, *J* = 7.8 Hz, 2H), 3.08 (s, 1H), 2.38 (s, 3H).



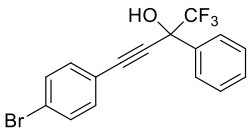
1,1,1-trifluoro-4-phenyl-2-(*p*-toluyl)but-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. Yield = 31%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 8.1 Hz, 2H), 7.48–7.43 (m, 2H), 7.35–7.25 (m, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 2.98 (s, 1H), 2.32 (s, 3H).



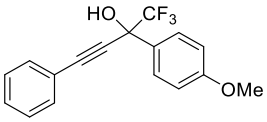
4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as yellow solid. Yield = 67%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.86-7.80 (m, 2H), 7.63-7.57 (m, 6H), 7.48 (m, 1H), 7.46 (m, 2H), 7.44 (d, *J* = 2.2 Hz, 2H), 7.41-7.36 (m, 1H), 3.09 (s, 1H).



4-(4-bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. With spectral data in agreement with the literature[13]. Yield = 90 %. R_f = 0.43 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.62 (d, *J* = 8.5 Hz, 2H), 7.53-7.43 (m, 4H), 7.38-7.27 (m, 3H), 3.09 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 134.5, 132.2, 131.6, 129.9, 129.1, 128.6, 124.0, 123.3 (q, *J* = 284.0 Hz), 120.8, 88.6, 84.0, 72.2 (q, *J* = 31.0 Hz).



4-(4-bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. With spectral data in agreement with the literature[13]. Yield = 52 %. 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). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 135.2, 133.6, 132.0, 129.8, 128.5, 127.3, 124.2, 123.3 (q, *J* = 32.2 Hz), 120.6, 87.08, 85.7, 73.2 (q, *J* = 32.5 Hz).



1,1,1-trifluoro-2-(4-methoxyphenyl)-4-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as pale yellow solid. Yield = 64%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.81 (d, *J* = 3.8 Hz, 2H), 7.50-7.40 (m, 5H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.08 (s, 1H).

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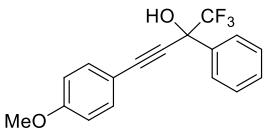
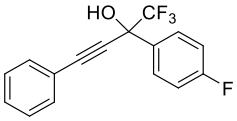
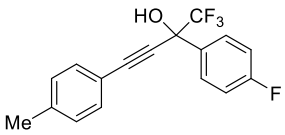


1,1,1-trifluoro-2-(4-methoxy-phenyl)-4-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. Yield = 91 %. R_f = 0.36 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.73 (d, *J* = 8.8 Hz, 2H), 7.56-7.51 (m, 2H), 7.45-7.33 (m, 3H), 6.93-6.10 (m, 2H), 3.84 (s, 3H), 3.10 (s, 1H). **^{13}C NMR (100 MHz, CDCl3)** δ (ppm) 160.3, 131.8, 129.3, 128.4, 128.3, 127.2, 123.3 (q, *J* = 283.6 Hz), 120.9, 133.4, 87.8, 84.4, 55.2, 73.0 (q, *J* = 14.3 Hz). **^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.)**: δ (ppm) -84.5 (s, 3F).



1,1,1-trifluoro-2-(4-fluorophenyl)-4-phenylbut-3-yn-2-ol was prepared according to *General procedure C* and isolated as a yellow oil. With spectral data in agreement with the literature[13]. Yield = 95 %. R_f = 0.40 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 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) **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 167.8 (d, *J* = 247.3 Hz), 132.1, 131.1 (d, *J* = 3.1 Hz) 129.6, 129.3 (q, *J* = 8.5 Hz), 128.5, 123.3 (q, *J* = 283.6 Hz), 120.8, 115.2 (d, *J* = 21.3 Hz) 88.2, 84.1, 72.9 (q, *J* = 32.2 Hz).

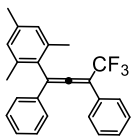


1,1,1-trifluoro-2-(4-fluorophenyl)-4-(*p*-toluyl)but-3-yn-2-ol was prepared according to *General procedure C* and isolated in 74% yield. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.80 (dd, *J* = 8.5 Hz, 5.3 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.11 (t, 8.6 Hz, 2H), 3.11 (s, 1H), 2.38 (s, 3H).

3. Characterization data for allenes

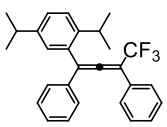
General procedure D: Experiments were conducted in sealed reaction tubes with (10 mol%) of catalyst and (2.5 mmol, 0.5 M) of propargylic alcohol in HFIP and 5 equivalent of nucleophile at room temperature during 5 min. Yields are obtained after silica gel chromatography.

General procedure E: Experiments were conducted in sealed reaction tubes with (10 mol%) of catalyst and (2.5 mmol, 1 M) of propargylic alcohol in HFIP and 3 equivalent of nucleophile at 80°C during 5 min. Yields are obtained after silica gel chromatography.

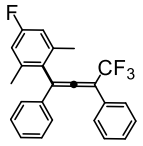


1-mesityl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11a) was prepared according to *General Procedure D* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (100.4 mg, 0.363 mmol) and mesitylene (253 µL, 1.817 mmol, 5 equiv.) with 5.9 mg (0.036 mmol) of $FeCl_3$, in 0.73 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 128.0 mg (93% yield) of white solid. R_f = 0.83 (petroleum ether/EtOAc

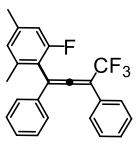
9:1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 7.49 (d, *J* = 7.5 Hz, 2H), 7.43–7.12 (m, 8H), 6.94 (s, 2H), 2.32 (s, 3H), 2.17 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 205.1 (q, *J* = 3.5 Hz), 138.1, 137.1, 133.3, 130.2, 129.9, 129.2, 128.9, 128.7, 128.6, 128.5, 127.6, 126.7, 123.7 (q, *J* = 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** ($APPI^+$): *m/z* for $C_{25}H_{21}F_3$ (M^+): calculated 378.1590; found 378.1596 (1.5 ppm).



1-(2,5-diisopropylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11b) was prepared according to <u>*General Procedure D*</u> from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (103.9 mg, 0.376 mmol) and diizopropyl benzene (356 µL, 1.881 mmol, 5 equiv.) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 0.75 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 103.4 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 NMR (100 MHz, $CDCl_3$):** δ (ppm) 205.5 (q, *J* = 3.6 Hz), 146.7, 145.1, 134.7, 132.1, 132.1, 130.1, 128.9, 128.6, 128.5, 128.3, 128.3, 128.2, 128.2, 126.5, 123.6 (q, *J* = 273.6 Hz), 116.5, 103.9 (q, *J* = 34.1 Hz), 33.7, 30.4, 27.2, 24.4, 24.1, 24.1. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.):** δ (ppm) –58.7 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{28}H_{27}F_3$ (M^+): calculated 420.2059; found 420.2062 (0.7 ppm).

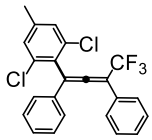


1-(2-(5-fluoro-*m*-xylenyl))-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11c) was prepared according to modified <u>*General Procedure D*</u> from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (103.8 mg, 0.376 mmol) and 5-fluoro-*m*-xylene (142 µL, 1.127 mmol, 3 equiv.) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 1.50 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 36.5 mg (25% yield) of colorless oil. R_f = 0,84 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) δ (ppm) 7.48 (d, *J* = 7.4 Hz, 2H), 7.40–7.29 (m, 6H), 7.25–7.20 (m, 2H), 7.13 (s, 2H), 2.18 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) 205.1 (q, *J* = 3.9 Hz), 163.7, 161.2, 132.9, 129.9, 129.3, 129.0, 128.8, 128.7, 127.6, 126.6, 123.6 (q, *J* = 275.2 Hz), 114.7, 114.5, 113.5, 104.3 (q, *J* = 34.6 Hz), 29.7, 20.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.):** δ (ppm) –58.1 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{24}H_{18}F_4$ (M^+): calculated 382.1339; found 382.1348 (2.4 ppm).

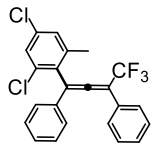


1-(6-(5-fluoro-*m*-xylenyl))-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene was prepared according to modified <u>*General Procedure D*</u> from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (103.8 mg, 0.376 mmol) and 5-fluoro-*m*-xylene (142 µL, 1.127 mmol, 3 equiv.) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 1.50 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica

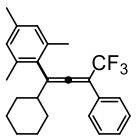
(with petroleum ether) gave 40.5 mg (28% yield) of colorless oil. R_f = 0.84 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.48 (d, *J* = 7.5 Hz, 2H), 7.41–7.29 (m, 6H), 7.25–7.20 (m, 2H), 6.84 (d, *J* = 9.4 Hz, 2H), 2.20 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 205.0 (q, *J* = 3.9 Hz), 163.5, 161.1, 132.8, 129.8, 129.2, 128.8, 128.7, 128.6, 127.5, 126.4, 123.5 (q, *J* = 275.2 Hz), 114.6, 114.4, 113.4, 104.2 (q, *J* = 34.6 Hz), 20.4. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –57.1 (s, 3F), –111.8 (s, 1F). **HRMS** (APPI$^+$): *m/z* for $C_{24}H_{18}F_4$ (M^+): calculated 382.1339; found 382.1339 (0.0 ppm).



(1-(2,6-dichloro-4-methylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11e) was prepared according to modified <u>*General Procedure D*</u> from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (108.2 mg, 0.392 mmol) and 3,5-dichlorotoluen (189.5 mg, 1.175 mmol, 3 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 during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 30.8 mg (23% yield) of white solid. R_f = (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.55 (d, *J* = 7.5 Hz, 2H), 7.41–7.30 (m, 7H), 7.24–7.19 (m, 3H), 2.26 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 204.9 (q, *J* = 5.1 Hz), 141.1, 135.3, 134.7, 132.1, 131.0, 129.3, 129.1, 129.0, 128.9, 127.7, 127.3, 126.5, 123.5 (q, *J* = 275.3 Hz), 112.8, 106.6 (q, *J* = 34.2 Hz), 20.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –58.1 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{23}H_{15}Cl_2F_3$ (M^+): calculated 418.0497; found 418.0500 (0.7 ppm).

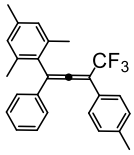


(1-(2,4-dichloro-5-methylphenyl)-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11e') was prepared according to modified <u>*General Procedure D*</u> from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (108.2 mg, 0.392 mmol) and 3,5-dichlorotoluen (189.5 mg, 1.175 mmol, 3 equiv.) with 6.4 mg (0.039 mmol) of $FeCl_3$, in 1.57 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 16.8 mg (10% yield) of white solid. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.60 (s, 2H), 7.58 (s, 2H), 7.25–7.22 (m, 6H), 2.37 (s, 3H). ^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.): δ (ppm) –56.8 (s, 3F). HRMS (APPI$^+$): *m/z* for $C_{23}H_{15}Cl_2F_3$ (M^+): calculated 418.0497; found 418.0500 (0.7 ppm).

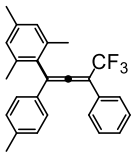


1-cyclohexyl-1-mesityl-3-phenyl-4,4,4-trifluoro-1,2-butadiene (11f) was prepared according to <u>*General Procedure D*</u> from 4-cyclohexyl-1,1,1-trifluoro-2-phenylbut-3yn-2-ol (48.5 mg, 0.17 mmol) and mesitylene (69.8 µL, 0.5 mmol, 3 equiv) with 2.7 mg (0.017 mmol) of $FeCl_3$, in 0.33 mL of HFIP. The reaction mixture was stirred at 50 °C during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 32.7 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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 201.5 (q, *J* = 4.0 Hz), 137.2, 131.9, 130.9, 128.7, 128.0, 127.3, 127.3, 124.1 (q,

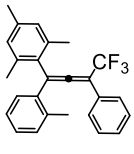
J = 272.7 Hz), 118.1, 102.2 (q, *J* = 33.8 Hz), 43.4, 32.1, 31.9, 26.7, 26.7, 26.2, 21.1. **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ (ppm) –58.1 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{25}H_{27}F_3$ (M^+): calculated 384.2059; found 384.2059 (–0.1 ppm).



1-mesityl-1-phenyl-3-toluyl-4,4,4-trifluoro-1,2-butadiene (11g) was prepared according to *General Procedure D* from 1,1,1-trifluoro-4-phenyl-2-(*p*-tolulyl)but-3-yn-2-ol (100.4 mg, 0.346 mmol) and mesitylene (241 µL, 1.729 mmol, 5 equiv.) with 3.5 mg (0.056 mmol) of $FeCl_3$, in 0.69 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 121.9 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 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) –57.1 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{26}H_{23}F_3$ (M^+): calculated 392.1746; found 392.1744 (–0.6 ppm).

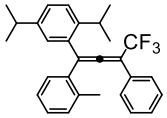


1-mesityl-4,4,4-trifluoro-1-(*p*-toluyl)-3-phenyl-1,2-butadiene (11h) was prepared according to *General Procedure D* from 1,1,1-trifluoro-2-phenyl-4-(*p*-tolulyl)but-3-yn-2-ol (84.9 mg, 0.29 mmol) and mesitylene (117 µL, 0.84 mmol, 5 equiv) with 4.6 mg (0.028 mmol) of $FeCl_3$, in 0.57 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 84.2 mg (74% yield) of the product. **^{1}H 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 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** ($APPI^+$): *m/z* for $C_{26}H_{23}F_3$ (M^+): calculated 392.1746; found 392.1750 (1.0 ppm).

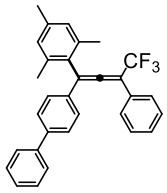


1-mesityl-3-phenyl-3-(2-toluyl)-4,4,4-trifluoro-1,2-butadiene (11i) was prepared according to *General Procedure D* from 1,1,1-trifluoro-4-phenyl-2-(*o*-tolulyl)but-3-yn-2-ol (90.9 mg, 0.313 mmol) and mesitylene (188 µL, 1.565 mmol, 5 equiv.) with 5.1 mg (0.031 mmol) of $FeCl_3$, in 0.63 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 118.1 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 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, $CDCl_3$,**

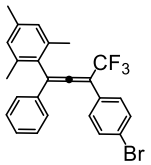
CF_3COOH-ext. st.): δ (ppm) –58.2 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{26}H_{23}F_3$ (M^+): calculated 392.1746; found 392.1747 (0.2 ppm).



1-(2,5-diisopropylphenyl)-3-phenyl-3-(2-toluyl)-4,4,4-trifluoro-1,2-butadiene (11j) was prepared according to modified *General Procedure D* from 1,1,1-trifluoro-4-phenyl-2-(*o*-tolulyl)but-3-yn-2-ol (62.6 mg, 0.216 mmol) and diisopropylbenzene (123 µL, 0.647 mmol, 3 equiv.) with 3.5 mg (0.022 mmol) of $FeCl_3$, in 0.86 mL of HFIP. The reaction mixture was stirred at room temperature during 3 h. Purification by flash column chromatography over silica (with petroleum ether) gave 62.6 mg (58% yield) of colorless oil. R_f = 0.84 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.49 (d, *J* = 7.7 Hz, 2H), 7.41–7.09 (m, 10H), 7.03 (d, *J* = 7.7 Hz, 2H), 3.06–2.95 (m, 1H), 2.93–2.80 (m, *J* = 6.8 Hz, 1H), 1.55 (s, 3H), 1.30–1.16 (m, 6H), 1.09–0.96 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 205.7 (q, *J* = 3.6 Hz), 146.6, 144.8, 137.0, 134.7, 134.0, 132.3, 131.3, 130.6, 129.7, 129.5, 128.9, 128.8, 128.3, 128.3, 128.2, 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, 24.4, 24.2, 24.1, 21.5, 20.8. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –57.7 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{29}H_{29}F_3$ (M^+): calculated 434.2216; found 434.2226 (2.3 ppm).

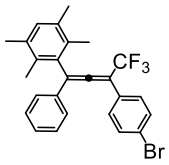


1-mesityl-1-(1,1'-biphenyl-4-yl)-4,4,4-trifluoro-3-phenyl-1,2-butadiene (11k) was prepared according to *General Procedure D* from 4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (58.7 mg, 0.17 mmol) and mesitylene (71.3 µL, 0.51 mmol, 3 equiv.) with 2.7 mg (0.017 mmol) of $FeCl_3$, in 0.34 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 31.1 mg (40% yield) of the product with 95% purity (the rest is the corresponding indene that started to form quickly). **^{1}H 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 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** ($APPI^+$): *m/z* for $C_{31}H_{25}F_3$ (M^+): calculated 454.1903; found 454.1903 (0.1 ppm).

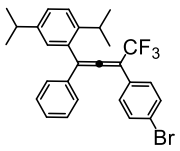


3-(4-bromophenyl)-1-mesityl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11l) was prepared according to *General Procedure D* from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (100.2 mg, 0.286 mmol) and mesitylene (199 µL, 1.430 mmol, 5 equiv.) with 4.3 mg (0.029 mmol) of $FeCl_3$, in 0.57 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 117.8 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 NMR**

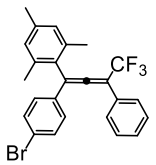
(100 MHz, $CDCl_3$): δ (ppm) 205.0 (q, *J* = 3.8 Hz), 138.2, 137.0, 132.9, 132.1, 129.6, 129.3, 129.2, 129.2, 128.8, 127.1, 126.7, 123.5 (q, *J* = 275.0 Hz), 122.7, 114.6, 103.2 (q, *J* = 34.6 Hz), 21.2, 20.4. **^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.)**: δ (ppm) –62.5 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{25}H_{20}{}^{79}BrF_3$ (M^+): calculated 456.0695; found 456.0699 (0.9 ppm).



3-(4-bromophenyl)-1-durenyl-1,3-diphenyl-4,4,4-trifluoro-1,2-butadiene (11m) was prepared according to modified <u>*General Procedure D*</u> 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (100.7 mg, 0.284 mmol) and durene (114.2 mg, 0.851 mmol, 3 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 during 3 h. Purification by flash column chromatography over silica (with petroleum ether) gave 124.7 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 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** ($APPI^+$): *m/z* for $C_{26}H_{22}{}^{79}BrF_3$ (M^+): calculated 470.0851; found 470.0862 (2.3 ppm).

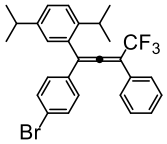


1-(4-bromophenyl)-1-(2,5-diisopropylphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene (11n) was prepared according to <u>*General Procedure D*</u> from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (10.2 mg, 0.282 mmol) and diisopropylbenzene (267 µL, 01.411 mmol, 5 equiv.) with 4.5 mg (0.0282 mmol) of FeCl3, in 0.56 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether) gave 55.6 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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 205.4 (q, *J* = 4.2 Hz), 146.8, 145.0, 134.3, 132.1, 131.9, 129.0, 128.8, 128.7, 128.2, 127.5, 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, 23.9, 23.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –58.8 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{28}H_{26}{}^{79}BrF_3$ (M^+): calculated 498.1165; found 498.1168 (0.6 ppm).

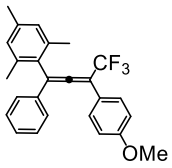


1-(4-bromophenyl)-1-mesityl-3-phenyl-4,4,4-trifluoro-1,2-butadiene (**11o**) was was prepared according to <u>*General Procedure D*</u> and isolated as a white solid. Yield = 81%. R_f = 0.79 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.52-7.41 (m, 4H), 7.41-7.29 (m, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.95 (s, 2H), 2.32 (s, 3H), 2.15 (s, 6H). **^{13}C 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

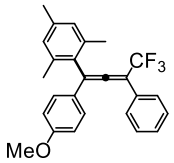
Hz), 122.7, 113.3, 104.3 (q, *J* = 34.3 Hz), 21.1, 20.3. **^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.)**: δ (ppm) –62.5 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{25}H_{20}{}^{79}BrF_3$ (M^+): calculated 456.0695; found 456.0700 (1.1 ppm).



1-(4-bromophenyl)-1-(2,5-diisopropylphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene (11p) was prepared according to *General Procedure D* from 4-(4-bromophenyl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (111.4 mg, 0.314 mmol) and diisopropylbenzene (297 µL, 1.568 mmol, 5 equiv.) with 4.7 mg (0.031 mmol) of $FeCl_3$, in 0.63 mL of HFIP. The reaction mixture was stirred at room temperature during 3 h. Purification by flash column chromatography over silica (with petroleum ether) gave 111.0 mg (70% yield) of a colorless oil. R_f = 0,88 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.52–7.48 (m, 2H), 7.40–7.28 (m, 7H), 7.25–7.20 (m, 2H), 7.12 (d, *J* = 1.8 Hz, 1H), 3.06–2.80 (m, 2H), 1.36–1.19 (m, 6H), 1.18–1.07 (m, 3H), 1.05–0.95 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 205.4 (q, *J* = 3.4 Hz), 146.8, 145.0, 137.9, 134.3, 132.1, 129.0, 128.8, 128.7, 128.2, 127.4, 127.3, 126.3, 122.6, 116.9, 123.4 (q, *J* = 275.1 Hz), 103.2 (q, *J* = 34.7 Hz), 100.1, 33.7, 30.4, 29.2, 27.8, 24.4, 24.1. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –58.8 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{28}H_{26}{}^{79}BrF_3$ (M^+): calculated 498.1165; found 498.1175 (2.0 ppm).

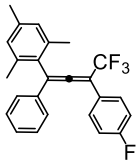


1-mesityl-3-(4-methoxyphenyl)-1-phenyl-trifluoro-1,2-butadiene (11q) was prepared according to modified *General Procedure D* from 1,1,1-trifluoro-2-(4-metoxyphenyl)-4-phenylbut-3-yn-2-ol ol (71.1 mg, 0.245 mmol) and mesitylene (102 µL, 0.735 mmol, 3 equiv.) with 4.0 mg (0.025 mmol) of $FeCl_3$, in 0.98 mL of HFIP. The reaction mixture was stirred at room temperature during 5 min. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 40:1 to 30:1) gave 78.9 mg (82% yield) of colorless oil. R_f = 0.81 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 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 NMR (100 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** ($APPI^+$): *m/z* for $C_{26}H_{23}F_3O$ (M^+): calculated 408.1696; found 408.1708 (2.9 ppm).



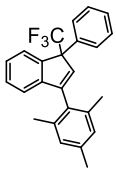
1-mesityl-4-(4-methoxyphenyl)-3-phenyl-4,4,4-trifluoro-1,2-butadiene (11r) was prepared according to modified *General Procedure D* from 1,1,1-trifluoro-4-(4-metoxyphenyl)-2-phenylbut-3-yn-2-ol ol (72.6 mg, 0.24 mmol) and mesitylene (83.7 µL, 0.735 mmol, 2.5 equiv.) with 3.9 mg (0.024 mmol) of $FeCl_3$, in 0.48 mL of HFIP. The reaction mixture was stirred at room temperature during 10 min. Purification by flash column chromatography over silica gave 26.3 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 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** (ESI+): *m/z* for $C_{26}H_{24}F_3O$ [M+H$^+$]: calculated 409.1774; found 409.1768 (–1.5 ppm).

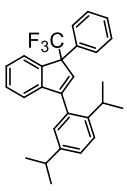


3-(4-fluorophenyl)-1-mesityl-1-phenyl-4,4,4-trifluoro-1,2-butadiene (**11s**) was prepared according to modified *General Procedure D* and isolated as a white solid. Yield = 52%. R_f = 0.81 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.56-7.48 (m, 2H), 7.44-7.33 (m, 3H), 7.33-7.27 (m, 2H), 7.16-7.07 (m, 2H), 7.02 (s, 2H), 2.39 (s, 3H), 2.23 (s, 6H). **^{13}C 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$^+$): *m/z* for $C_{25}H_{20}F_4$ (M$^+$): calculated 396.1496; found 396.1500 (1.0 ppm).

4. Characterization data for indenes

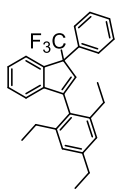


3-mesityl-1-phenyl-1-(trifluoro-methyl)-1*H*-indene (12a) was prepared according to *General Procedure E* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (105.6 mg, 0.382 mmol) and mesitylene (160 µL, 1.148 mmol, 3 equiv.) with 6.2 mg (0.038 mmol) of $FeCl_3$, in 1.53 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 136.5 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) 7.72–7.65 (m, 1H), 7.64–7.57 (m, 2H), 7.42–7.29 (m, 5H), 7.01 (s, 1H), 6.97 (s, 1H), 6.96–6.93 (m, 1H), 6.47 (s, 1H), 2.37 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 147.1, 145.0, 143.5, 137.6, 136.9, 136.5, 135.0, 133.4, 130.5, 129.0, 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 (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –67.4 (s, 3F). **HRMS** (CI): *m/z* for $C_{25}H_{21}F_3$ [M$^+$]: calculated 378.1590; found 378.1593 (0.8 ppm).

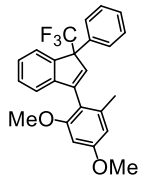


3-(2,5-diisopropylphenyl)-1-phenyl-1-(trifluoromethyl)-1*H*-indene (12b) was prepared according to *General Procedure E* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (103.7 mg, 0.375 mmol) and diizopropyl benzene (213 µL, 1.126 mmol, 3 equiv.) with 6.1 mg (0.038 mmol) of $FeCl_3$, in 0.75 mL of HFIP. The reaction mixture was stirred at room temperature during 3 h. Purification by flash column chromatography over silica (with petroleum ether) gave 141.7 mg (90% yield) of a white solid. Rf = 0,91 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.42–7.28 (m, 11H),

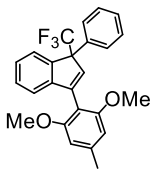
7.17 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 2.90 (m, *J* = 6.8, 3.7 Hz, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.00 (m, 6H), 0.66 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 148.2, 143.7, 141.6, 141.2, 138.4, 137.1, 135.6, 131.2, 128.8, 128.4, 128.2, 127.8, 127.5, 126.9, 125.5, 121.7, 64.8 (q, *J* = 26.1 Hz), 29.3, 27.2, 24.3, 23.9, 23.6, 23.3. **^{19}F NMR (376 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –62.5, (s, 3F). **HRMS** (CI): *m/z* for $C_{28}H_{27}F_3$ [M^+]: calculated 420.2059; found 420.2061 (1.9 ppm).



1-phenyl-3-(2,4,6-triethylphenyl)-1-(trifluoromethyl)-1*H*-indene (12c') was prepared according to *General Procedure E* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (117.0 mg, 0.424 mmol) and 1,3,5-triethylbenzene (239 µL, 1.271 mmol, 3 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 during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 126.7 mg (71% yield) of colorless oil. R_f = 0.88 (petroleum ether/EtOAc 9:1)**. ^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.70–7.61 (m, 1H), 7.63–7.51 (m, 2H), 7.32 (tdd, *J* = 6.4, 3.7, 1.5 Hz, 4H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.99 (s, 1H), 6.96–6.89 (m, 1H), 6.47 (s, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.57–2.25 (m, 5H), 1.38–1.23 (m, 3H), 1.19–1.02 (m, 3H), 1.02–0.92 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 146.3, 144.1, 143.2, 142.7, 134.8, 133.7, 129.2, 128.8, 128.6, 128.0, 127.7, 126.5, 125.6, 125.4, 125.2, 121.4, 64.7 (d, *J* = 26.9 Hz), 28.7, 26.9, 26.8, 16.1, 16.0, 15.5. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –65.0 (s, 3F). **HRMS** (CI): *m/z* for $C_{28}H_{27}F_3$ [M^+]: calculated 420.2059; found 420.2055 (–1.2 ppm).

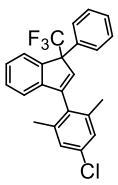


12d'

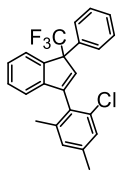


12d''

3-(2,4-dimethoxy-6-methylphenyl)-1-phenyl-1-(trifluoromethyl)-1*H*-indene (12d') and **3-(2,6-dimethoxy-4-methylphenyl)-1-phenyl-1-(trifluoromethyl)-1*H*-indene (12d'')** was prepared according to modified *General Procedure E* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (108.1 mg, 0.391 mmol) and 3,5-dimethoxytoluene (172 µL, 1.174 mmol, 3 equiv.) with 6.3 mg (0.039 mmol) of $FeCl_3$, in 1.57 mL of HFIP. The reaction mixture was heated at 80°C during 3 h. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 40:1 to 30:1) gave 64.2 mg (40% yield) of a colorless oil. R_f = 0.58 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) (characteristic peaks are reported only) 7.70–7.51 (m, 5.1H), 7.40–7.20 (m, 10.7H), 7.05–6.90 (m, 1.5H), 6.57–6.37 (m, 5H), 3.91–3.83 (m, 5.4H), 3.72–3.67 (m, 5.4H), 2.22 (s, 3H), 2.09 (s, 1.4H). **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –65.6 (s, 3F), -66.0 (s, 3F). **HRMS** (CI): *m/z* for $C_{25}H_{21}F_3O_2$ [M^+]: calculated 410.1488; found 410.1492 and 410.1491 (1.0 and 0.7 ppm).

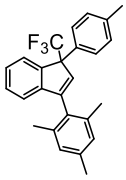


12e'

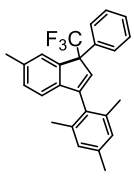


12e''

3-(2-(5-chloro-*m*-xylenyl))-1-phenyl-1-(trifluoro-methyl)-1*H*-indene (12e') was prepared according to modified *General Procedure E* from 1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (113.2 mg, 0.410 mmol) and 5-chloro-*m*-xylene (165 µL, 1.229 mmol, 3 equiv.) with 6.1 mg (0.041 mmol) of $FeCl_3$, in 1.64 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica (with petroleum ether) gave 31 mg (19 % yield) of a white solid in roughly 90% purity as a mixture of regioisomers **12e'** and **12e''**, as well as 10% of the corresponding allene. R_f = 0.31 (petroleum ether). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm): 7.70–7.57 (m, 3H), 7.44–7.31 (m, 7H), 7.01–6.96 (m, 1H), 6.53 (s, 1H), 2.40 (s, 3H), 2.24 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 145.3, 144.2, 139.3, 139.1, 134.7, 134.7, 133.6, 129.8, 129.5, 129.2, 128.9, 128.8, 128.1, 127.7, 127.5, 126.8, 126.6, 125.2, 123.6 (t, *J* = 275.3 Hz), 65.0 (q, *J* = 27.0 Hz), 21.1, 20.3. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –67.7 (s, 3F). **HRMS** (CI): *m/z* for $C_{24}H_{18}ClF_3$ [M^+]: calculated 398.1044; found 398.1050 (1.5 ppm).

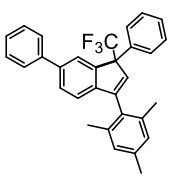


3-mesityl-1-toluyl-1-(trifluoromethyl)-1*H*-indene (12g) was prepared according to *General Procedure E* from 1,1,1-trifluoro-4-phenyl-2-(*p*-tolulyl)but-3-yn-2-ol (92.5 mg, 0.319 mmol) and mesitylene (133 µL, 0.956 mmol, 3 equiv.) with 5.1 mg (0.032 mmol) of $FeCl_3$, in 1.27 mL of HFIP. The reaction mixture was stirred at room temperature during 3 h. Purification by flash column chromatography over silica (with petroleum ether) gave 119.8 mg (96% yield) of colorless oil. R_f = 0.83 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.78-7.69 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.41-7.30 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 7.03 (s, 1H), 7.01-6.98 (m, 1H), 6.51 (s, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 146.8, 144.9, 137.8, 137.5, 136.8, 136.4, 133.4, 130.5, 129.4, 129.1, 128.7, 128.3, 128.1, 127.6, 127.4, 126.8 (q, *J* = 281.3 Hz), 126.5, 125.3, 121.2, 64.5 (q, *J* = 26.8 Hz), 21.2, 21.0, 20.2, 19.9. **^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6-ext. st.)**: δ (ppm) –67.4 (s, 3F). **HRMS** (CI): *m/z* for $C_{26}H_{23}F_3$ [M^+]: calculated 392.1746; found 392.1747 (0.3 ppm).

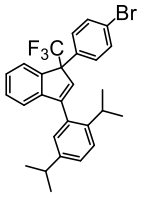


3-mesityl-6-methyl-1-phenyl-1-(trifluoromethyl)-1*H*-indene (12h) was prepared according to modified *General Procedure E* from 1,1,1-trifluoro-2-phenyl-4-(*p*-toluyl)but-3-yn-2-ol (80.1 mg, 0.28 mmol) and mesitylene (117 µL, 0.84 mmol, 3 equiv.) with 4.5 mg (0.028 mmol) of $FeCl_3$, in 0.55 mL of HFIP. The reaction mixture was heated at 50 °C for 6 h. Purification by flash column chromatography over silica (with petroleum ether) gave 98.2 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 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,

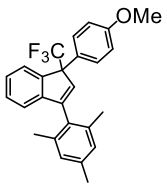
121.1, 64.7 (q, *J* = 26.3 Hz), 21.8, 21.2, 20.3, 20.0. **^{19}F NMR (376.5 MHz, $CDCl_3$)**: δ (ppm) –66.0 (s, 3F). **HRMS** (ESI+): *m/z* for $C_{26}H_{24}F_3$ [M+H$^+$]: calculated 393.1825; found 393.1815 (2.5 ppm).



3-mesityl-1,6-diphenyl-1-(trifluoromethyl)-1*H*-indene (12k) was prepared according to modified *General Procedure E* from 4-((1,1'-biphenyl)-4-yl)-1,1,1-trifluoro-2-phenylbut-3-yn-2-ol (70.2 mg, 0.20 mmol) and mesitylene (83.9 µL, 0.60 mmol, 3 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 (with petroleum ether) gave 82.1 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 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$^+$): *m/z* for $C_{31}H_{25}F_3$ (M$^+$): calculated 454.1903; found 454.1904 (0.2 ppm).

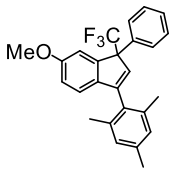


1-(4-bromophenyl)-3-(2,5-diisopropylphenyl)-1-(trifluoromethyl)-1*H*-indene (12n) was prepared according to modified *General Procedure E* from 4-(4-bromophenyl)-1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-ol (102.4 mg, 0.288 mmol) and diisopropylbenzene (164 µL, 0.865 mmol, 3 equiv.) with 4.7 mg (0.0288 mmol) of $FeCl_3$, in 1.15 mL of HFIP. The reaction mixture was heated at 80°C during 1 h. Purification by flash column chromatography over silica (with petroleum ether) gave 111.0 mg (77% yield) of yellow solid. R_f = 0.88 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.57–7.29 (m, 8H), 7.22–7.12 (m, 3H), 6.10 (s, 1H), 2.97–2.79 (m, 2H), 1.40–1.19 (m, 3H), 1.15 (m, 3H), 0.99 (dd, *J* = 9.0, 6.8 Hz, 4H), 0.72 (d, *J* = 6.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 148.5, 143.7, 141.9, 138.1, 136.4, 134.9, 131.9, 131.6, 128.7, 128.2, 128.1, 127.9, 127.8, 125.7, 121.9, 121.5, 64.4 (q, *J* = 26.5 Hz), 29.4–29.2 (m), 27.1, 24.3, 23.9, 23.6, 23.4. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –61.5 (s, 3F). **HRMS** (CI): *m/z* for $C_{28}H_{26}{}^{81}BrF_3$ [M$^+$]: calculated 500.1150; found 500.1145 (–1.0 ppm).



3-mesityl-1-(4-methoxyphenyl)-1-(trifluoromethyl)-1*H*-indene (12q) was prepared according to modified *General Procedure E* from 1,1,1-trifluoro-2-(4-metoxyphenyl)-4-phenylbut-3-yn-2-ol (109.1 mg, 0.356 mmol) and mesitylene (149 µL, 1.069 mmol, 3 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 during 1 h. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 40:1 to 30:1) gave 131.2 mg (90% yield) of yellow oil. R_f = 0.58 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.71 (q, *J* = 4.4, 3.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.37–7.30 (m, 2H), 7.03 (s, 1H), 6.99 (s, 1H), 6.97–6.89 (m, 3H), 6.48 (s, 1H), 3.83 (s, 3H), 2.39 (s, 3H), 2.20 (s, 3H), 2.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.0, 146.4, 144.6, 143.3, 137.2, 136.6, 136.2, 133.1, 130.2, 128.8, 128.8, 128.5, 128.1, 127.9, 126.4, 126.3, 125.9 (q, *J* = 141.9 Hz), 121.0, 113.8, 63.9 (q, *J* = 27.2 Hz), 55.0, 20.9, 20.0, 19.7. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3COOH-ext. st.)**: δ (ppm) –67.4 (s, 3F). **HRMS** (CI): *m/z* for $C_{26}H_{23}F_3O$ [M^+]: calculated 408.1696; found 408.1697 (0.2 ppm).

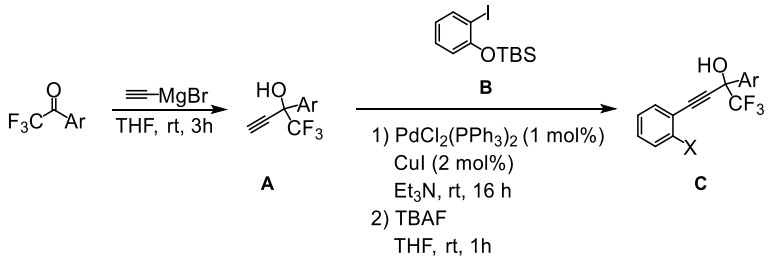


3-mesityl-5-methoxy-1-phenyl-1-(trifluoromethyl)-1*H*-indene (12r) was prepared according to <u>*General Procedure E*</u> from 1,1,1-trifluoro-4-metoxyphenyl-2-phenylbut-3-yn-2-ol (105.6 mg, 0.345 mmol) and mesitylene (144 µL, 1.034 mmol, 3 equiv.) with 5.6 mg (0.035 mmol) of $FeCl_3$, in 1.03 mL of HFIP. The reaction mixture was heated at 80°C during 24 h. Purification by flash column chromatography over silica (with petroleum ether/EtOAc 40:1 to 30:1) gave 84.2 mg (60% yield) of acolorless oil. R_f = 0.74 (petroleum ether/EtOAc 9:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.62–7.52 (m, 2H), 7.41–7.28 (m, 3H), 7.20 (s, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 6.87–6.78 (m, 2H), 6.29 (s, 1H), 3.82 (s, 3H), 2.34 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H). **^{13}C 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 (2C), 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) –73.7 (s, 3F). **HRMS** (CI): *m/z* for $C_{26}H_{23}F_3O$ [M^+]: calculated 408.1696; found 408.1695 (–0.2 ppm).

5. Preparation of tertiary propargylic alcohols for synthesis of chromenes

General procedure F: propargylic alcohols preparation[221]

A To a 0.5 M solution of ethynylmagnesium bromide (10 mmol) in THF was slowly added trifluoromethyl ketone (10 mmol) in THF (20 mL). After 3 h at rt the reaction mixture was quenched with water and then sat. 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 that was engaged in the next step without further purification.



B To a solution of 2-iodophenol (10 mmol) and imidazole (20 mmol) in dry THF (20 mL) was added TBSCl (20 mmol) in one portion and the reaction mixture was stirred at rt for 1 h. The

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

mixture was then diluted with DCM and filtered through celite. The residue was purified by flash column chromatography (petroleum ether 100 %) to provide the desired product.

C To a stirred solution of **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 rt. Then **A** (1.3 eq) was added. The mixture was allowed to stir overnight. The reaction was quenched with NH_4Cl sat. (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 TBAF (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 product **C**.

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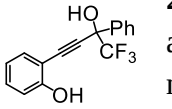
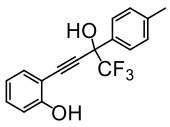
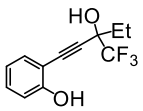


2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol was prepared according to *General Procedure F* using 2,2,2-trifluoro-1-phenylethan-1-one (1.4 mL, 10 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 263 mg (90% yield) of light yellow yellow solid. **Mp**: 92–93 ºC. **^{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 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$^+$): *m/z* for $C_{16}H_{10}O_2F_3$ ($[M+H]^+$): calculated 293.0784; found 293.0783 (–0.2 ppm).

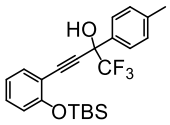


2-(4,4,4-trifluoro-3-hydroxy-3-(*p*-tolyl)but-1-yn-1-yl)phenol was prepared according to *General Procedure F* using 2,2,2-trifluoro-1-(p-tolyl)ethan-1-one (1.5 mL, 10 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 110 mg (36% yield) of brown oil. **^{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 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$^+$): *m/z* for $C_{17}H_{12}O_2F_3$ ($[M-H]^+$): calculated 305.0789; found 305.0783 (–2.0 ppm).

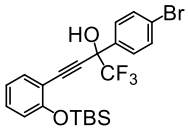


2-(3-hydroxy-3-(trifluoromethyl)pent-1-yn-1-yl)phenol was prepared according to *General Procedure F* using 1,1,1-trifluorobutan-2-one (1 g, 8 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 54 mg (22% yield) of brown oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: 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 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$^+$): *m/z* for $C_{12}H_{11}O_2F_3$ ([M]$^+$): calculated 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 was prepared according to <u>*General Procedure F*</u> 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 (with 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 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) –77.9 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{23}H_{28}O_2F_3Si$ ([M+H]$^+$): calculated 421.1805; found 421.1797 (–2.0 ppm).

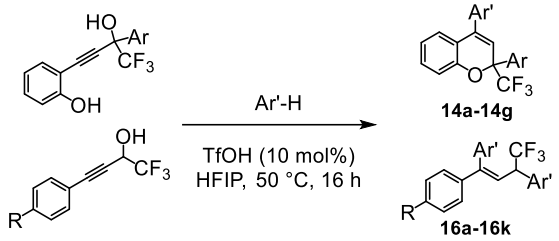


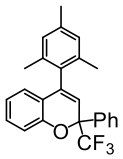
2-(4-bromophenyl)-4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro- but-3-yn-2-ol was prepared according to <u>*General Procedure F*</u> using 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (2.5 g, 10 mmol), without deprotection step. Purification by flash column chromatography over silica (with 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 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$^+$): *m/z* for $C_{22}H_{25}O_2BrF_3Si$ ([M]$^+$): calculated 485.0754; found 485.0756 (0.4 ppm).

6. Characterization data for chromenes

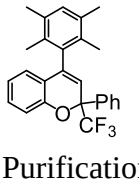
General procedure G: Catalytic arylation of propargylic alcohols

To the 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 ^{o}C for 16 h. The target product was isolated by flash column chromatography.

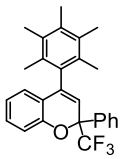




4-mesityl-2-phenyl-2-(trifluoromethyl)-2*H*-chromene (14a) was prepared according to *General Procedure G* from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (72.5 mg, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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 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) –79.4 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{25}H_{20}OF_3$ ($[M–H]^+$): calculated 393.1461; found 393.1460 (–0.1 ppm).

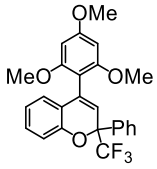


2-phenyl-4-(2,3,5,6-tetramethylphenyl)-2-(trifluoromethyl)-2*H*-chromene (14b) was prepared according to *General Procedure G* from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (72.5 mg, 0.25 mmol) and durene (102 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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 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 ($APPI^+$): *m/z* for $C_{26}H_{22}OF_3$ ($[M-H]^+$): calculated 407.1617; found 407.1618 (0.1 ppm).

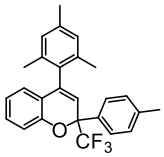


4-(2,3,4,5,6-pentamethylphenyl)-2-phenyl-2-(trifluoromethyl)-2*H*-chromene (14c) was prepared according to *General Procedure G* from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (72.5 mg, 0.25 mmol) and pentamethylbenzene (111 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with

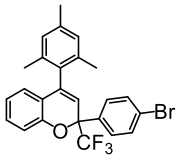
petroleum ether) gave 132 mg (quantitative yield) of white solid. **Mp**: 92–94 °C. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.65 (d, *J* = 7.3 Hz, 2H), 7.44–7.30 (m, 3H), 7.23–7.17 (m, 1H), 7.12 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.77 (td, *J* = 7.5, 1.2 Hz, 1H), 6.56 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.00 (s, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H), 1.95 (s, 3H). **^{13}C 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) –80.4 (s, 3F). HRMS (APPI$^+$): *m/z* for $C_{27}H_{24}OF_3$ ([M-H]$^+$): calculated 421.1774; found 421.1782 (0.8 ppm).



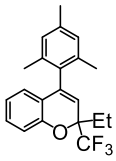
2-phenyl-2-(trifluoromethyl)-4-(2,4,6-trimethoxyphenyl)-2*H*-chromene (14d) was prepared according to <u>*General Procedure G*</u> from 2-(4,4,4-trifluoro-3-hydroxy-3-phenylbut-1-yn-1-yl)phenol (72.5 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (115.5 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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 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. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –79.9 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{25}H_{22}O_4F_3$ ([M+H]$^+$): calculated 443.1465; found 443.1464 (–0.2 ppm).



4-mesityl-2-(p-tolyl)-2-(trifluoromethyl)-2*H*-chromene (4e) was prepared according to <u>*General Procedure G*</u> 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 (with petroleum ether) gave 55 mg (54% yield) of white solid. **4e** was also prepared according to <u>*General Procedure G*</u> 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 (with 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 NMR (100 MHz, $CDCl_3$): δ (ppm) 151.4, 139.4, 137.4, 136.9, 136.0, 133.2, 130.2, 128.3, 128.1, 125.3, 124.7 (q, *J* = 284.6 Hz), 121.5, 119.5, 118.7, 117.1, 115.5, 80.4 (q, *J* = 30.5 Hz), 27.7, 21.1, 19.8, 19.5, 7.5. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –80.5 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{26}H_{22}OF_3$ ([M-H]$^+$): calculated 407.1617; found 407.1615 (–0.5 ppm).



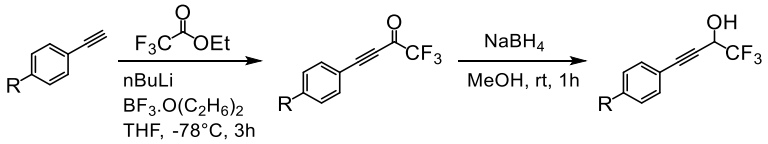
2-(4-bromophenyl)-4-mesityl-2-(trifluoromethyl)-2*H*-chromene (14f) was prepared according to *General Procedure G* from 2-(4-bromophenyl)-4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-1,1,1-trifluoro-but-3-yn-2-ol (121 mg, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with petroleum ether) gave 89 mg (75% yield) white solid. **Mp**: 113–115 °C. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.52 (s, 4H), 7.21 (t, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.94 (s, 1H) , 6.93 (s, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 6.6 Hz, 1H), 5.97 (s, 1H), 2.33 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H). **^{13}C 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** ($APPI^+$): *m/z* for $C_{25}H_{21}OBrF_3$ ($[M]^+$): calculated 473.0722; found 473.0716 (–1.3 ppm).



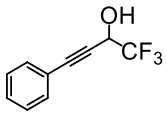
2-ethyl-4-mesityl-2-(trifluoromethyl)-2*H*-chromene (14g) was prepared according to *General Procedure G* from 2-(3-hydroxy-3-(trifluoromethyl)pent-1-yn-1-yl)phenol (61 mg, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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 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** ($APPI^+$): *m/z* for $C_{21}H_{21}OF_3$ ($[M-H]^+$): calculated 346.1539; found 346.1539 (–0.0 ppm).

7. Preparation of secondary propargylic alcohols

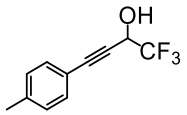
General procedure H: secondary propargylic alcohols preparation



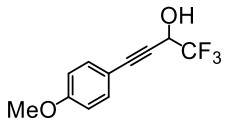
Secondary propargylic alcohols were prepared via two-step Kitazume/Sato sequence.[222] To a mixture of alkyne (10 mmol) and anhydrous THF (30 mL) at –78 °C was added *n*BuLi (10 mmol, 2.5 M solution) for 5 min. After 20 min stirring at –78 °C, ethyl fluoroacetate (10 mmol), boron trifluoride diethyl 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[1] was prepared according to <u>*General Procedure H*</u> using phenylacetylene (0.540 mL, 5 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 88 mg (44% yield) of yellow oil. **^{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 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) –79.1 (s, 3F).

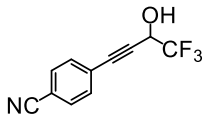


1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol was prepared according to <u>*General Procedure H*</u> using 1-ethynyl-4-methylbenzene (0.634 mL, 5 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 98 mg (46% yield) of white solid. **Mp**: 69–71 °C. **^{1}H 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 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** ($APPI^+$): *m/z* for $C_{11}H_{10}OF_3$ ($[M+H]^+$): calculated 215.0678; found 215.0678 (–0.0 ppm).

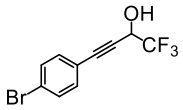


1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol was prepared according to <u>*General Procedure H*</u> using 1-ethynyl-4-methoxybenzene (0.648 mL, 5 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 85:15) gave 69 mg (30% yield) of yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.82 (m, 1H), 3.76 (s, 3H), 2.40 (d, *J* = 8.3 Hz, 1H). **^{13}C 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) –77.3 (s, 3F). HRMS ($APPI^+$): *m/z* for $C_{11}H_9O_2F_3$ ($[M]^+$): calculated 230.0055; found 230.0551 (–1.7 ppm).

[222] T. Kitazume et al., *J. Fluorine Chem*. **1985**, *30*, 189; L. Xiao et al., *Tetrahedron: Asymmetry* **1997**, *8*, 3597.

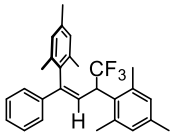


4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)benzonitrile was prepared according to *General Procedure H* using 1-ethynyl-4-isocyanobenzene (636 mg, 5 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 56 mg (25% yield) of yellow solid. **Mp**: 90–92 °C. **^{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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 132.9, 132.5, 126.0, 122.8 (q, *J* = 282.3 Hz), 118.4, 113.3, 86.3, 84.7, 63.3 (q, *J* = 36.6 Hz). **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –80.0 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{11}H_7ONF_3$ ($[M+H]^+$): calculated 226.0480; found 226.0475 (–2.3 ppm).

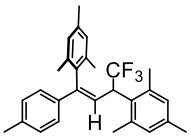


4-(4-bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol was prepared according to *General Procedure H* using 1-ethynyl-4-bromobenzene (0.600 mL, 5 mmol). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 9:1) gave 167 mg (60% yield) of yellow/dark yellow solid. **Mp**: 62–63 °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 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** ($APPI^+$): *m/z* for $C_{10}H_7OBrF_3$ ($[M]^+$): calculated 279.9765; found 279.9707 (–0.7 ppm).

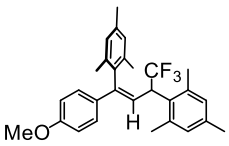
8. Characterization data for Friedel-Crafts reaction products of secondary propargylic alcohols



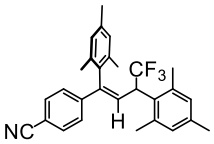
(*Z*)-2,2'-(4,4,4-trifluoro-1-phenylbut-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) (16a) was prepared according to *General Procedure G* from 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (50 μL, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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), 4.35 (p, *J* = 10.4 Hz, 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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 143.3, 139.4, 139.1, 138.1, 137.8, 137.7, 137.5, 137.4, 135.5, 134.6, 131.1, 129.4, 128.9, 128.8, 128.1, 127.3 (q, *J* = 281.8 Hz), 127.2, 126.2, 121.9, 46.1 (q, *J* = 27.8 Hz), 21.5, 21.4, 21.1, 19.8, 19.5, 18.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –67.4 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{28}H_{29}F_3$ ($[M]^+$): calculated 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) (16b) was prepared according to *General Procedure G* from 1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (52.5 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 (with petroleum ether) gave 84 mg (77% yield) of white solid. **Mp**: 90–91 ºC. **^{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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 142.7, 139.1, 137.6, 137.5, 137.4, 137.0, 135.9, 135.1, 134.4, 130.7, 129.3, 129.3, 128.5, 128.2, 127.5 (q, *J* = 282.6 Hz), 126.1, 120.6, 45.6 (q, *J* = 26.8 Hz), 22.5, 21.1, 21.0, 20.7, 19.7, 19.5, 18.2. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –68.3 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{29}H_{31}F_3$ ([M]$^+$): calculated 436.2372; found 436.2377 (1.1 ppm).

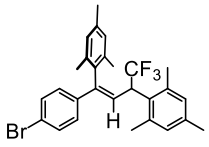


(Z)-2,2'-(4,4,4-trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) (16c) was prepared according to *General Procedure G* from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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 NMR (100 MHz, $CDCl_3$)**: δ (ppm) 159.3, 142.3, 139.1, 137.5, 137.4, 137.1, 137.0, 135.1, 134.4, 131.1, 130.8, 129.0, 128.5, 128.3, 127.5 (q, *J* = 280.1 Hz), 127.0, 119.5, 113.9, 55.3, 45.7 (q, *J* = 27.5 Hz), 22.5, 22.5, 21.0, 20.7, 19.8, 19.5, 18.2. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –67.4 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{29}H_{31}OF_3$ ([M]$^+$): calculated 452.2322; found 452.2323 (0.3 ppm).

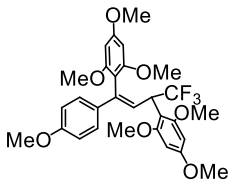


(Z)-4-(4,4,4-trifluoro-1,3-dimesitylbut-1-en-1-yl)benzonitrile (16d) was prepared according to *General Procedure G* from 4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)benzonitrile (56 mg, 0.25 mmol) and mesitylene (105 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (88 h, 100 °C). Purification by flash column chromatography over silica (with petroleum ether/EtOAc 98:2) gave 25 mg (22% yield) of colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.50 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.91 (s, 1H), 6.70 (s, 1H), 6.60 (d, *J* = 8.6 Hz, 2H), 4.34–4.23 (m, 1H), 2.42 (s, 3H), 2.23 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 1.33 (s, 3H), 1.03 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 143.1, 141.6, 139.1, 137.8, 137.4, 137.3, 137.2, 135.0, 132.8, 132.5, 132.1, 130.8, 129.2, 128.8, 128.6, 127.5 (q, *J* = 281.0 Hz), 118.9, 111.2, 45.8 (q, *J* = 28.3 Hz), 22.6, 21.0, 20.7, 19.7, 19.4, 18.2. **^{19}F NMR (376.5 MHz,**

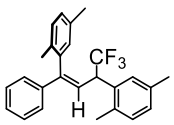
$CDCl_3$, CF_3CO_2H - ext. st.): δ (ppm) –67.3 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{29}H_{28}NF_3$ ($[M]^+$): calculated 447.2168; found 447.2172 (0.8 ppm).



(Z)-2,2'-(1-(4-bromophenyl)-4,4,4-trifluorobut-1-ene-1,3-diyl)bis(1,3,5-trimethylbenzene) (16e) was prepared according to *General Procedure G* from 4-(4-bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol (69.8 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 (with petroleum ether) gave 77 mg (61% yield) of colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.32 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.89 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.69 (s, 1H), 6.59 (d, *J* = 6.1 Hz, 2H), 4.31–4.20 (m, 1H), 2.41 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.33 (s, 3H), 1.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 141.9, 139.1, 137.7, 137.4, 137.38, 137.2, 135.1, 134.2, 133.6, 131.7, 130.8, 129.1, 128.6, 128.4, 127.7 (q, *J* = 281.2 Hz), 127.4, 126.0, 122.8, 121.9, 45.8 (q, *J* = 27.8 Hz), 22.6, 21.2, 20.7, 19.8, 19.5, 18.2. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –67.3 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{28}H_{28}BrF_3$ ($[M]^+$): calculated 500.1321; found 500.1331 (1.9 ppm).

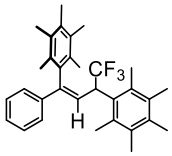


(Z)-2,2'-(4,4,4-trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,3,5-trimethoxybenzene) (16f) was prepared according to *General Procedure G* from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and 1,3,5-trimethoxybenzene (115.5 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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) 7.17 (d, *J* = 8.9 Hz, 2H), 6.72 (dd, *J* = 21.3, 8.5 Hz, 3H), 6.14 (d, *J* = 2.1 Hz, 1H), 6.02 (s, 1H), 5.83 (s, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 4.54–4.43 (m, 1H), 3.76 (s, 6H), 3.71 (s, 3H), 3.69 (s, 6H), 3.37 (s, 3H), 3.02 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 160.8, 160.2, 158.7, 158.5, 158.0, 135.2, 133.6, 127.5 (q, *J* = 280.9 Hz), 127.0, 122.9, 113.4, 109.2, 105.6, 91.3, 90.2, 90.1, 89.9, 56.1, 55.9, 55.4, 55.3 (2C), 55.2, 54.9, 29.9 (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** ($APPI^+$): *m/z* for $C_{29}H_{32}O_7F_3$ ($[M+H]^+$): calculated 549.0217; found 549.0219 (0.3 ppm).

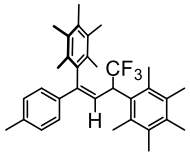


(Z)-2,2'-(4,4,4-trifluoro-1-phenylbut-1-ene-1,3-diyl)bis(1,4-dimethylbenzene) (16g) was prepared according to *General Procedure G* from 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (50 μL, 0.25 mmol) and *p*-xylene (92 μL, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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

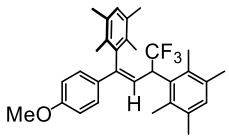
(s, 6H, major), 2.16 (s, 3H, major), 2.06 (s, 3H, major), 1.78 (s, 3H, minor), 1.68 (s, 3H, minor), 1.45 (s, 3H, minor). **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –69.2 (s, 2.2F - minor), –69.5 (s, 3F - major). **HRMS** ($APPI^+$): *m/z* for $C_{26}H_{25}F_3$ ($[M]^+$): calculated 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-pentamethylbenzene) (16h) was prepared according to <u>*General Procedure G*</u> 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 (with petroleum ether) gave 114 mg (95% yield) of white solid. **Mp**: 183–185 °C. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.23–7.20 (m, 3H), 7.19–7.12 (m, 2H), 6.85 (d, *J* = 7.4 Hz, 1H), 4.45–4.34 (m, 1H), 2.32 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 2.12 (d, *J* = 4.1 Hz, 6H), 2.07 (s, 3H), 1.93 (s, 3H), 1.73 (s, 3H), 1.21 (s, 3H), 0.85 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 144.1, 139.7, 134.8, 134.5, 134.1, 133.7, 133.4, 133.1, 132.9, 132.6, 132.4, 132.1, 130.0, 129.4, 128.5, 127.5, 127.5 (q, *J* = 280.5 Hz), 125.9, 122.5, 45.9 (q, *J* = 27.9 Hz), 19.6, 19.5, 17.2, 17.1, 17.0, 16.8, 16.6, 16.5, 15.9, 15.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –66.3 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{32}H_{38}F_3$ ($[M+H]^+$): calculated 479.2920; found 479.2923 (0.6 ppm).



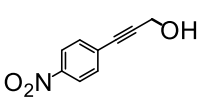
(Z)-6,6'-(4,4,4-trifluoro-1-(p-tolyl)but-1-ene-1,3-diyl)bis(1,2,3,4,5-pentamethylbenzene) (16i) was prepared according to <u>*General Procedure G*</u> from 1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (52.5 mg, 0.25 mmol) and pentamethylbenzene (111 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with petroleum ether) gave 108 mg (88% yield) of white solid. **Mp**: 206–209 °C. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.11 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 7.4 Hz, 1H), 4.43–4.31 (m, 1H), 2.31 (s, 3H), 2.24 (s, 3H), 2.17 (d, *J* = 6.1 Hz, 6H), 2.12 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 1.93 (s, 3H), 1.73 (s, 3H), 0.85 (s, 3H), –0.00 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 143.8, 137.4, 136.9, 134.8, 134.6, 134.1, 133.6, 133.4, 133.1, 132.9, 132.5, 132.4, 132.0, 130.0, 129.5, 129.2, 127.5 (q, *J* = 281.1 Hz), 125.8, 121.5, 45.9 (q, *J* = 27.8 Hz), 21.1, 19.6, 19.5, 17.2, 17.1, 16.9, 16.7, 16.6, 16.5, 15.9, 15.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –66.3 (s, 3F). **HRMS** ($APPI^+$): *m/z* for $C_{33}H_{39}F_3$ ($[M]^+$): calculated 492.2998; found 492.3005 (1.2 ppm).



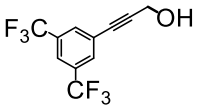
(Z)-3,3'-(4,4,4-trifluoro-1-(4-methoxyphenyl)but-1-ene-1,3-diyl)bis(1,2,4,5-tetramethylbenzene) (16j) was prepared according to <u>*General Procedure G*</u> from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (58 mg, 0.25 mmol) and durene (102 mg, 0.75 mmol), with 2.2 μL (0.025 mmol) of triflic acid, in 0.125 mL of HFIP (16 h, 50 °C). Purification by flash column chromatography over silica (with 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) 7.12 (d, *J* = 8.8 Hz, 2H), 6.82 (s, 1H), 6.76 (d, *J* = 7.9 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.38–4.28 (m, 1H), 3.71 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.81 (s, 3H), 1.16 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ (ppm) 159.3, 143.1, 137.4, 135.4, 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, 55.4, 45.9 (q, *J* = 27.8 Hz), 21.1, 20.8, 20.2, 19.9, 19.7, 18.3, 15.8, 15.1, 14.6. **^{19}F NMR (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. st.)**: δ (ppm) –66.3 (s, 3F). **HRMS** (APPI$^+$): *m/z* for $C_{31}H_{34}OF_3$ ([M-H]$^+$): calculated 479.2555; found 479.2555 (–0.3 ppm).

9. Preparation of primary propargylic alcohols



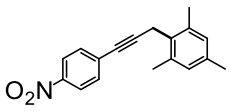
3-(4-nitrophenyl)propargyl alcohol was prepared from *p*-nitrobenzene-bromide (2.706 g, 13.4 mmol), propargyl alcohol (1.00 g, 17.9 mmol), $PdCl_2(PPh_3)_2$ (0.411 g, 0.586 mmol) and tetrabutylammonium fluoride monohydrate (12.1 g, 43.3 mmol) by heating under Ar(g) atmosphere at 80 °C for 2 h. To the crude reaction mixture water was added, and extracted several times with diethyl ether, dried over anh. Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (petroleum ether/EtOAc 7/3 to 6/4). Yield: 1.15 g, 49%, orange solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, *J* = 8.9 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 4.53 (s, 2H), 2.43 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 132.6, 129.6, 126.4, 123.8, 92.6, 84.0, 51.7.



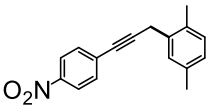
3-(3,5-bis(trifluoromethyl)phenyl)propargyl alcohol was prepared from 1-iodo-3,5-bis-(trifluoromethyl)benzene (169.0 mg, 0.497 mmol), propargyl alcohol (35 μL, 0.612 mmol), $PdCl_2(PPh_3)_2$ (11.4 mg, 0.016 mmol) and tetrabutylammonium fluoride monohydrate (420.4 mg, 1.507 mmol) by heating under Ar(g) atmosphere at 80 °C for 1.5 h. Purified by column chromatography (petroleum ether/EtOAc 8/2). Yield: 66.1 mg, 25%, orange product. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.83 (s, 2H), 7.77 (s, 1H), 4.50 (s, 2H), 2.70 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 132.2 (q, *J* = 33.6 Hz), 133.6 (m), 125.13, 123.0 (q, *J* = 271.1 Hz), 121.9 (sept, *J* = 3.7 Hz), 91.2, 82.6, 51.3. **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ (ppm): –63.4 (6H).

10. Characterization data for Friedel-Crafts reaction products of primary propargylic alcohols

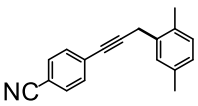
All catalytic reactions were conducted in 10 mL glass tubes under air. Elevated temperatures were achieved by way of a stirrer-hotplate, metal heating block and thermocouple. Purifications of the reaction was carried out by column chromatography using silica gel (40-63 μm). NMR spectra were recorded on a Bruker UltraShield 400 MHz spectrometer at rt and are reported in ppm.



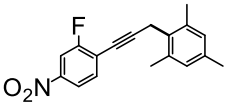
1,3,5-Trimethyl-2-(3-(4-nitrophenyl)prop-2-yn-1-yl)benzene (18a) was synthesized from 3-(4-nitrophenyl)propargyl alcohol (0.044 g, 0.25 mmol), mesitylene (174 μL, 1.25 mmol) with $HSbF_6 \cdot 6H_2O$ (6.0 μL, 0.05 mmol) in 0.5 mL HFIP. Reaction mixture was heated at 100 °C for 16 h. Purification by silica gel column chromatography (petroleum ether/EtOAc 99:1) gave 0.048 g of yellow oil (69% yield, with impurities). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.10 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 6.90 (s, 2H), 3.73 (s, 2H), 2.41 (s, 6H), 2.28 (s, 3H).



1,4-Dimethyl-2-(3-(4-nitrophenyl)prop-2-yn-1-yl)benzene (18b) was synthesized from 3-(4-nitrophenyl)propargyl alcohol (44.4 mg, 0.251 mmol), *p*-xylene (154 μL, 1.25 mmol) with $HSbF_6 \cdot 6H_2O$ (two additions of 3.0 μL, 0.05 mmol in total) in 0.5 mL HFIP. Reaction mixture was heated at 100 °C for 24 h, then the second increment of $HSbF_6 \cdot 6H_2O$ was added and the reaction was continued under identical conditions for another 16 h. Purification by silica gel column chromatography (petroleum ether/EtOAc 99:1) gave 29.0 mg of yellow oil (44% yield, with impurities). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.16 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.23 (s, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 2H), 2.35 (s, 6H).



4-(3-(2,5-dimethylphenyl)prop-1-yn-1-yl)benzonitrile (18c) was synthesized from 3-(4-cyanophenyl)propargyl alcohol (39.4 mg, 0.251 mmol), *p*-xylene (154 μL, 1.25 mmol) with $HSbF_6 \cdot 6H_2O$ (two additions of 3.0 μL, 0.05 mmol in total) in 0.5 mL HFIP. Reaction mixture was heated at 100 °C for 24 h, then the second increment of $HSbF_6 \cdot 6H_2O$ was added and the reaction was continued under identical conditions for another 16 h. Purification by silica gel column chromatography (petroleum ether/EtOAc 99:1) gave 36.6 mg of yellow oil (60% yield, with impurities). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 3.74 (s, 2H), 2.34 (s, 6H).



1,3,5-Trimethyl-2-(3-(2-fluoro-4-nitrophenyl)prop-2-yn-1-yl)benzene (18d) was synthesized from 3-(2-fluoro-4-nitrophenyl)propargyl alcohol (0.045 g, 0.250 mmol), mesitylene (174 μL, 1.25 mmol) with $HSbF_6 \cdot 6H_2O$ (two additions of 3.0 μL, 0.05 mmol in total) in 0.5 mL HFIP. Reaction mixture was heated at 100 °C for 24 h, then the second increment of $HSbF_6 \cdot 6H_2O$ was added and the reaction was continued under identical conditions for another 16 h. Purification by silica gel column chromatography (petroleum ether/EtOAc 99:1) gave 0.036 g of off-white solid (48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.00-7.90 (m, 2H), 7.51 (dd, *J* = 8.3 Hz, 6.9 Hz, 1H), 6.92 (s, 2H), 3.79 (s, 2H), 2.44 (s, 6H), 2.30 (s, 3H).

EXPERIMENTAL SECTION – CHAPTER 4
FRIEDEL-CRAFTS REACTIONS OF ALIPHATIC ALCOHOLS IN HFIP

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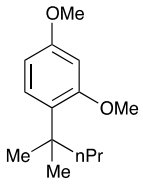
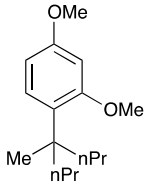
1. Characterization data for Friedel-Crafts reaction products of tertiary alcohols

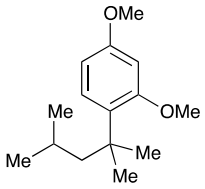
General Procedure I: A 10 mL Pyrex reaction tube equipped with a stir bar was charged with the requisite alcohol (0.25 to 1 mmol), nucleophile (3 equiv) and HFIP. TfOH (5 mol%) was then added, the tube capped and heated at 50 ^{o}C for 1 h. After cooling to room temperature, the reaction was quenched with Et_3N (2 drops), and filtered through a celite plug (CH_2Cl_2). The filtrate was collected and concentrated in vacuo to yield the crude reaction product from which excess nucleophile was removed by Kugelrohr distillation according to the conditions stated.



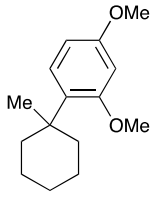
2,4-Dimethoxy-1-(2-methylpentan-2-yl)benzene (19a) was prepared according to *General Procedure I* from 2-methyl-2-pentanol (0.124 mL, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (50 ^{o}C). Yield: 0.194 g, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.85 (d, *J* = 3.2 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.7 and 3.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.82-1.76 (m, 2H), 1.35 (s, 6H), 1.09-0.98 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 153.4, 153.1, 138.8, 115.5, 112.4, 109.8, 55.8, 55.7, 43.5, 38.4, 28.5, 18.6, 15.0. **HRMS** (EI): *m/z* for $C_{14}H_{22}O_2$: calculated 222.16198; found 222.16081.



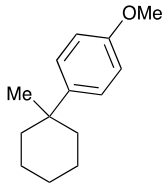
2,4-Dimethoxy-1-(4-methylheptan-4-yl)benzene (19b) was prepared according to *General Procedure I* from 4-methyl-4-heptanol (0.130 g, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (50 °C). Yield: 0.242 g, 97%, colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.04 (1H, d, *J* = 8.5 Hz), 6.46 (1H, d, *J* = 2.5 Hz), 6.42 (1H, dd, *J* = 8.5, 2.5 Hz), 3.81 (3H, s), 3.80 (3H, s), 2.02 (2H, td, *J* = 12.7, 4.0 Hz), 1.43 (2H, ddd, *J* = 13.1, 11.6, 4.6 Hz), 1.29 (3H, s), 1.17-1.11 (2H, m), 0.92-0.85 (3H, m), 0.82 (6H, t, *J* = 6.7 Hz). **HRMS** (ESI): *m/z* for $C_{16}H_{27}O_2$ ($[M+H]^+$): calculated 251.2006; found 251.1998 (3.1 ppm).



1-(2,4-Dimethylpentan-2-yl)-2,4-dimethoxybenzene (19c) was prepared according to *General Procedure I* from 2,4-dimethyl-2-pentanol (0.116 g, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation. Yield: 0.205 g, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.11 (1H, d, *J* = 8.4 Hz), 6.43 (1H, d, *J* = 2.5 Hz), 6.41 (1H, dd, *J* = 8.4, 2.5 Hz), 3.79 (6H, s), 1.72 (2H, d, *J* = 5.7 Hz), 1.39 (1H, t, *J* = 7.3 Hz), 1.31 (6H, s), 0.67 (6H, d, *J* = 6.7 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.6, 159.0, 129.5, 128.0, 103.2, 99.4, 55.3, 54.9, 49.5, 46.9, 37.9, 29.7, 25.5, 24.8, 8.8. **HRMS** (ESI): *m/z* for $C_{15}H_{25}O_2$ ($[M+H]^+$): calculated 237.1849; found: 237.1840 (3.7 ppm).

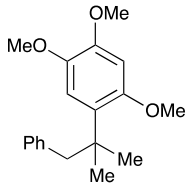


2,4-Dimethoxy-1-(1-methylcyclohexyl)benzene (19d) was prepared according to *General Procedure I* from 1-methylcyclohexanol (0.124 mL, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (50 °C). Analytical data are in agreement with the literature.[223] Yield: 0.225 g, 96%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): major regioisomer: 7.19 (1H, dd, *J* = 8.5, 0.9 Hz), 6.49-6.46 (1H, m), 6.44 (1H, ddd, *J* = 8.5, 2.5, 1.0 Hz), 3.80 (3H, s), 3.80 (3H, s), 2.07 (2H, t, *J* = 10.4 Hz), 1.68-1.47 (8H, m), 1.26 (3H, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): major regioisomer: 159.8, 158.8, 130.3, 128.0, 103.5, 100.0, 55.3, 55.1, 37.7, 37.3, 26.9, 26.0, 23.0.

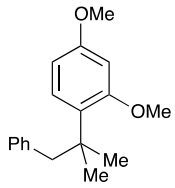


1-Methoxy-4-(1-methylcyclohexyl)benzene (19e) was prepared according to *General Procedure I* from 1-methylcyclohexanol (0.031 mL 0.25 mmol), anisole (0.082 mL, 0.75 mmol) and TfOH (1.1 μL, 5 mol%) in HFIP (0.25 mL) and purified by Kugelrohr distillation (30 °C). Analytical data are in agreement with the literature.[224] Yield: 0.257 g, quantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.29 (2H, d, *J* = 8.9 Hz), 6.87 (2H, d, *J* = 8.9 Hz), 3.80 (3H, s), 1.97 (2H, app. dd, *J* = 13.3, 8.1 Hz), 1.58-1.51 (4H, m), 1.45-1.40 (4H, m), 1.16 (3H, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 157.1, 142.1, 126.7, 113.5, 55.2, 38.1, 37.3, 30.7, 26.4, 22.7.

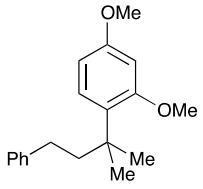
[223] M. Niggemann, N. Bisek *Chem. Eur. J.* **2010**, *16*, 11246.
[224] Y. Yamamoto, K. Itonaga *Chem. Eur. J.* **2008**, *14*, 10705.



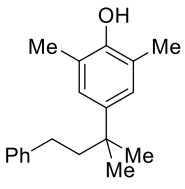
1,2,4-Trimethoxy-5-(2-methyl-1-phenylpropan-2-yl)benzene (19f) was prepared according to *General Procedure I* from 2-methyl-3-phenyl-2-propanol (0.038 g, 0.25 mmol), 1,2,4-trimethoxybenzene (0.112 mL, 0.75 mmol) and TfOH (1.1 μL, 5 mol%) in HFIP (0.25 mL) and purified by Kugelrohr distillation (up to 100 °C). Yield: 0.213 g, 71%, pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.13-7.09 (3H, s), 6.84-6.82 (2H, m), 6.59 (1H, s), 6.55 (1H, s), 3.91 (6H, s), 3.71 (3H, s), 3.09 (2H, s), 1.33 (6H, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 152.7, 147.8, 142.1, 140.1, 130.4, 128.1, 127.5, 125.6, 113.3, 98.3, 57.0, 56.2, 56.0, 46.5, 38.8, 28.3. **HRMS** (ESI): *m/z* for $C_{19}H_{25}O_3$ ($[M+H]^+$): calculated 301.1798; found: 301.1785 (4.5 ppm).



2,4-Dimethoxy-1-(2-methyl-1-phenylpropan-2-yl)benzene (19g) was prepared according to *General Procedure I* from 2-methyl-3-phenyl-2-propanol (0.150 g, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (55 °C). Analytical data are in agreement with the literature.[225] Yield: 0.235 g, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.13-7.09 (3H, m), 6.86 (1H, d, *J* = 8.6 Hz), 6.82 (2H, dd, *J* = 6.8, 2.6 Hz), 6.53 (1H, d, *J* = 2.6 Hz), 6.32 (1H, dd, *J* = 8.6, 2.6 Hz), 3.91 (3H, s), 3.79 (3H, s), 3.09 (2H, s), 1.32 (6H, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.3, 159.2, 140.3, 130.4, 128.6, 128.3, 127.4, 125.6, 103.2, 99.5, 55.4, 55.1, 46.3, 38.7, 28.4.



2,4-Dimethoxy-1-(2-methyl-4-phenylbutan-2-yl)benzene (19h) was prepared according to *General Procedure I* from 2-methyl-4-phenyl-2-butanol (0.164 g, 1 mmol), 1,3-dimethoxybenzene (0.392 mL, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (50 °C). Analytical data are in agreement with the literature.[225] Yield: 0.279 g, 98%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.22 (2H, td, *J* = 7.8, 2.8 Hz), 7.16 (1H, d, *J* = 8.5 Hz), 7.14-7.11 (1H, m), 7.08 (2H, d, *J* = 7.2 Hz), 6.48 (1H, dd, *J* = 2.5 Hz), 6.45 (1H, dd, *J* = 8.5, 2.6 Hz), 3.82 (3H, s), 3.81 (3H, s), 2.28-2.23 (2H, m), 2.12-2.08 (2H, m), 1.38 (6H, s). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.4, 159.2, 143.9, 128.7, 128.4, 128.3, 128.2, 125.4, 103.4, 99.5, 55.3, 55.1, 43.3, 37.9, 32.1, 28.8.



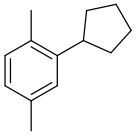
2,6-Dimethyl-4-(2-methyl-4-phenylbutan-2-yl)phenol (19i) was prepared according to *General Procedure I* from 2-methyl-4-phenyl-2-butanol (0.170 mL, 1 mmol), 2,6-dimethylphenol (0.368 g, 3 mmol) and TfOH (4.4 μL, 5 mol%) in HFIP (1 mL) and purified by Kugelrohr distillation (55 °C). Analytical data are in agreement with the literature.[225] Yield: 0.236 g, 88%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.24 (2H, d, *J* = 7.6 Hz), 7.14 (1H, t, *J* = 7.4 Hz), 7.10 (2H, d, *J* = 7.0 Hz), 7.00 (2H, s), 4.48 (1H, s), 2.40-2.35 (2H, m), 2.27 (6H, s), 1.90-1.86 (2H, m), 1.33 (6H, s).

[225] M. Dryzhakov, J. Moran *ACS Catalysis*, **2016**, *6*, 3670.

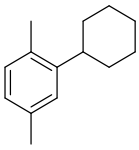
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 150.1, 143.5, 141.0, 128.4, 126.4, 125.6, 122.5, 46.8, 37.3, 31.5, 29.3, 16.4.

2. Characterization data for Friedel-Crafts reaction products of secondary aliphatic alcohols

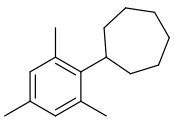
General Procedure J: A 10 mL Pyrex reaction tube equipped with a stir bar was charged with the requisite secondary alcohol (0.25 to 1 mmol), nucleophile (5 equiv) and HFIP. TfOH (10 mol%) was then added, the tube capped and heated at 50 °C for 3-6 h. After cooling to room temperature, the reaction product was purified by silica gel column chromatography.



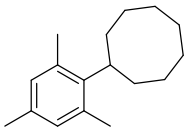
2-cyclopentyl-1,4-dimethylbenzene (**20a**) was prepared from cyclopentanol (23.0 μL, 0.262 mmol), *p*-xylene (162 μL, 1.312 mmol) and TfOH (2.32 μL, 0.026 mmol) in HFIP (0.52 mL). Reaction mixture was heated 3 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20a** as a colorless oil. Yield = 36.5 mg, 80%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.07 (d, *J* = 0.8 Hz, 1H), 7.04–7.02 (m, 1H), 6.91 (dd, *J* = 6.4 Hz, 1.1 Hz, 1H), 3.25–3.08 (m, 1H), 2.32 (s, 6H), 2.10–1.94 (m, 2H), 1.90–1.76 (m, 2H), 1.76–1.64 (m, 2H), 1.64–1.55 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 144.4, 135.5, 132.9, 130.1, 126.3, 126.2, 41.8, 33.8, 25.7, 21.4, 19.5.



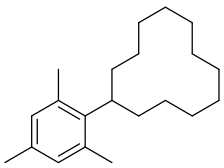
2-cyclohexyl-1,4-dimethylbenzene (**20b**) was prepared from cyclohexanol (26.4 μL, 0.308 mmol), *p*-xylene (190 μL, 1.538 mmol) and TfOH (2.72 μL, 0.031 mmol) in HFIP (0.61 mL). Reaction mixture was heated 3 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20b** as a colorless oil. Yield = 6.5 mg, 11%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.05–7.00 (m, 2H), 6.90 (dd, *J* = 7.8 Hz, 0.8 Hz, 1H), 2.68 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.90–1.70 (m, 5H), 1.50–1.20 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 145.9, 135.5, 132.1, 130.2, 126.3, 126.3, 40.2, 33.8, 27.4, 26.5, 21.4, 19.0.



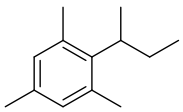
2-cycloheptyl-1,3,5-trimethylbenzene (**20c**) was prepared from cycloheptanol (120 μL, 0.974 mmol), mesitylene (677 μL, 4.869 mmol) and TfOH (8.62 μL, 0.097 mmol) in HFIP (1.95 mL). Reaction mixture was heated 3 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20c** as a pale yellow oil. Yield = 170.5 mg, 81%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.81 (s, 2H), 3.18 (dddd, *J* = 10.8 Hz, 10.8 Hz, 3.7 Hz, 3.7 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H), 1.98–1.87 (m, 2H), 1.86–1.55 (m, 10H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 142.7, 136.0, 135.2, 134.7, 131.1, 129.0, 41.8, 32.9, 29.6, 28.6, 21.7, 21.4, 20.7. **HRMS** ($APPI^+$): *m/z* for $C_{16}H_{24}$ (M^+): calculated 216.1873; found 216.1874 (0.6 ppm).



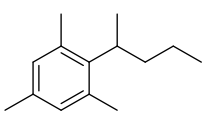
2-cyclooctyl-1,3,5-trimethylbenzene (**20d**) was prepared from cyclooctanol (132 μL, 0.897 mmol), mesitylene (624 μL, 4.485 mmol) and TfOH (7.94 μL, 0.090 mmol) in HFIP (1.79 mL). Reaction mixture was heated 3 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20d** as a yellow oil. Yield = 123.5 mg, 60%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.82 (s, 2H), 3.35–3.15 (m, 1H), 2.29 (s, 6H), 2.24 (s, 3H), 1.90–0.60 (m, broad). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 137.8, 134.5, 131.0, 126.9, 38.8, 33.4, 27.5, 27.2, 26.6, 21.2, 20.6. **HRMS** ($APPI^+$): *m/z* for $C_{17}H_{26}$ (M^+): calculated 230.2029; found 230.2032 (1.4 ppm).



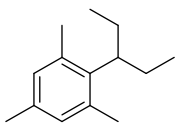
2-cyclododecyl-1,3,5-trimethylbenzene (**20e**) was prepared from cyclododecanol (0.18 g, 0.98 mmol), mesitylene (683 μL, 4.910 mmol) and TfOH (8.69 μL, 0.098 mmol) in HFIP (1.96 mL). Reaction mixture was heated 3 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20e** as a white solid. Yield = 286 mg, quantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.81 (s), 3.19 (quint., *J* = 6.7 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 2.24 (s, 3H), 2.00–1.85 (m, 2 H), 1.75–1.20 (m, 20H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 140.8, 136.8, 136.6, 134.8, 131.4, 129.0, 34.1, 29.9, 24.9, 24.6, 24.6, 23.2, 22.3, 22.1, 21.9, 20.8. **HRMS** ($APPI^+$): *m/z* for $C_{21}H_{34}$ (M^+): calculated 286.2655; found 286.2663 (2.8 ppm).



2-(2-butyl)-1,3,5-trimethylbenzene (**20f**) was prepared from 2-butanol (23.1 μL, 0.246 mmol), mesitylene (137 μL, 0.982 mmol) and TfOH (2.18 μL, 0.025 mmol) in HFIP (0.49 mL). Reaction mixture was heated 24 h at 80 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave **20f** as a colorless oil. Yield = 15.2 mg, 35%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 2H), 3.14 (qt, *J* = 7.4 Hz, 7.4 Hz, 1H), 2.36 (s, 6H), 2.26 (s, 3H), 1.76 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 3H), 0.88 (t, 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 140.2, 136.4, 134.8, 131.1, 129.2, 127.1, 36.7, 28.4, 21.7, 20.7, 19.0, 13.3.

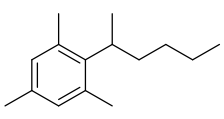


20f

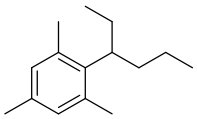


20f'

2-(2-pentyl)-1,3,5-trimethylbenzene (**20f**) and **2-(3-pentyl)-1,3,5-trimethylbenzene** (**20f'**) were prepared from 3-pentanol (108 μL, 1.00 mmol), mesitylene (698 μL, 5.01 mmol) and TfOH (8.88 μL, 0.10 mmol) in HFIP (2.00 mL). Reaction mixture was heated 6 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave mixture of **20f** and **20f'** as a colorless oil. Yield = 131.4 mg, 69%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): (characteristic peaks are reported) 6.83 (s, 1H, **20f**), 6.82 (s, 1.7H, **20f** and **20f'** overlapping), 6.80 (s, 0.9H, **20f'**), 3.24 (qt, *J* = 7.4 Hz, 7.4 Hz, 1H, **20f**), 2.95 (tt, *J* = 7.6 Hz, 0.8H, **20f'**), 2.36 (s, 6H, **20f**), 2.26 (s, 5H, **20f'**), 1.30 (d, *J* = 7.2 Hz, 3H, **20f**), 0.91 (t, *J* = 7.3 Hz, 3H, **20f**), 0.84 (t, *J* = 7.4 Hz, 4.8H, **20f'**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 140.4, 138.5, 137.9, 137.5, 136.3, 136.2, 134.8, 134.7, 131.2, 129.2, 129.1, 44.2, 38.0, 34.7, 27.1, 22.4, 21.9, 21.7, 21.4, 21.3, 20.8, 20.7, 19.3, 14.5, 13.2. **HRMS** ($APPI^+$): *m/z* for $C_{14}H_{22}$ ($[M–1]^+$): calculated 189.1638; found 189.1639 (0.4 ppm).

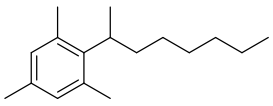


20g

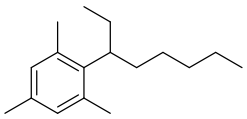


20g'

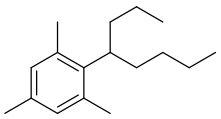
2-(2-hexyl)-1,3,5-trimethylbenzene (**20g**) and **2-(3-hexyl)-1,3,5-trimethylbenzene** (**20g'**) were prepared from 3-hexanol (126 μL, 1.06 mmol), mesitylene (737 μL, 5.30 mmol) and TfOH (9.38 μL, 0.11 mmol) in HFIP (2.12 mL). Reaction mixture was heated 6 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave mixture of **20g** and **20g'** as a colorless oil. Yield = 125.4 mg, 58%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): (characteristic peaks are reported) 6.82 (s, 2.7H, **20g** and **20g'** overlapping), 6.80 (s, 1.2H, **20g'**), 3.21 (qt, *J* = 7.4 Hz, 7.4 Hz, 1H, **20g**), 3.02 (tt, *J* = 7.0 Hz), 2.36 (s, 7.2H, **20g'**), 2.31 (5H), 2.25 (s, 6H), 1.85–1.62 (m, 6.7H), 1.30 (d, *J* = 7.3 Hz, 4.5H), 0.88 and 0.89 (two t overlap, *J* = 7.3 Hz and *J* = 7.3 Hz, 6.5H), 0.83 (t, *J* = 7.4 Hz, 3H, **20g**) **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 140.5, 138.9, 137.3, 136.3, 134.8, 134.7, 131.2, 129.1, 42.3, 36.8, 35.4, 34.9, 31.0, 27.3, 23.1, 22.3, 21.9, 21.7, 21.5, 20.8, 20.8, 19.3, 14.6, 14.2, 13.2. **HRMS** ($APPI^+$): *m/z* for $C_{15}H_{24}$ ($[M–1]^+$): calculated 203.1794; found 203.1796 (1.0 ppm).



20h



20h'

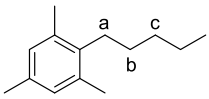


20h''

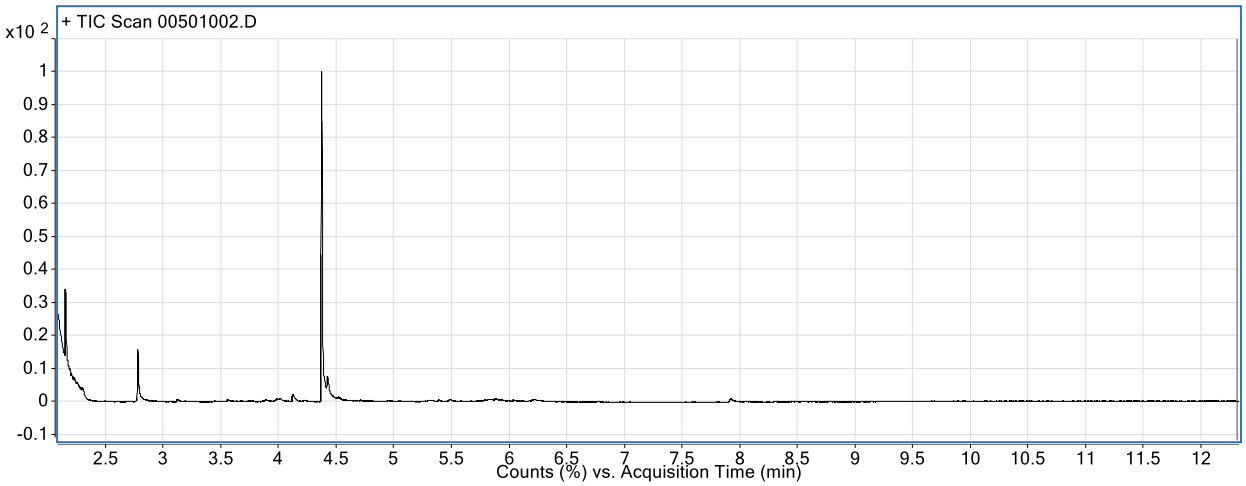
2-(2-octyl)-1,3,5-trimethylbenzene (**20h**), **2-(3-octyl)-1,3,5-trimethylbenzene** (**20h'**) and **2-(4-octyl)-1,3,5-trimethylbenzene** (**20h''**) were prepared from 3-octanol (159 μL, 1.03 mmol), mesitylene (714 μL, 5.13 mmol) and TfOH (9.09 μL, 0.10 mmol) in HFIP (2.05 mL). Reaction mixture was heated 6 h at 50 °C. Purification by flash column chromatography over silica (100% petroleum ether) gave mixture of **20h, 20g'** and **20g''** as a colorless oil. Yield = 207.5 mg, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): (characteristic peaks are reported) 6.82 (s, 4.2H), 6.79 (s, 2.3H), 3.20 (qt, *J* = 7.4 Hz, 7.4 Hz, 1H), 3.08 (tt, *J* = 8.2 Hz, 6.9 Hz, 1H), 3.00 (tt, *J* = 8.0 Hz, 7.4 Hz, 1.2H), 0.83 (t, 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 140.4, 139.2, 138.8, 137.8, 137.1, 136.9, 136.2, 134.6, 134.5, 131.0, 129.0, 126.9, 42.4, 40.4, 37.0, 36.6, 34.8, 34.3, 34.3, 32.4, 31.9, 30.9, 29.6, 28.7, 28.4, 27.2, 23.1, 22.7, 22.6, 22.2, 22.1, 21.8, 21.6, 21.4, 21.4, 21.2, 20.7, 20.6, 19.2, 14.5, 14.2, 14.1, 14.1, 13.1. **HRMS** ($APPI^+$): *m/z* for $C_{17}H_{28}$ ($[M–1]^+$): calculated 231.2107; found 231.2108 (0.2 ppm).

3. Experimental data for Friedel-Crafts reactions of primary aliphatic alcohols

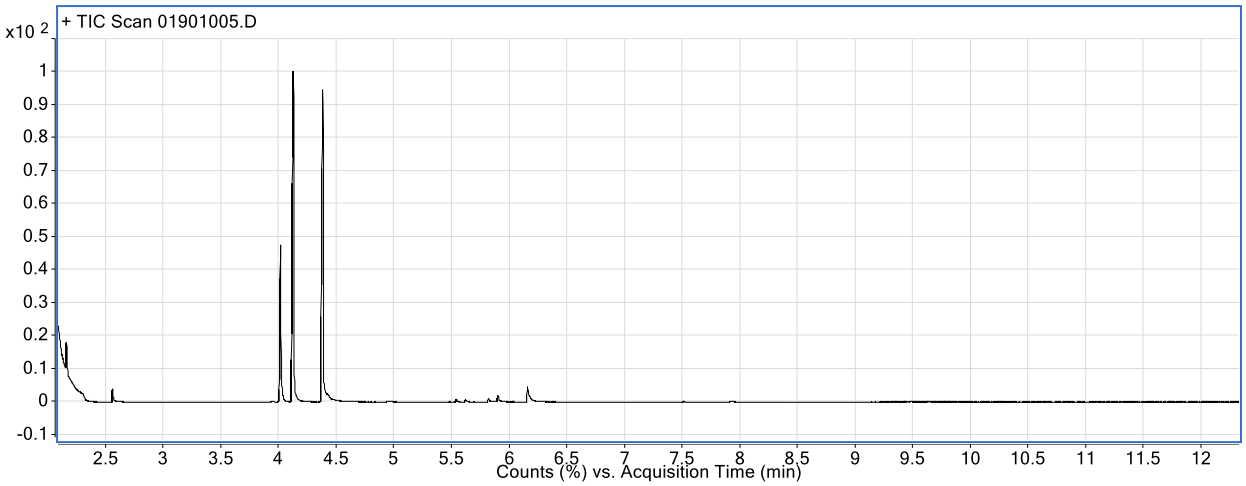
General Procedure K: A 15 mL ACE pressure reaction tube equipped with a stir bar was charged with the requisite alcohol (1 mmol), nucleophile (5 equiv) and HFIP. TfOH (10 mol%) was then added, the tube capped and heated at 120 °C for 24 h. Temperature on the thermocouple was 140 °C, but when the temperature of the oil bath was measured with a thermometer, it was around 120 °C. After cooling to room temperature, the reaction mixture was analyzed by GC/MS.

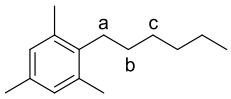


2-Pentyl-1,3,5-trimethylbenzene was prepared from 1-pentanol (54.3 µL, 0.486 mmol, ~0.25 M), mesitylene (338 µL, 2.428 mmol), TfOH (4.30 µL, 0.049 mmol) and HFIP (1.94 mL). Regioisomer **a** was detected with the GC/MS at retention time 4.37 min. Peak at 2.85 min corresponds to mesitylene.

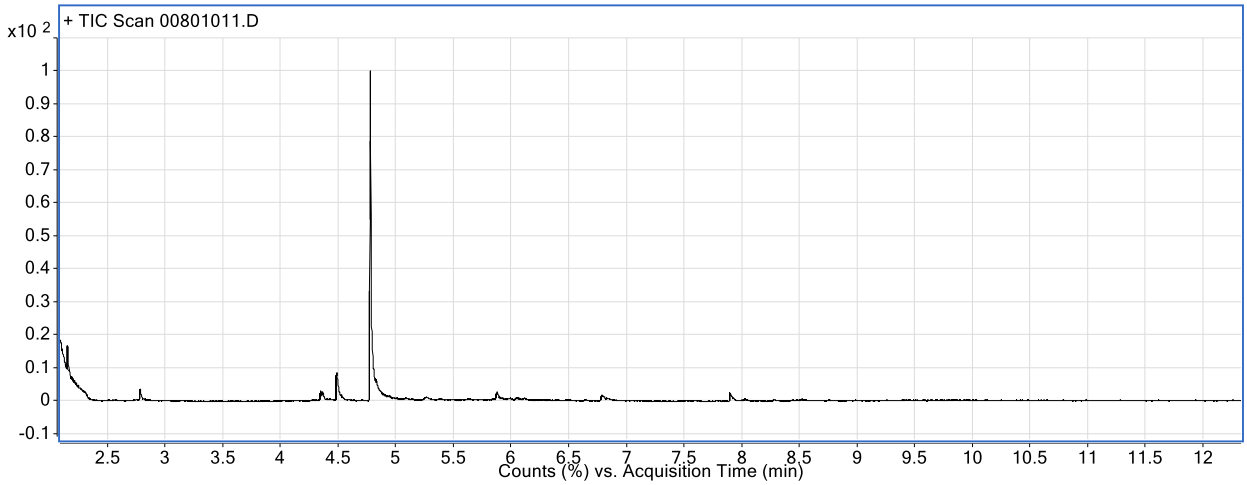


2-Pentyl-1,3,5-trimethylbenzene and two regioisomers (**2-pentyl** and **3-pentyl**) were prepared from 1-pentanol (54.3 µL, 0.499 mmol, ~1.0 M), mesitylene (347 µL, 2.496 mmol), TfOH (4.42 µL, 0.05 mmol) and HFIP (0.5 mL). The regioisomer ratio is: **a**:**b**:**c** = 42:42:16 at retention times 4.38, 4.12 and 4.01 min, respectively.

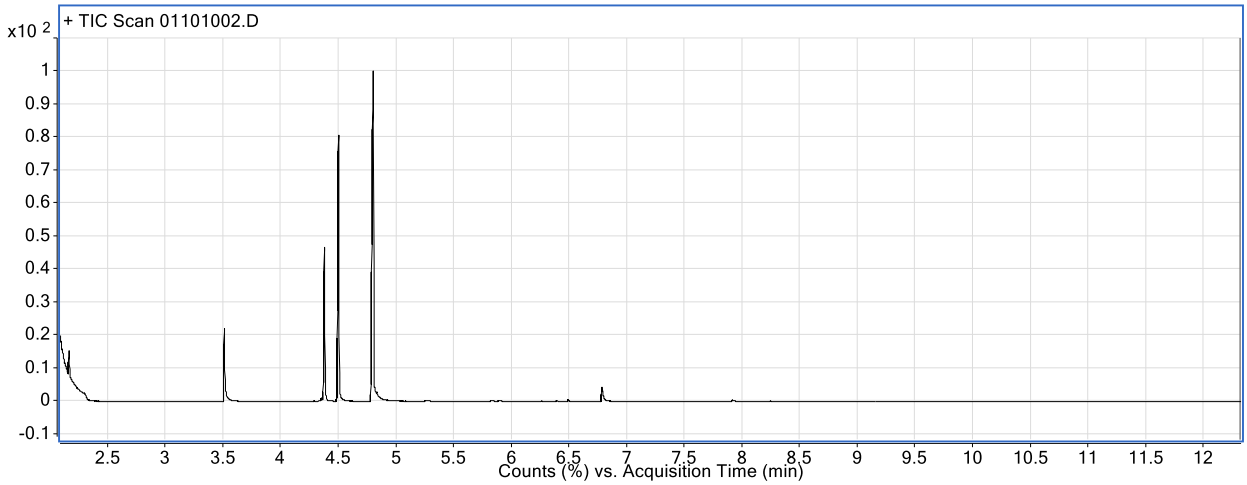


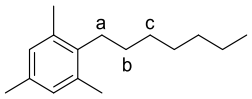


2-Hexyl-1,3,5-trimethylbenzene was prepared from 1-hexanol (51.9 mg, 0.508 mmol, ~0.25 M), mesitylene (353 μL, 2.54 mmol), TfOH (4.50 μL, 0.051 mmol) and HFIP (2.03 mL). The regioisomer ratio is: **a**:**b**:**c** = 86:10:4 at retention times 4.78, 4.49 and 4.35 min, respectively.

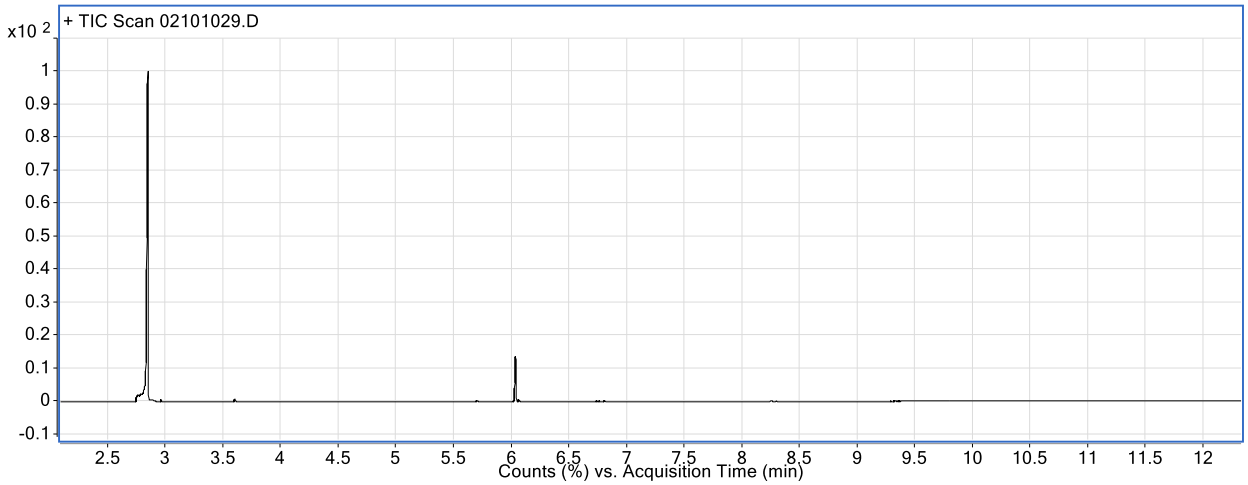


2-Hexyl-1,3,5-trimethylbenzene and two regioisomers (**2-hexyl** and **3-hexyl**) were prepared from 1-hexanol (126 μL, 1.019 mmol, ~1.0 M), mesitylene (709 μL, 5.09 mmol), TfOH (9.02 μL, 0.102 mmol) and HFIP (1.0 mL). The regioisomer ratio is: **a**:**b**:**c** = 50:34:16 at retention times 4.79, 4.50 and 4.38 min, respectively.

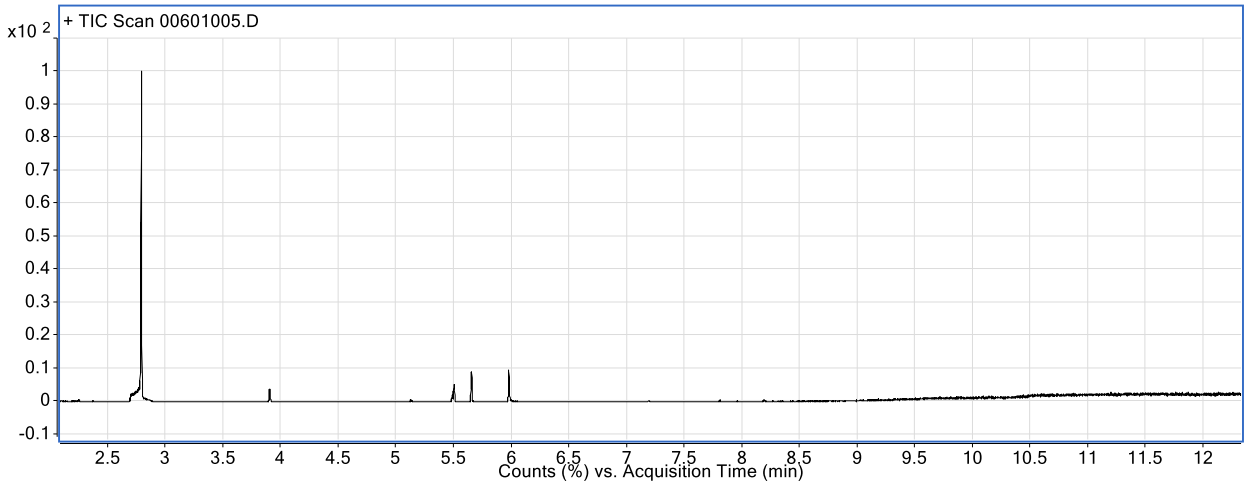


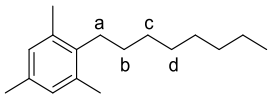


2-Heptyl-1,3,5-trimethylbenzene was prepared from 1-heptanol (71 µL, 0.497 mmol, ~0.25 M), mesitylene (346 µL, 2.487 mmol), TfOH (4.40 µL, 0.05 mmol) and HFIP (1.99 mL). Regioisomer **a** was detected with the GC/MS at retention time 6.03 min. Peak at 2.85 min corresponds to mesitylene.

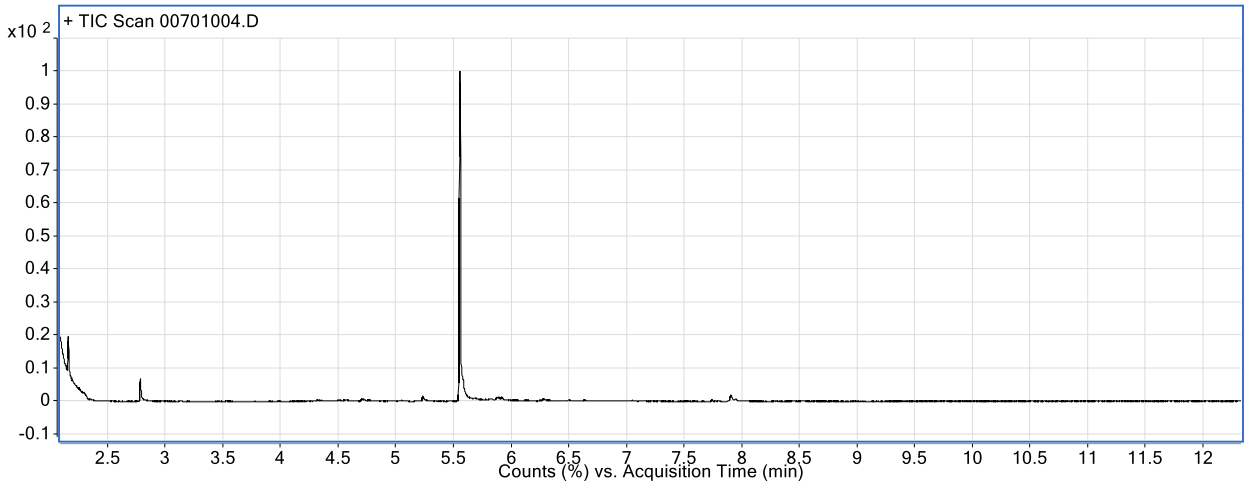


2-Heptyl-1,3,5-trimethylbenzene and two regioisomers (**2-heptyl** and **3-heptyl**) were prepared from 1-heptanol (71 µL, 0.491 mmol, ~1.0 M), mesitylene (341 µL, 2.453 mmol), TfOH (4.34 µL, 0.049 mmol) and HFIP (0.49 mL). The regioisomer ratio is: **a**:**b**:**c** = 43:30:26 at retention times 6.03, 5.65 and 5.49 min, respectively.

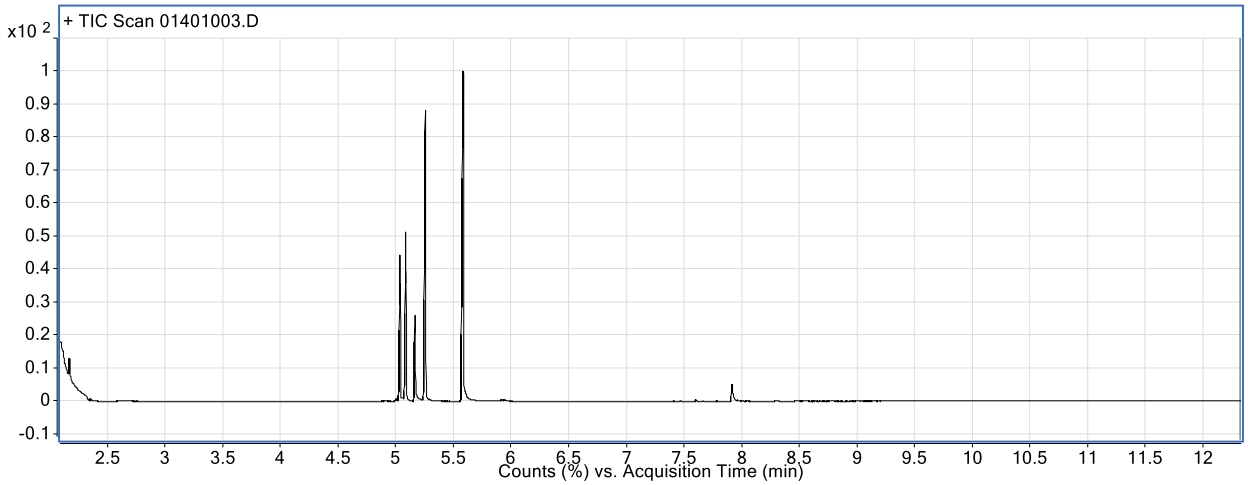


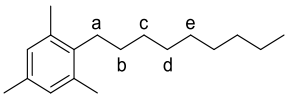


2-Octyl-1,3,5-trimethylbenzene was prepared from 1-octanol (79.4 µL, 0.476 mmol, ~0.25 M), mesitylene (331 µL, 2.380 mmol), TfOH (4.21 µL, 0.048 mmol) and HFIP (1.90 mL). Regioisomer **a** was detected with the GC/MS at retention time 5.55 min (old GC column). Peak at 2.78 min corresponds to mesitylene.

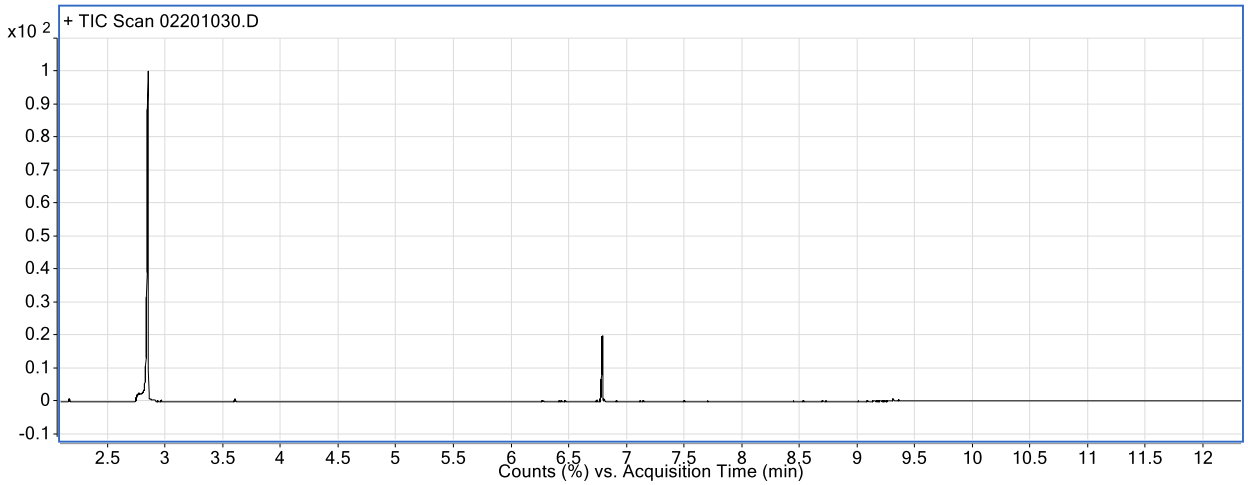


2-Octyl-1,3,5-trimethylbenzene and three regioisomers (**2-octyl**, **3-octyl** and **4-octyl**) were prepared from 1-octanol (159 µL, 0.994 mmol, ~1.0 M), mesitylene (696 µL, 5.00 mmol), TfOH (8.85 µL, 0.10 mmol) and HFIP (1.0 mL). The regioisomer ratio is: **a**:**b**:**c**:**d** = 41:27:13:11 at retention times 5.57, 5.25, 5.08 and 5.03 min, respectively.

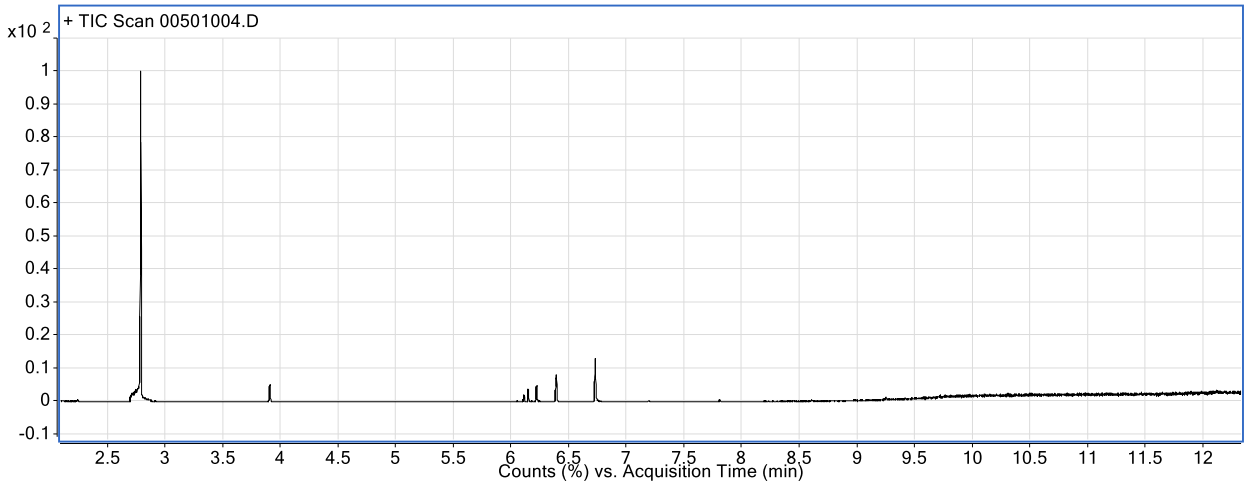


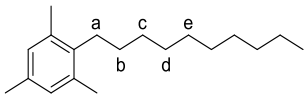


2-Nonyl-1,3,5-trimethylbenzene was prepared from 1-nonanol (87 µL, 0.498 mmol, ~0.25 M), mesitylene (347 µL, 2.492 mmol), TfOH (4.41 µL, 0.05 mmol) and HFIP (1.99 mL). Regioisomer **a** was detected with the GC/MS at retention time 6.78 min. Peak at 2.78 min corresponds to mesitylene.

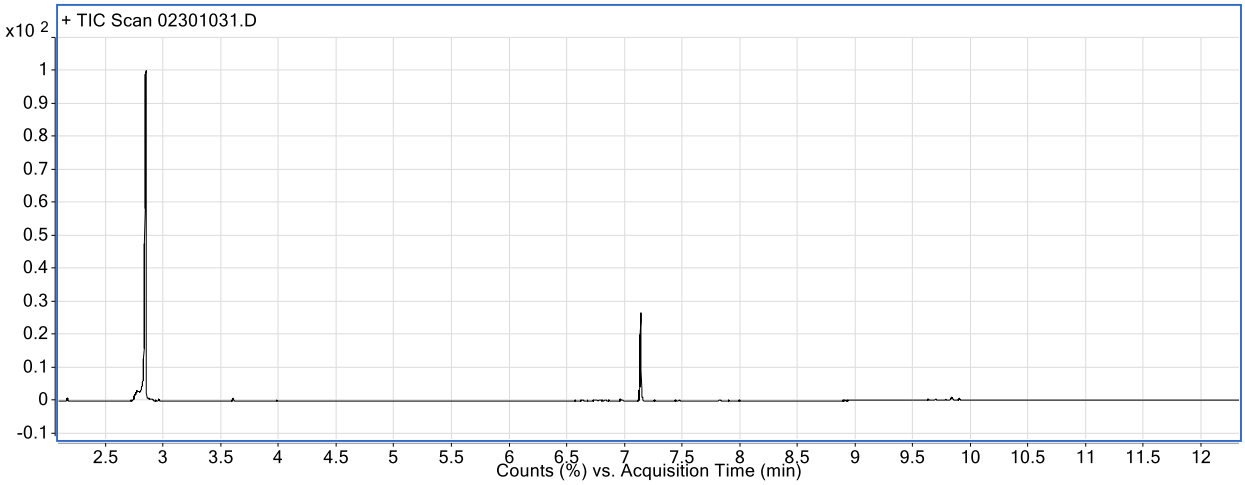


2-Nonyl-1,3,5-trimethylbenzene and four regioisomers (**2-nonyl**, **3-nonyl**, **4-nonyl** and **5-nonyl**) were prepared from 1-nonanol (87 µL, 0.484 mmol, ~1.0 M), mesitylene (337 µL, 2.419 mmol), TfOH (4.28 µL, 0.048 mmol) and HFIP (0.48 mL). The regioisomer ratio is: **a**:**b**:**c**:**d**:**e** = 50:23:11:9:6.

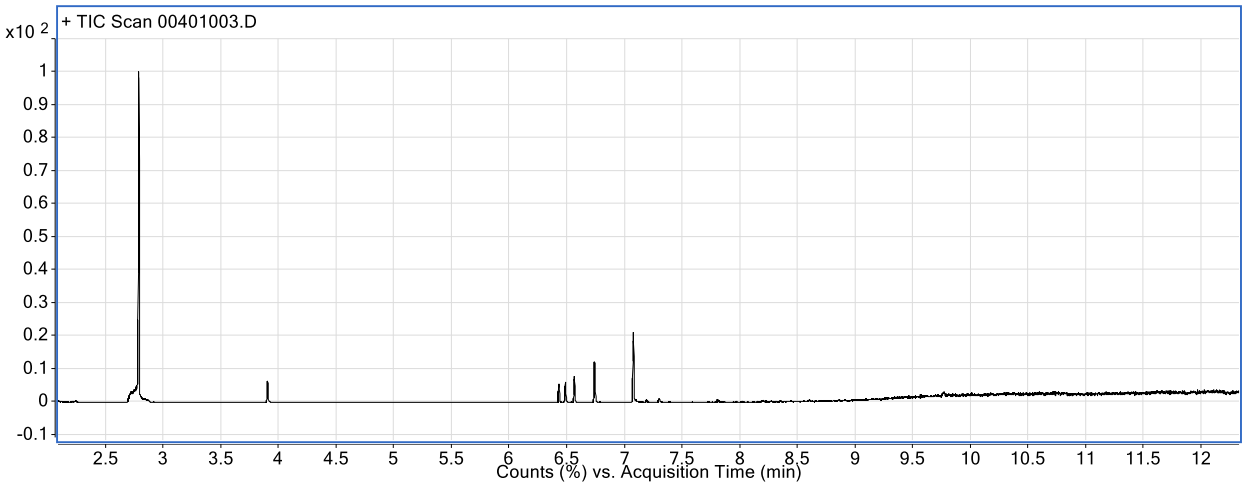


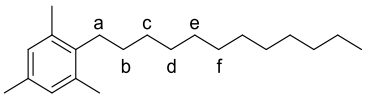


2-Decyl-1,3,5-trimethylbenzene was prepared from 1-decanol (95 µL, 0.506 mmol, ~0.25 M), mesitylene (352 µL, 2.530 mmol), TfOH (4.48 µL, 0.051 mmol) and HFIP (2.02 mL). Regioisomer **a** was detected with the GC/MS at retention time 7.13 min. Peak at 2.85 min corresponds to mesitylene.

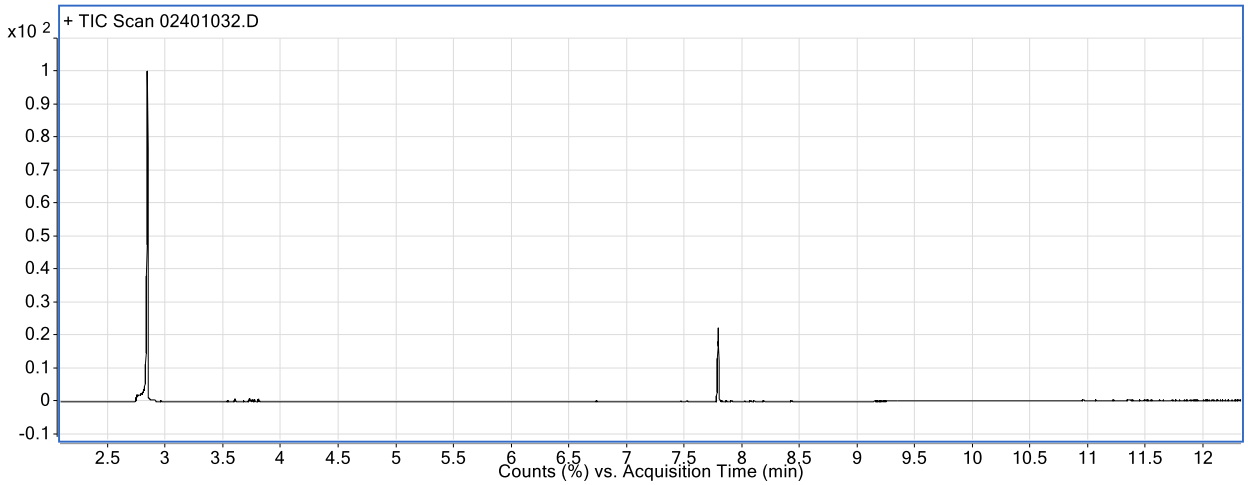


2-Decyl-1,3,5-trimethylbenzene and four regioisomers (**2-decyl**, **3-decyl**, **4-decyl** and **5-decyl**) were prepared from 1-decanol (95 µL, 0.484 mmol, ~1.0 M), mesitylene (337 µL, 2.420 mmol), TfOH (4.28 µL, 0.048 mmol) and HFIP (0.48 mL). The regioisomer ratio is: **a**:**b**:**c**:**d**:**e** = 38:25:13:12:12.

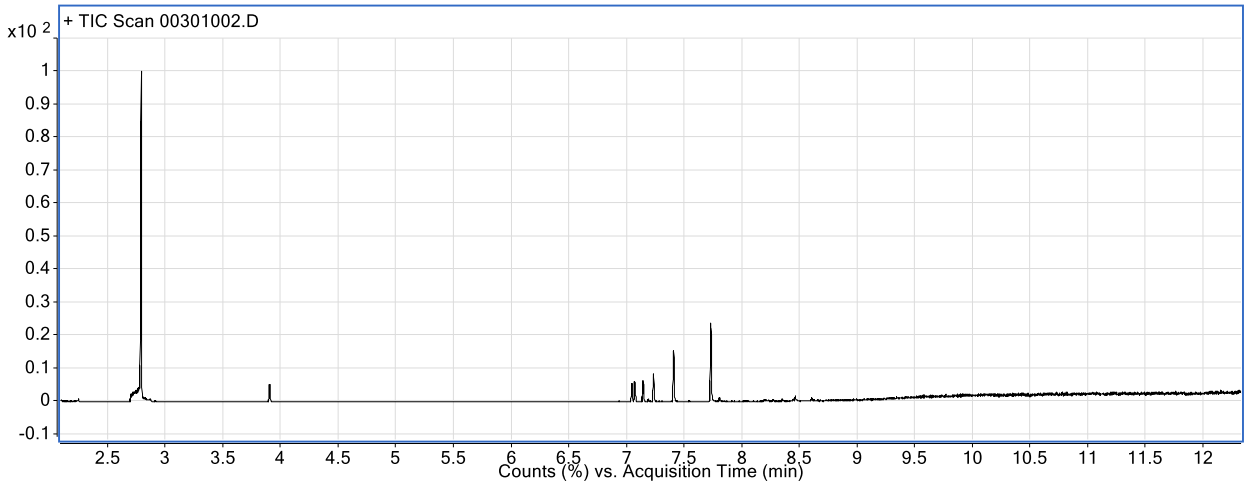


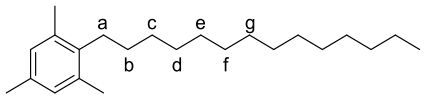


2-Dodecyl-1,3,5-trimethylbenzene was prepared from 1-dodecanol (112 μL, 0.538 mmol, ~0.25 M), mesitylene (374 μL, 2.691 mmol), TfOH (4.76 μL, 0.054 mmol) and HFIP (2.15 mL). Regioisomer **a** was detected with the GC/MS at retention time 7.79 min. Peak at 2.84 min corresponds to mesitylene, and peaks around 3.7 min correspond to dodecenes.

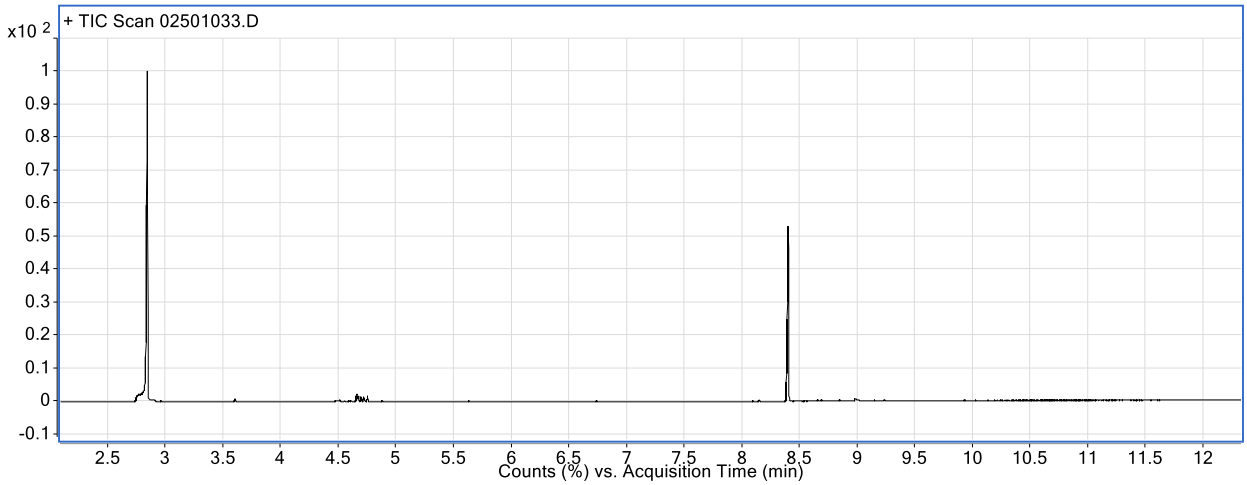


2-Dodecyl-1,3,5-trimethylbenzene and four regioisomers (**2-dodecyl**, **3-dodecyl**, **4-dodecyl**, **5-decyl** and **6-dodecyl)** were prepared from 1-dodecanol (112 μL, 0.518 mmol, ~1.0 M), mesitylene (360 μL, 2.589 mmol), TfOH (4.58 μL, 0.052 mmol) and HFIP (0.52 mL). The regioisomer ratio is: **a**:**b**:**c**:**d**:**e**:**f** = 60:14:6:5:6:7.

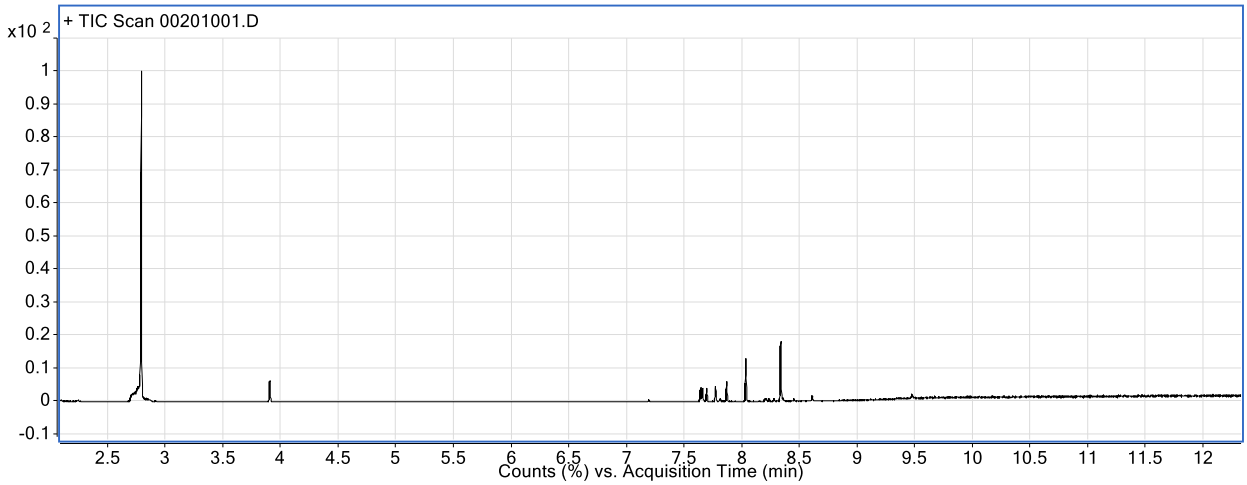


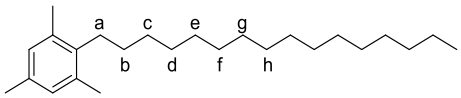


2-Tetradecyl-1,3,5-trimethylbenzene was prepared from 1-tetradecanol (105.8 mg, 0.493 mmol, ~0.25 M), mesitylene (343 μL, 2.467 mmol), TfOH (4.36 μL, 0.049 mmol) and HFIP (1.97 mL). Regioisomer **a** was detected with the GC/MS at retention time 8.39 min. Peak at 2.84 min corresponds to mesitylene, and peak around 4.7 min to tetradecenes.

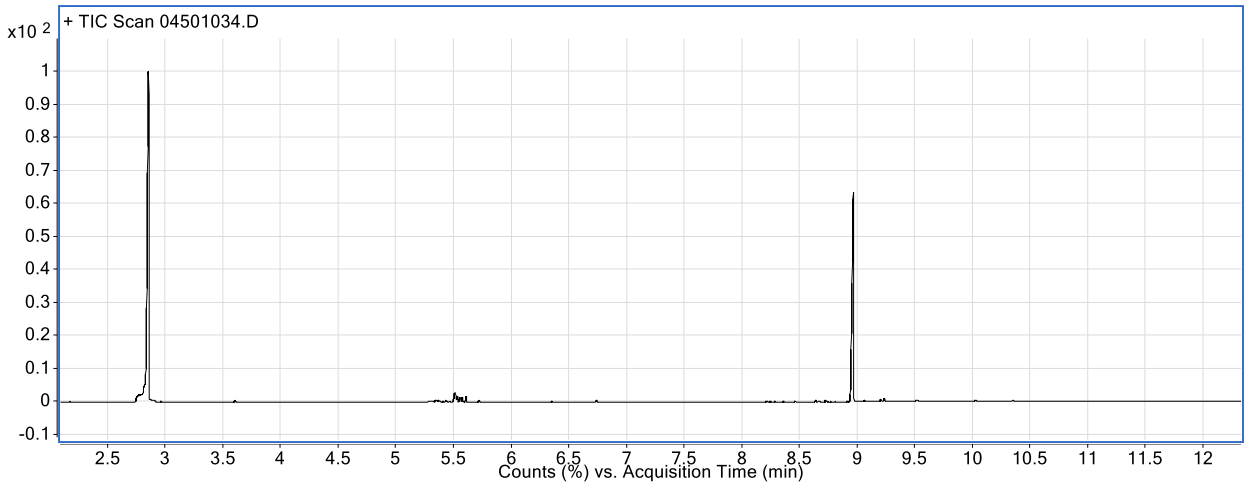


2-Tetradecyl-1,3,5-trimethylbenzene and six regioisomers (**2-tetradecyl**, **3-tetradecyl**, **4-tetradecyl**, **5-tetradecyl**, **6-tetradecyl** and **7-tetradecyl**) were prepared from 1-tetradecanol (104.5 mg, 0.487 mmol, ~1.0 M), mesitylene (339 μL, 2.437 mmol), TfOH (4.31 μL, 0.049 mmol) and HFIP (0.49 mL). The regioisomer ratio is: **a**:**b**:**c**:**d**:**e**:**f**:**g** = 32:22:11:9:9:9:8.

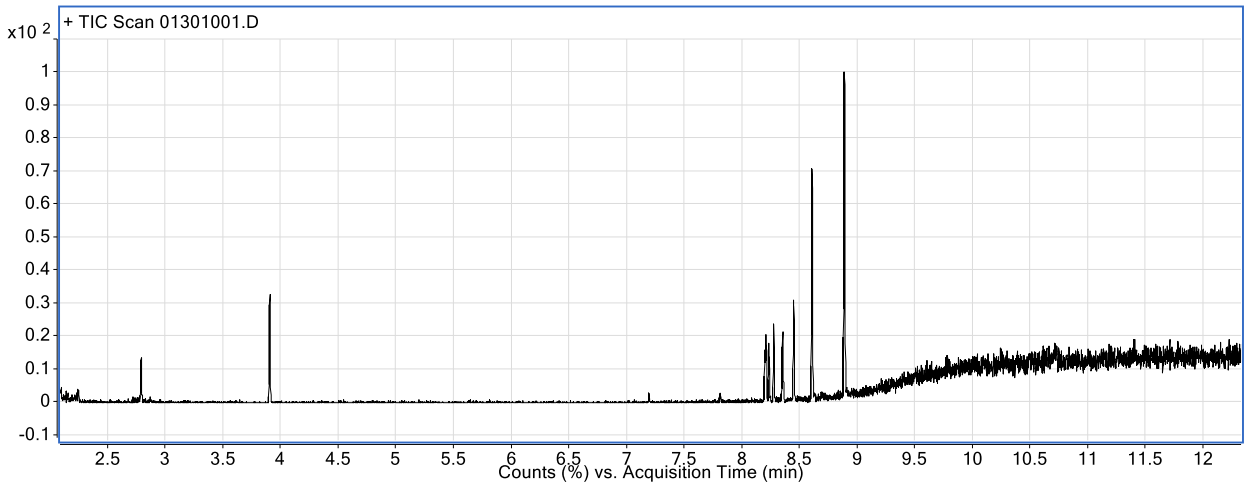


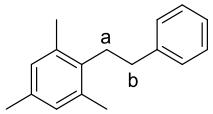


2-Hexadecyl-1,3,5-trimethylbenzene was prepared from 1-hexadecanol (118.7 mg, 0.490 mmol, ~0.25 M), mesitylene (341 µL, 2.448 mmol), TfOH (4.34 µL, 0.049 mmol) and HFIP (1.96 mL). Regioisomer **a** was detected with the GC/MS at retention time 8.96 min. Peak at 2.85 min corresponds to mesitylene, and peak around 5.50 min to hexadecenes.

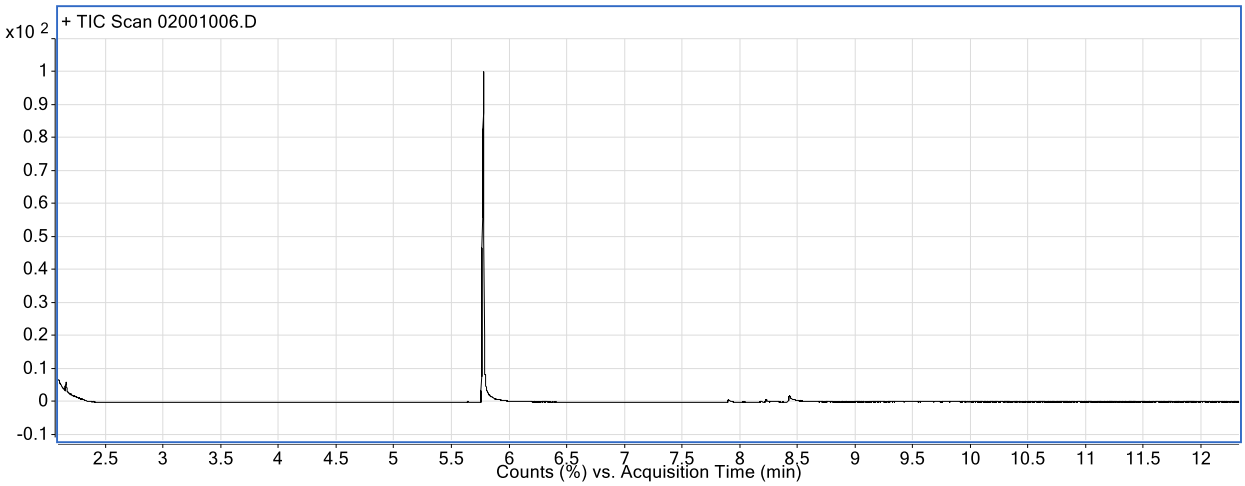


2-Hexadecyl-1,3,5-trimethylbenzene and seven regioisomers (**2-hexadecyl**, **3-hexadecyl**, **4-hexadecyl**, **5-hexadecyl**, **6-hexadecyl**, **7-hexadecyl** and **8-hexadecyl**) were prepared from 1-hexadecanol (117.5 mg, 0.485 mmol, ~1.0 M), mesitylene (337 µL, 2.423 mmol), TfOH (4.29 µL, 0.049 mmol) and HFIP (0.49 mL). The regioisomer ratio is: **a**:**b**:**c**:**d**:**e**:**f**:(**g**+**h**) = 34:18:9:8:7:8:15.

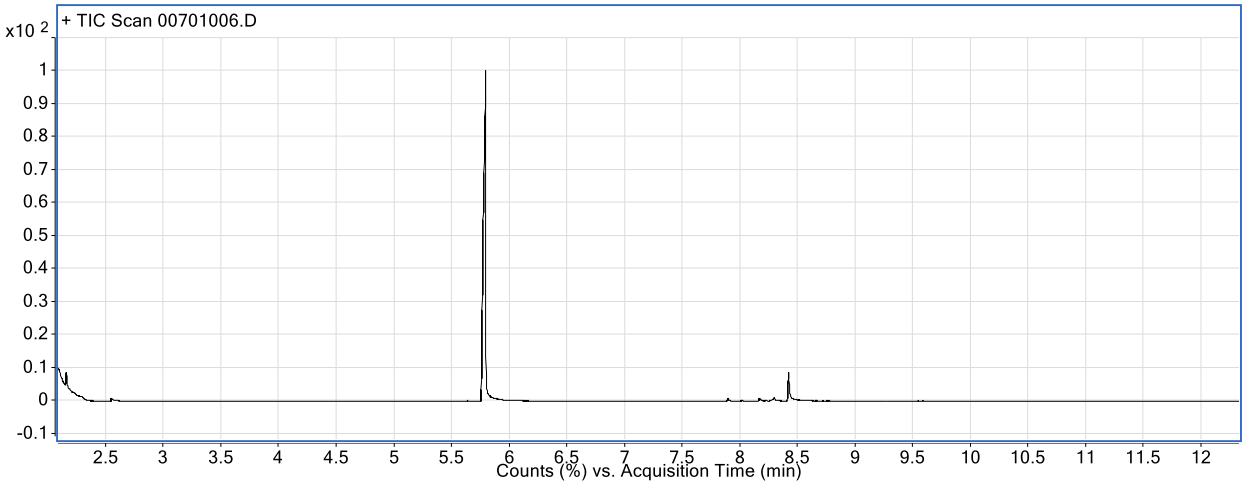




1,3,5-trimethyl-2-phenethylbenzene was prepared from 2-phenylethanol (59.9 μL, 0.507 mmol, ~0.25 M), mesitylene (352 μL, 2.533 mmol), TfOH (4.49 μL, 0.051 mmol) and HFIP (2.03 mL). Regioisomer **a** was detected with the GC/MS at retention time 5.77 min. Purification with silica gel column chromatography (petroleum ether 100%) gave 106.8 mg of colorless oil (94% yield). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ (ppm): 7.34–7.31 (m, 2H), 7.26–7.20 (m, 2H), 6.87 (s, 2H), 2.91–2.87 (m, 2H), 2.77–2.72 (m, 2H), 2.33 (s, 6H), 2.28 (s, 3H).



1,3,5-trimethyl-2-phenethylbenzene was also prepared from 2-phenylethanol (59.9 μL, 0.520 mmol, ~1.0 M), mesitylene (362 μL, 2.599 mmol), TfOH (4.60 μL, 0.052 mmol) and HFIP (0.52 mL). Regioisomer **a** was detected with the GC/MS at retention time 5.79 min. Regioisomer **b** was not detected. Purification with silica gel column chromatography (petroleum ether 100%) gave 97.1 mg of colorless oil (83% yield).



3. 1. Calibration curve for 1-hexadecanol

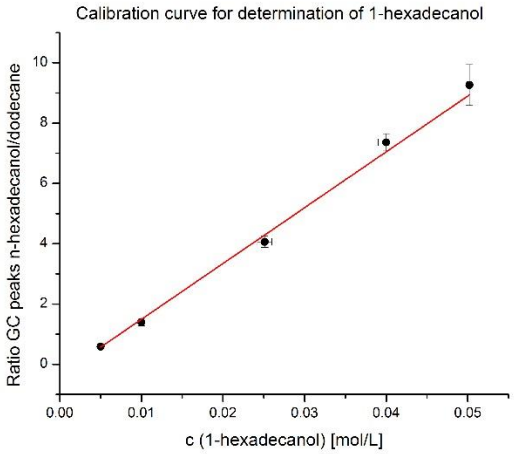
A series of standard solutions of 1-hexadecanol was prepared as follows: 121.6 mg (0.50157 mmol) of 1-hexadecanol was dissolved in petroleum ether/EtOAc (1:9) in 10.00 mL volumetric flask. Concentration of this solution was: c_1 = (0.0502 ± 0.0003) mol L^{-1}. 4.00 mL of this solution was transferred to a 5.00 mL volumetric flask and diluted with petroleum ether/EtOAc (1:9). Concentration of this solution was: c_2 = (0.040 ± 0.001) mol L^{-1}. Similarly, three another solutions with concentrations c_3 = (0.0251 ± 0.0009) mol L^{-1}, c_4 = (0.0100 ± 0.0003) mol L^{-1} and c_5 = (0.0050 ± 0.0002) mol L^{-1} were prepared. 1.5 μL of each solution was taken and transferred in a GC vial containing 300 μL of isopropanol solution of dodecane (standard solution of 1.91 μL dodecane in 200.0 mL isopropanol). The ratios of the 1-hexadecanol peak and dodecane peak were calculated from chromatograms.

The same procedure was repeated for two more times, with exactly the same starting mass of 1-hexadecanol. Therefore, three standard series of 1-hexadecanol solutions were prepared. Each solution from the series was analyzed by GC with two independent probes, and average values of 1-hexadecanol/dodecane peak ratios were calculated from all repetitions.

Data used for construction of the calibration curve for 1-hexadecanol

c [mol L^{-1}]	Error *c* [mol L^{-1}]	1-hexadecanol/dodecane GC peak ratios					Average ratio	Ratio st. dev.
		St. ser. I	St. ser. II		St. ser. III			
		Rep. 1	Rep. 1	Rep. 2	Rep. 1	Rep. 2		
0.0502	0.0003	8.32931	10.05215	9.011549	9.775155	9.144533	**9.26254**	0.677145
0.04	0.001	7.284416	7.541722	6.890475	7.53935	7.544405	**7.360074**	0.285202
0.0251	0.0009	3.877833	4.287793	3.872227	4.166707	4.106659	**4.062244**	0.182942
0.01	0.0003	1.431565	1.492707	1.30167	1.526979	1.25513	**1.40161**	0.118699
0.005	0.0002	0.633656	0.616306	0.541736	0.600158	0.533624	**0.585096**	0.044968

(St. ser. - standard series; Rep. - repetition; St. dev. - standard deviation)



The equation of the calibration curve ($R^2 = 0.9952$) is thus:

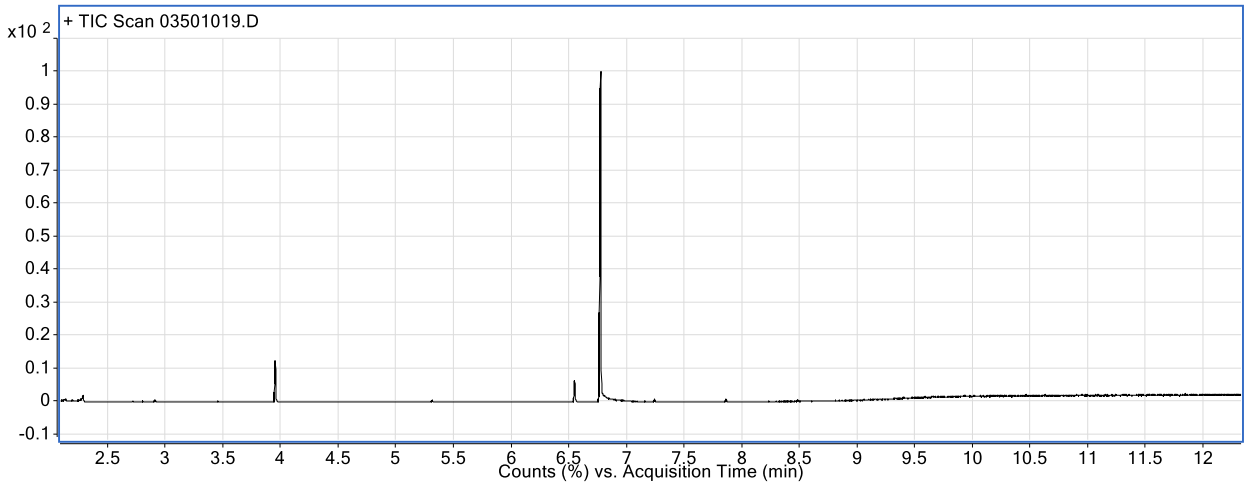
$$\text{Ratio} = (185 \pm 7)\ \text{L mol}^{-1}\ c - (0.36 \pm 0.07),$$

which gave the corresponding expression for calculation of the 1-hexadecanol concentration from the GC chromatograms:

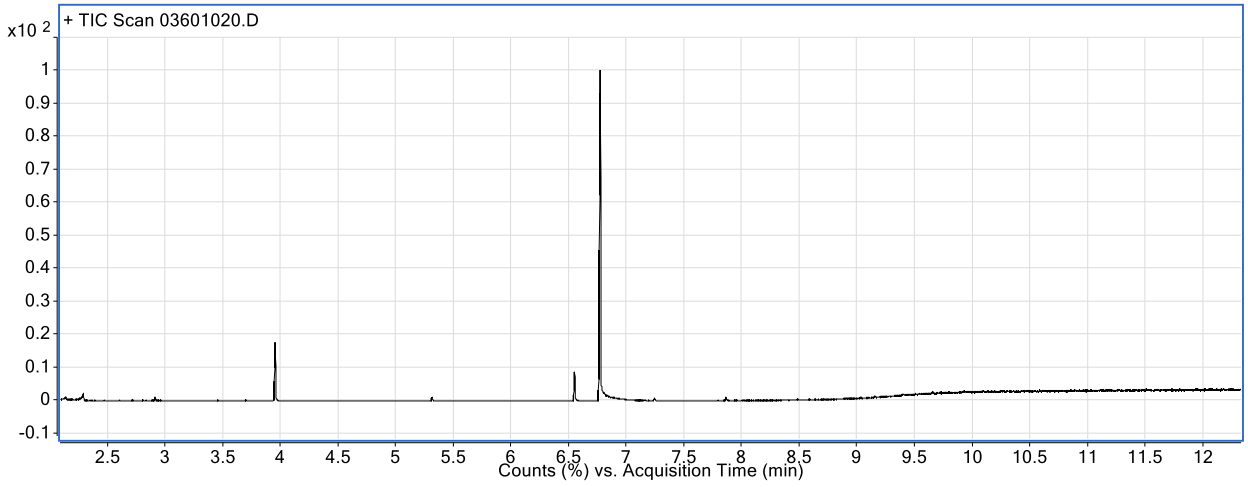
$$c = (\text{Ratio} + 0.36)\ \text{mol L}^{-1} / 185.$$

Representative GC chromatograms from standard series II, repetition 1 are given below. Dodecane peak is at 3.95 min, and 1-hexadecanol peak is at 6.77 min. Other peaks are impurities.

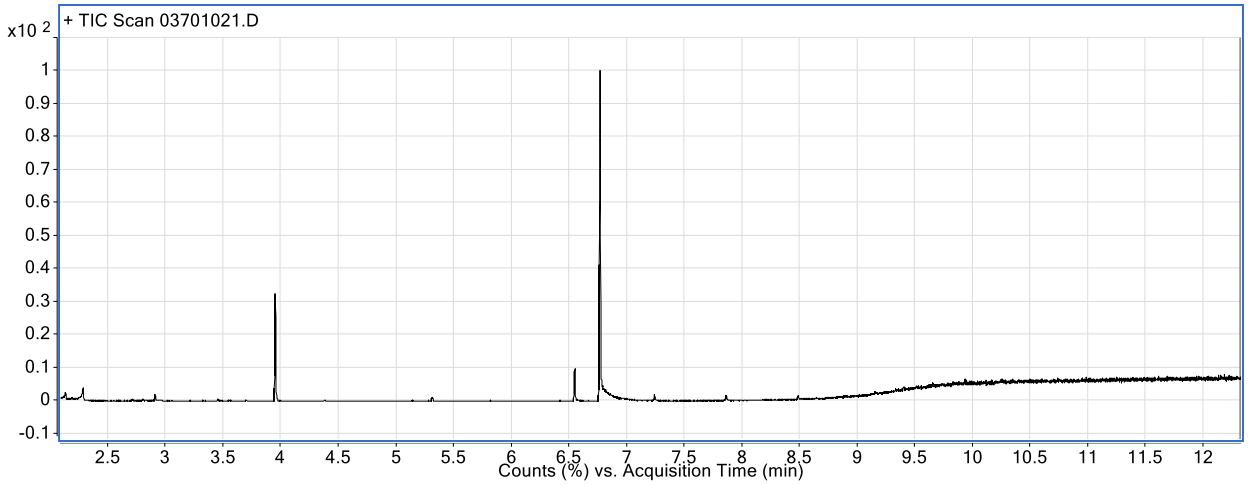
$c_1 = (0.0502 \pm 0.0003)$ mol L^{-1}, Ratio = 10.05215



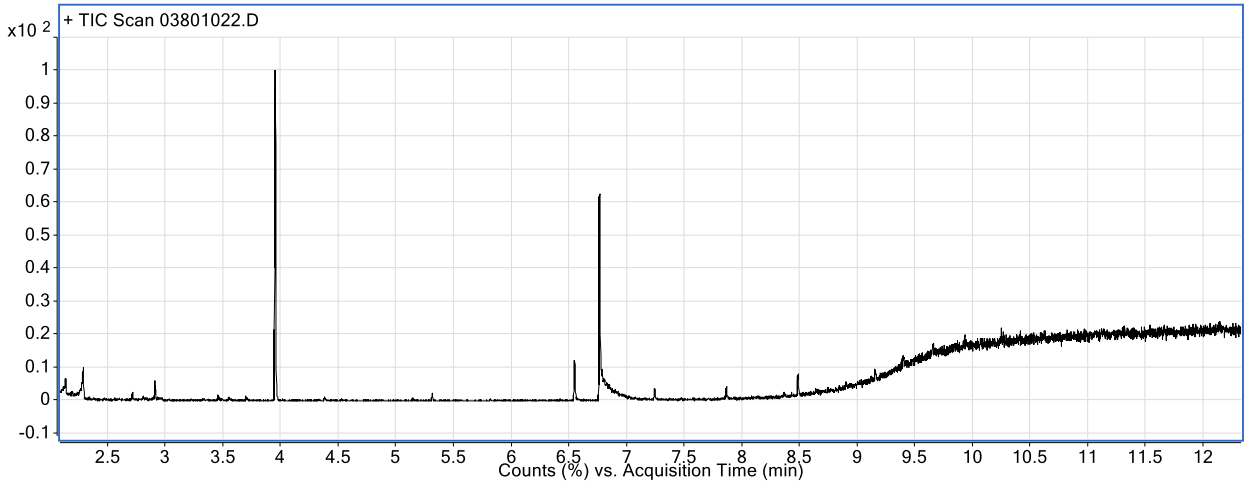
$c_2 = (0.040 \pm 0.001)$ mol L^{-1}, Ratio = 7.541722



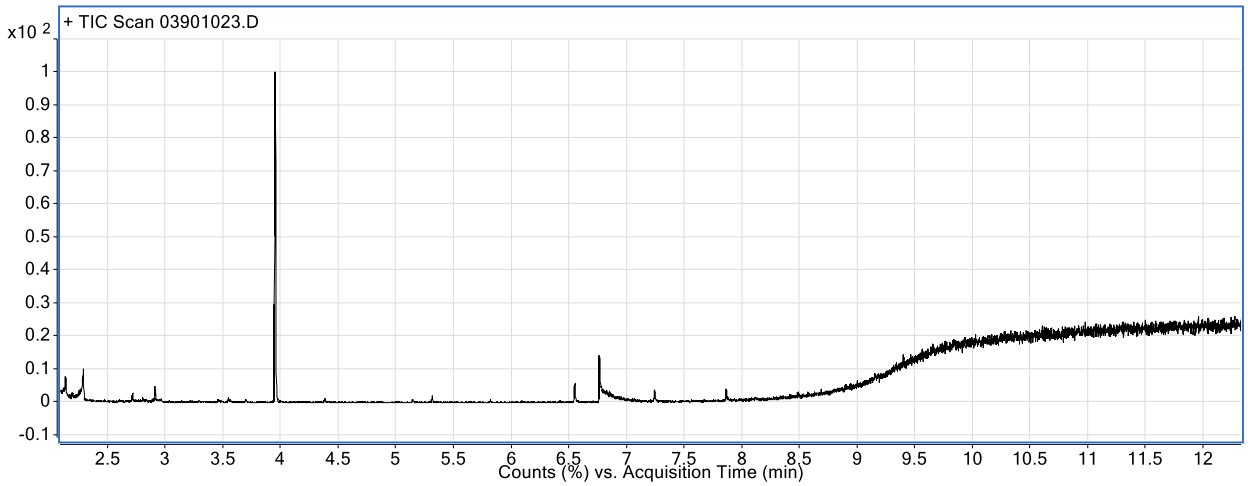
c_3 = (0.0251 ± 0.0009) mol L^{-1}, Ratio = 4.287793



c_4 = (0.0100 ± 0.0003) mol L^{-1}, Ratio = 1.492707



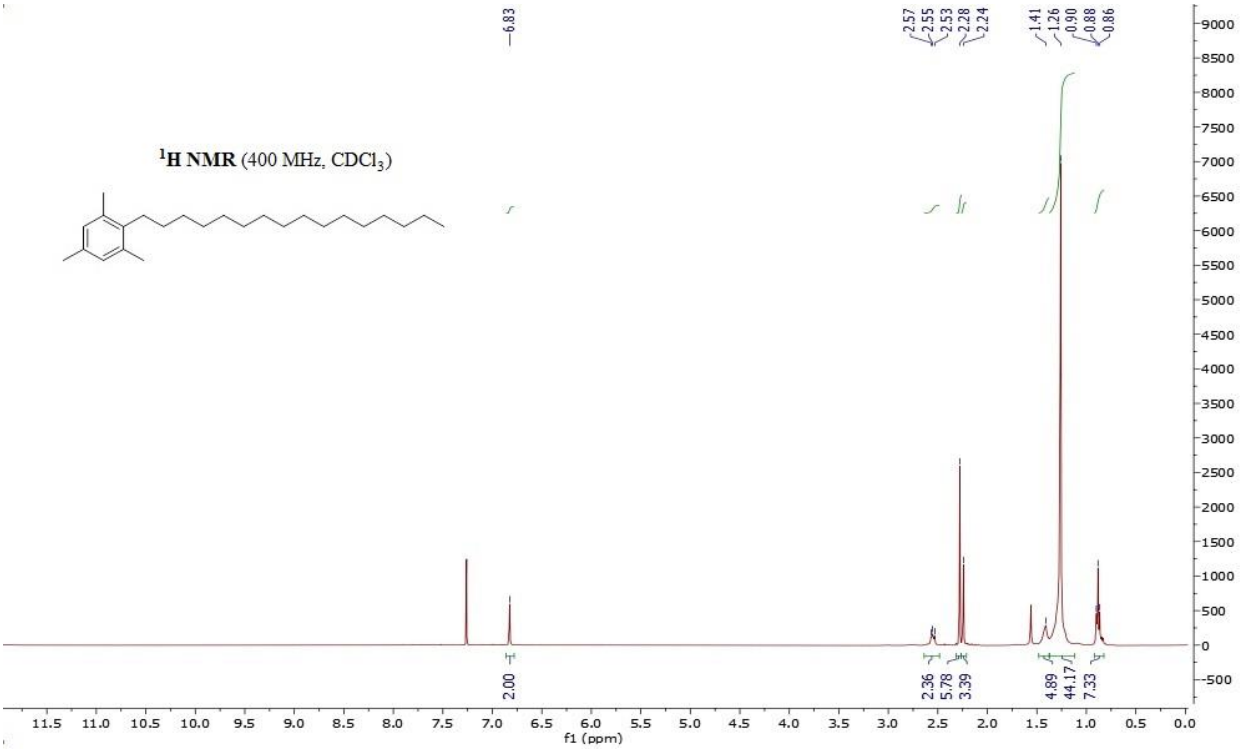
c_5 = (0.0050 ± 0.0002) mol L^{-1}, Ratio = 0.616306

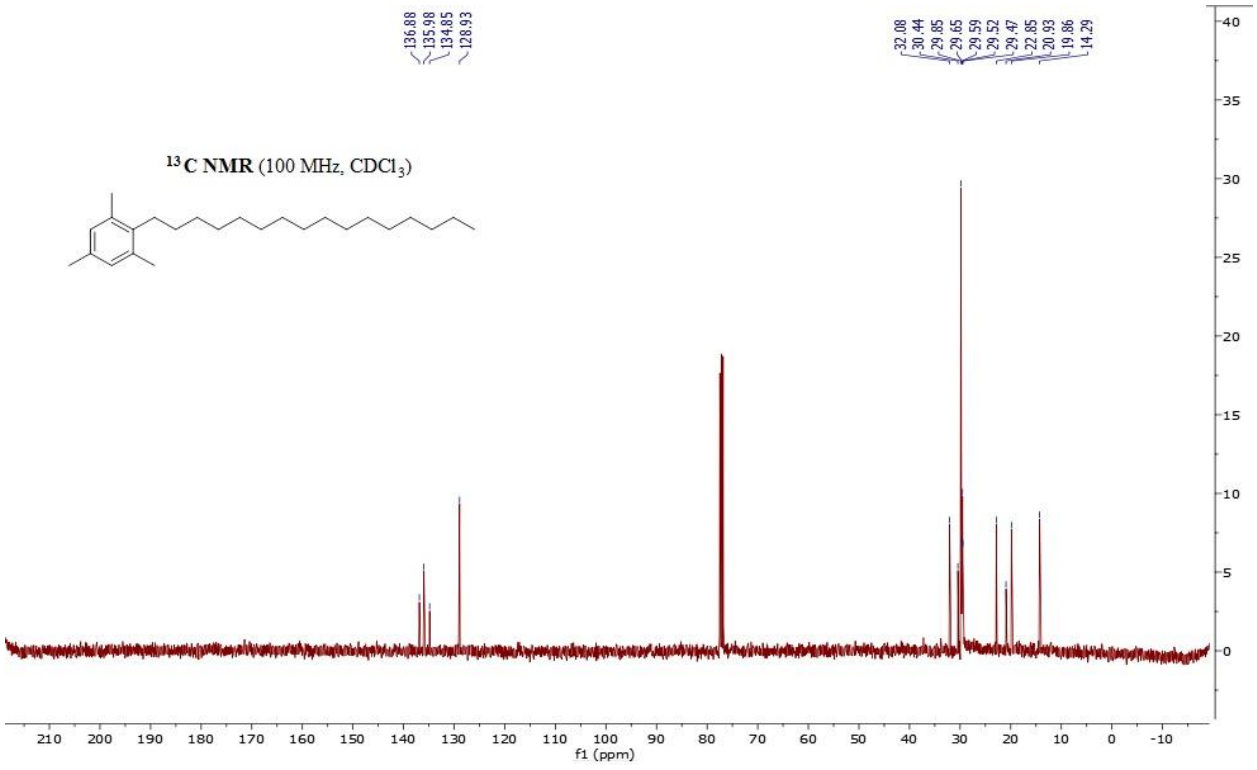


3. 2. Isolation of *n*-hexadecylmesitylene

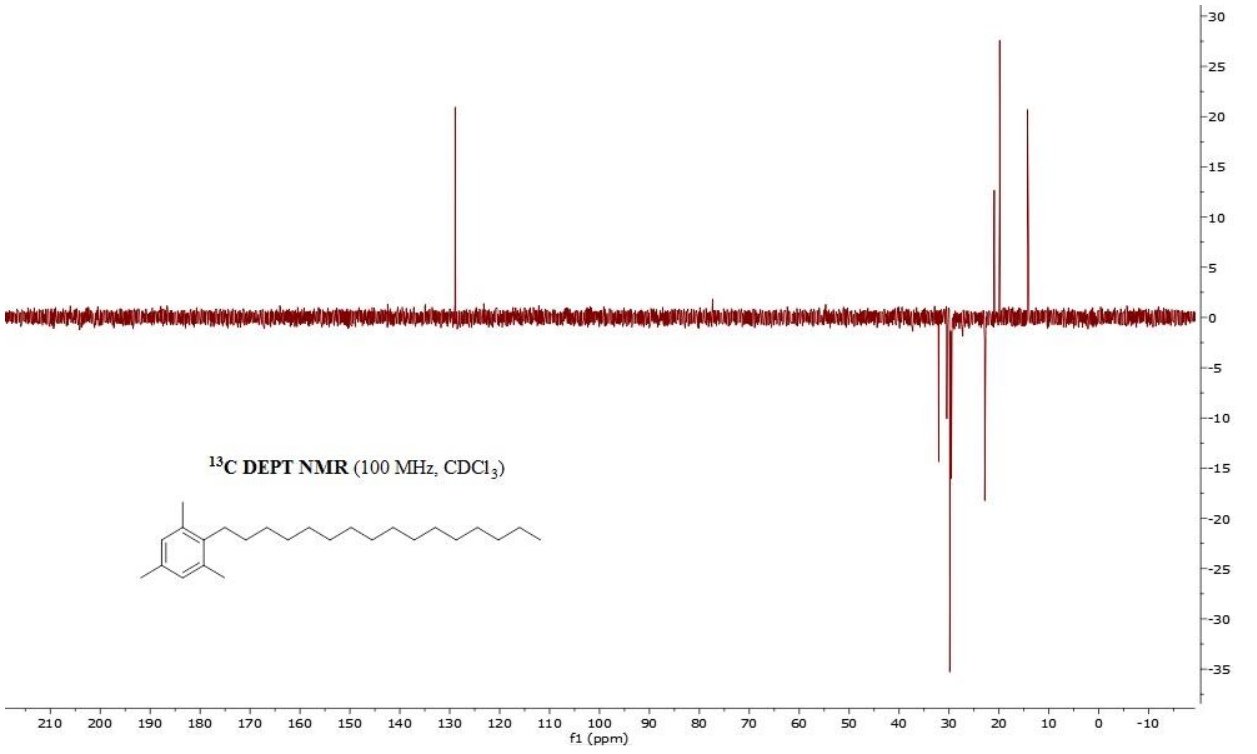
In order to provide enough material for the construction of the calibration curve, *n*-hexadecylmesitylene (i. e. 2-hexadecyl-1,3,5-trimethylbenzene) was synthesized from *n*-hexadecanol (121 mg, 0.5 mmol) and mesitylene (348 μL, 2.5 mmol) with TfOH (4.42 μL, 0.05 mmol) in HFIP (2.0 mL). The reaction mixture was heated for 24 h at 120 °C. Due to the lack of bigger reaction flask suitable for reactions under high pressure, this procedure was repeated approximately 30 times. All crude reaction residues were combined. Mesitylene and HFIP distilled off by Kugelrohr, and the rest was passed through a silica column to remove the traces of TfOH. In order to separate the product from the mixture with alkenes, multiple crystalization in acetone was performed. Cold acetone was added to the *n*-hexadecylmesitylene/hexadecenes mixture, the mixture was agitated, and quickly left in the freezer over night. The next day, the white solid was recuperated from the acetone layer (upper layer), new quantity of cold acetone was added, and the crystalization process repeated another 10 times. Altogether, 1.84 g of white solid was isolated, resulting in ~36% overall isolated yield. The purity of the compound was verified by GC, ^{1}H, ^{13}C and DEPT NMR.

Characterization data for 2-hexadecyl-1,3,5-trimethylbenzene: **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 2H), 2.60–2.50 (m, 2H), 2.28 (s, 6H), 2.24 (s, 3H), 1.48–1.38 (m), 1.26 (s), 0.92–0.82 (m) [integrations of last three peaks exceed the real number of protons in the compound due to the overlap of the signals]. **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 136.9, 136.0, 134.9, 128.9, 32.1, 30.4, 29.9 (m), 29.7, 29.6, 29.5, 29.5, 22.9, 20.9, 19.9, 14.3.

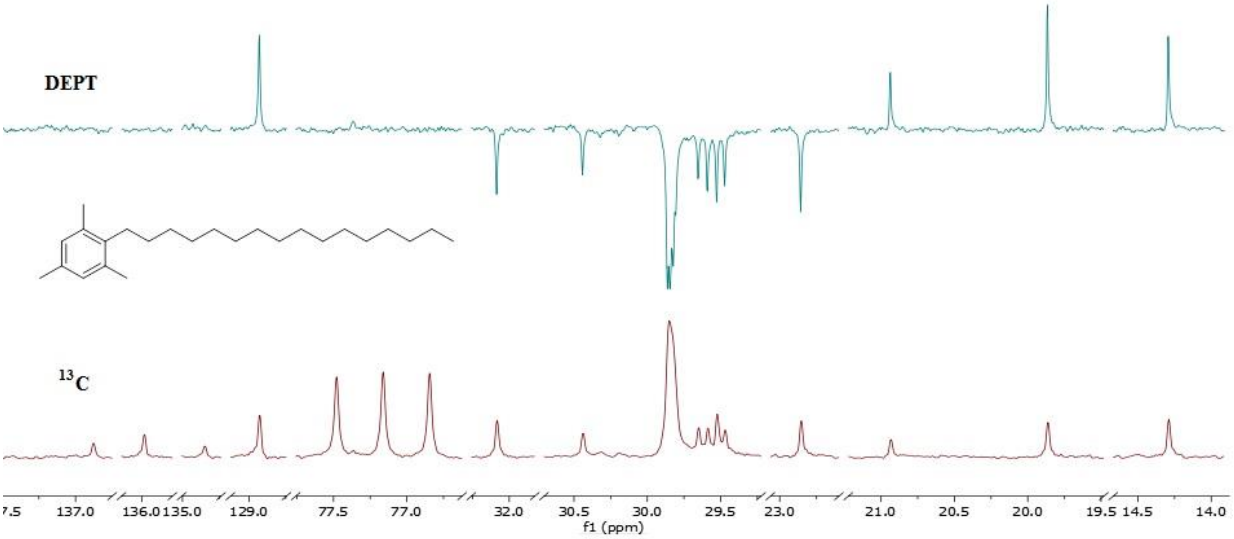




^{13}C NMR (100 MHz, $CDCl_3$)



^{13}C DEPT NMR (100 MHz, $CDCl_3$)



3. 3. Calibration curve for *n*-hexadecylmesitylene

A series of standard solutions of *n*-hexadecylmesitylene was prepared as follows: 87.6 mg (0.2542 mmol) of *n*-hexadecylmesitylene was dissolved in petroleum ether/EtOAc (1:9) in 5.00 mL volumetric flask. Concentration of this solution was: $c = (0.0508 \pm 0.0005)$ mol L^{-1}. From this solution, the rest of the standard series solutions were prepared by dilution. Concentrations of standard solutions were: $c_1 = (0.0203 \pm 0.0002)$ mol L^{-1}, $c_2 = (0.0102 \pm 0.0003)$ mol L^{-1}, $c_3 = (0.0051 \pm 0.0001)$ mol L^{-1}, $c_4 = (0.0025 \pm 0.0001)$ mol L^{-1} and $c_5 = (0.0010 \pm 0.0001)$ mol L^{-1}. 1.5 μL of each solution was taken and transferred in a GC vial containing 300 μL of isopropanol solution of dodecane (standard solution of 1.91 μL dodecane in 200.0 mL isopropanol). The ratios of the *n*-hexadecylmesitylene peak and dodecane peak were calculated from chromatograms.

The same procedure was repeated for two more times, with exactly the same starting mass of *n*-hexadecylmesitylene. Therefore, three standard series of *n*-hexadecylmesitylene solutions were prepared. Each solution from the series was analyzed by GC with two independent probes, and average values of *n*-hexadecylmesitylene/dodecane peak ratios were calculated from all repetitions. The equation of the calibration curve ($R^2 = 0.9931$) is:

$$\text{Ratio} = (421 \pm 20)\ \text{L mol}^{-1}\ c - (0.12 \pm 0.06),$$

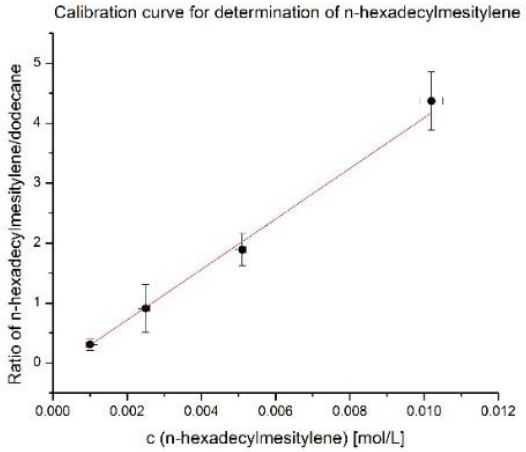
which gave the corresponding expression for calculation of *n*-hexadecylmesitylene concentration from the GC chromatograms:

$$c = (\text{Ratio} + 0.12)\ \text{mol L}^{-1} / 421.$$

Data used for construction of the calibration curve for *n*-hexadecylmesitylene

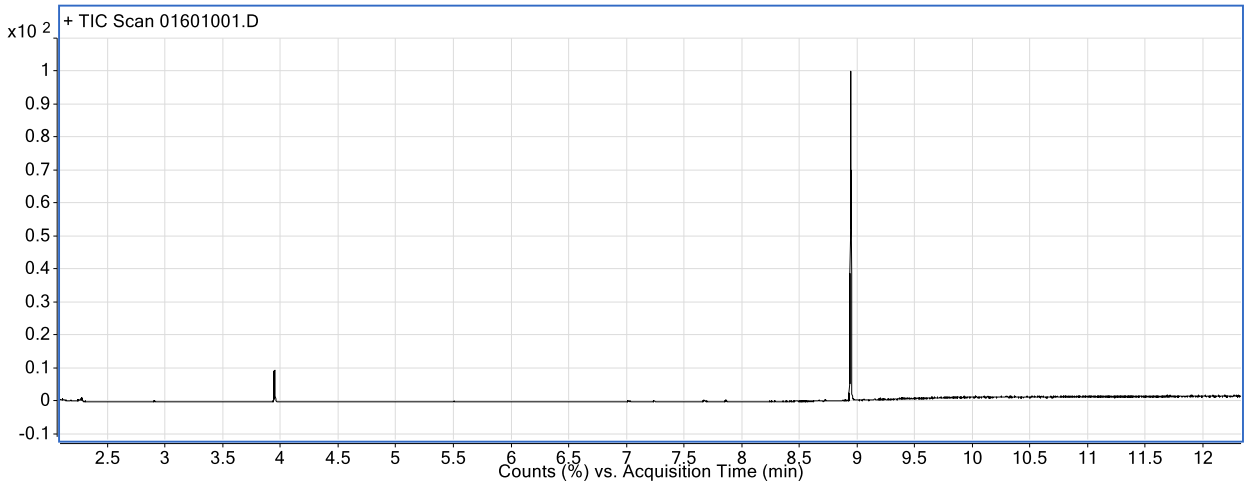
c [mol L^{-1}]	Error *c* [mol L^{-1}]	*n*-hexadecylmesitylene/dodecane GC peak ratios						Average ratio	Ratio st. dev.
		St. ser. I		St. ser. II		St. ser. III			
		Rep. 1	Rep. 2	Rep. 1	Rep. 2	Rep 1.	Rep. 2		
0.0203	0.0006	11.19804	9.020509	9.977838	8.915588	10.86621	9.621277	**9.933244**	0.942142
0.0102	0.0003	4.352657	4.875182	4.270776	3.711105	4.978716	4.030406	**4.369807**	0.4869
0.0051	0.0001	1.998123	2.146768	1.746793	1.647431	2.222943	1.584191	**1.891042**	0.268824
0.0025	0.0001	0.730333	1.715446	0.702661	0.770936	0.798492	0.734444	**0.908719**	0.396635
0.001	0.0001	0.285226	0.48751	0.303801	0.246299	0.31723	0.203851	**0.307319**	0.097464

(St. ser. - standard series; Rep. - repetition; St. dev. - standard deviation)

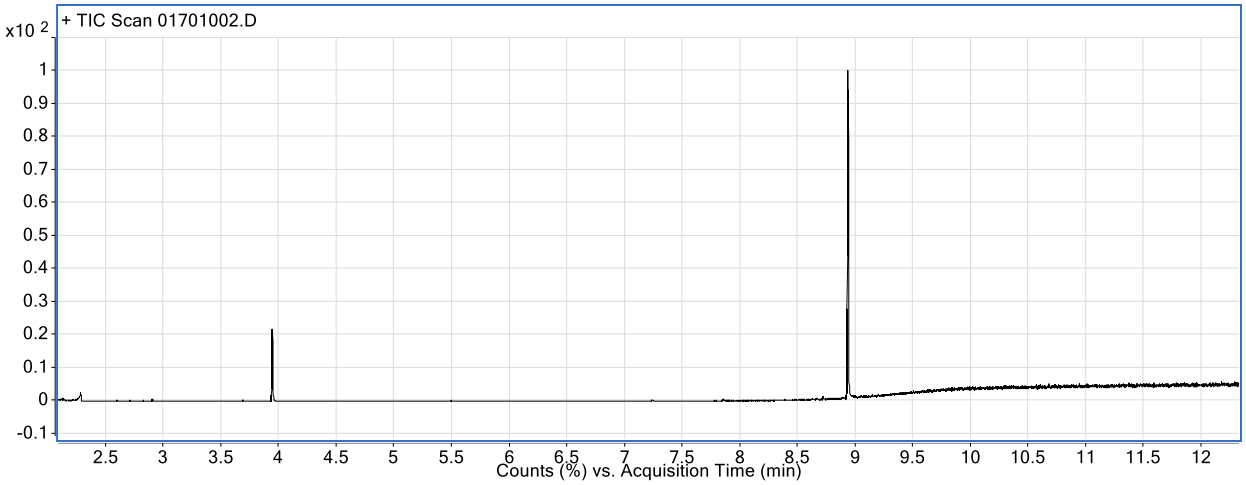


Representative GC chromatograms from standard series III, repetition 1 are given below. Dodecane peak is at 3.95 min, and n-hexadecylmesitylene peak is at 8.96 min. Other peaks are impurities.

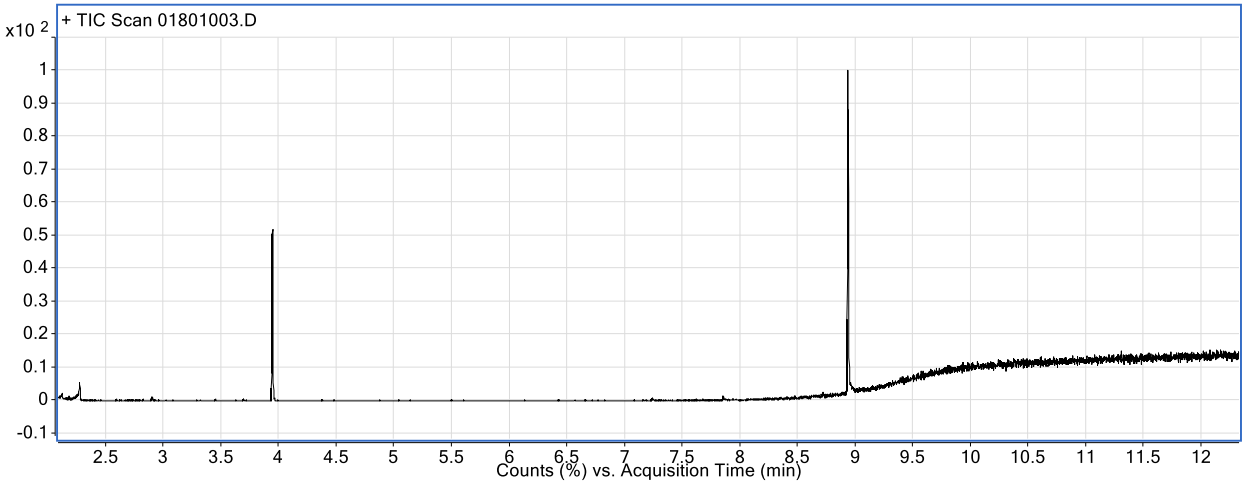
c_1 = (0.0203 ± 0.0002) mol L^{-1}, Ratio = 10.86621



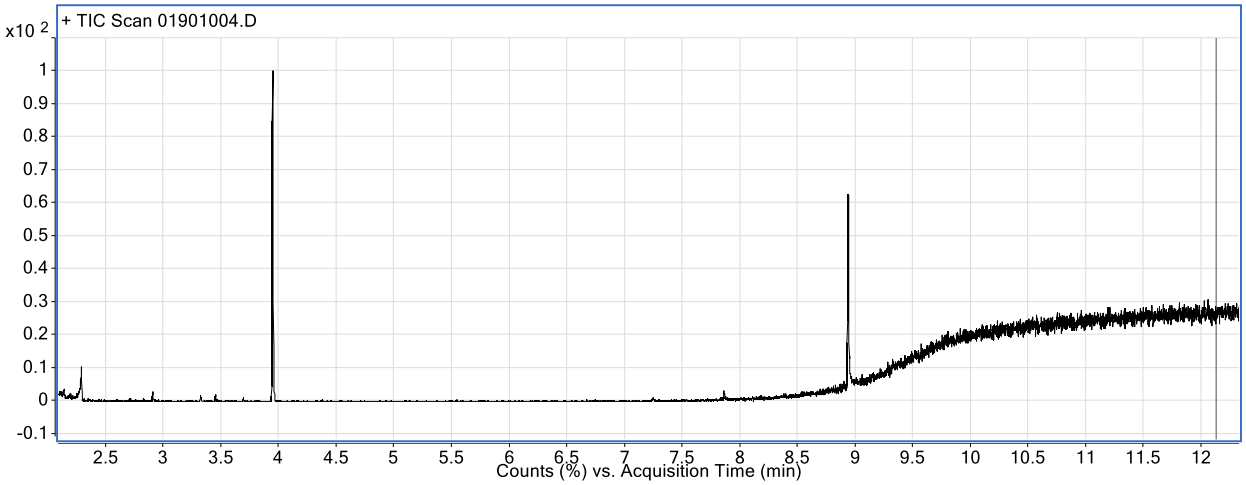
c_2 = (0.0102 ± 0.0003) mol L^{-1}, Ratio = 4.978716



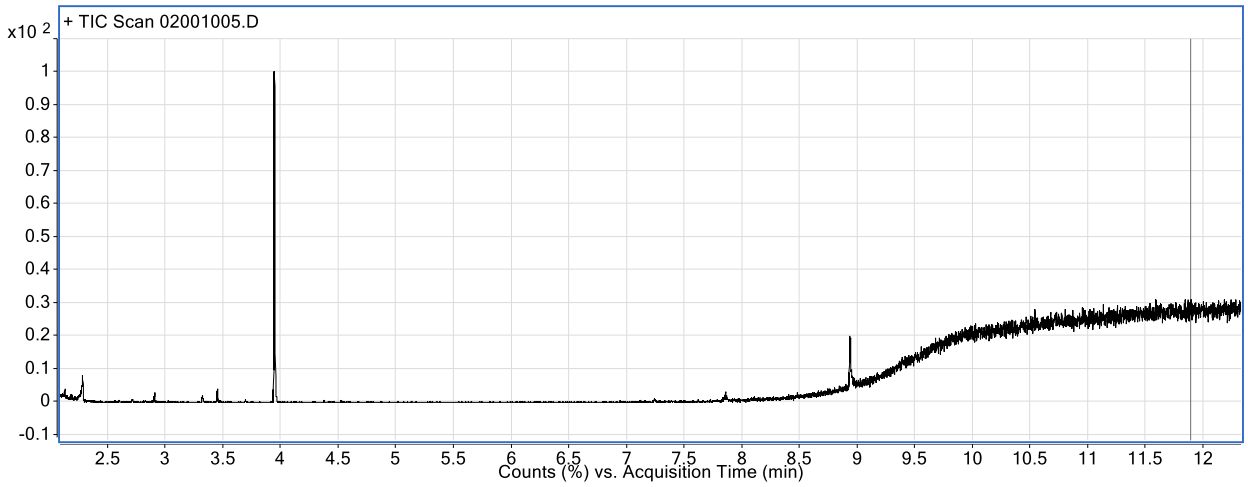
c_3 = (0.0051 ± 0.0001) mol L^{-1}, Ratio = 2.222943



c_4 = (0.0025 ± 0.0001) mol L^{-1}, Ratio = 0.798492

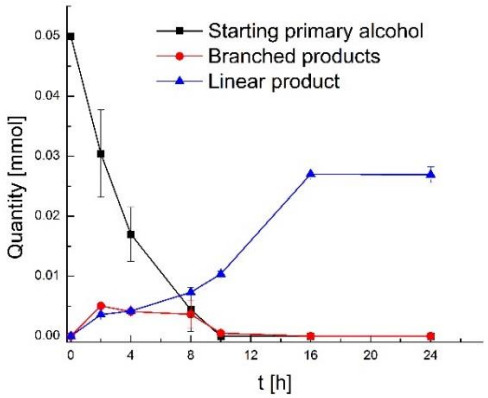


c_5 = (0.0010 ± 0.0001) mol L^{-1}, Ratio = 0.31723



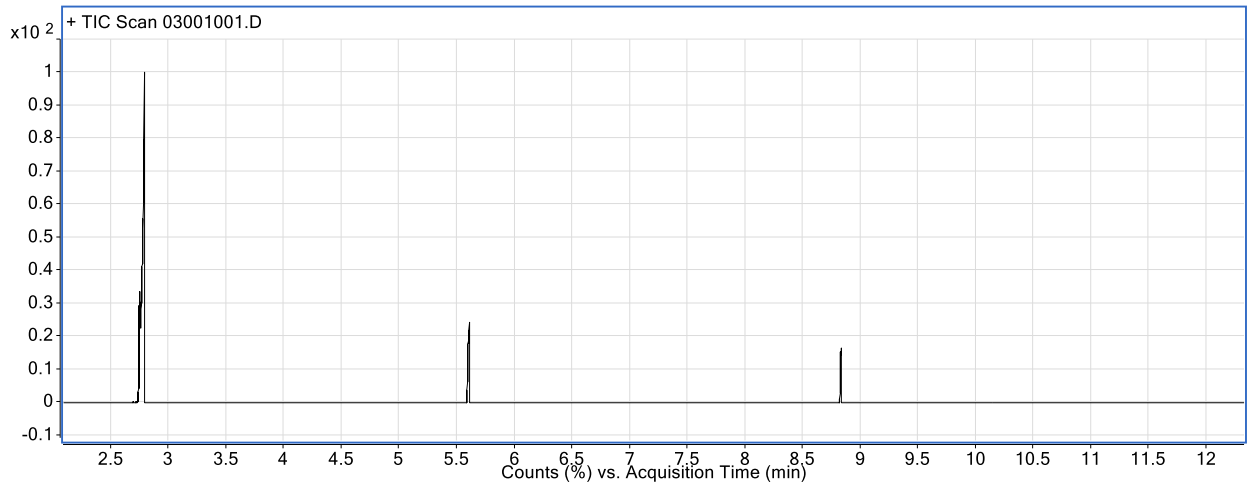
3. 4. Reaction progress analysis

Based on previously shown calibration curves for determination of concentration of 1-hexadecanol and *n*-hexadecylmesitylene, the reaction progress was monitored. The experimental setup and reaction conditions did not allow *in situ* monitoring. Therefore, a set of identical reactions was set up and each reaction was stopped after certain period of time and further analyzed. Each reaction was set up at with 121.0-121.5 mg of 1-hexadecanol, 348 μL mesitylene, 4.42 μL TfOH in 2.0 mL HFIP. After cooling down to room temperature, the reaction mixture was quantitatively transferred to a 10.00 mL volumetric flask, diluted with petroleum ether and isopropanol, and 1.5 μL of this solution was transferred to a GC vial containing 300 μL of dodecane in isopropanol standard solution (1.91 μL dodecane in 200.0 mL isopropanol). Based on the ratios of 1-hexadecanol and *n*-hexadecylmesitylene peaks with dodecane peak, the concentration of the starting alcohol, linear and branched products was determined. It was approximated that the response factors for linear and branched products are equal. For each reaction time, the reaction was repeated several times, in order to get consistent results.



3. 5. Yield estimation

In order to estimate the yield of linear products, relative response factors of mesitylene, 1-hexadecene and *n*-hexadecylmesitylene were determined. Therefore, 18.7 mg (0.054 mmol) of *n*-hexadecylmesitylene was dissolved in 1 mL *n*-hexane. 1.57 µL of 1-hexadecene and 0.75 µL of mesitylene were added to 100 µL of this solution. 3 µL of this solution was transferred to a GC vial with 300 µL of isopropanol and analyzed by GC. It was found that not enough mesitylene was added to observe an intense peak in gas chromatogram. Then, additional 0.20 µL of mesitylene was added directly to the GC vial, and the analysis was repeated. Relative ratios of the peak surfaces can be obtained from the chromatogram:



The GC vial therefore contained:

1.60 µmol of mesitylene (R_t = 2.79 min, peak surface area = 81.66%),
0.3738 µmol of 1-hexadecene (R_t = 5.60 min, peak surface area = 13.52%),
0.1626 µmol of *n*-hexadecylmesitylene (R_t = 8.83 min, peak surface area = 4.82%).

In order to get relative response factors, molar ratio of the three mixture components was calculated by diving them all with the value of the least quantity (0.1626 µmol). On the other hand, to get the relative peak surface areas of these compounds, the peak areas were divided by the least peak area observed (4.82%). The following values were obtained:

	Peak area ratio	Molar ratio
mesitylene	16.942	9.882
1-hexadecene	2.805	2.295
n-hexadecylmesitylene	1.000	1.000

Finally, the response factors were obtained by dividing the peak area ratios with molar ratios as follows:

	Peak area ratio	:	Molar ratio	=	**Response factor**	:	Equimolar ratio
mesitylene	16.942	:	9.882	=	**1.725**	:	1.000
1-hexadecene	2.805	:	2.295	=	**1.222**	:	1.000
n-hexadecylmesitylene	1.000	:	1.000	=	**1.000**	:	1.000

These values practically mean that if an equimolar mixture of mesitylene, 1-hexadecene and *n*-hexadecylmesitylene is analyzed by GC, mesitylene will give the biggest peak with surface 1.725 times bigger than the surface of the *n*-hexadecylmesitylene peak, whereas the peak of 1-hexadecene will be 1.222 times greater than the *n*-hexadecylmesitylene peak.

When the reaction of 1-hexadecanol (118.7 mg, 0.490 mmol, ~0.25 M) with mesitylene (341 μL, 2.448 mmol), TfOH (4.34 μL, 0.049 mmol) and HFIP (1.96 mL) was performed, the reaction mixture was passed through a silica column. Then mesitylene was distilled of by Kugelrohr, and the remaining crude mixture was weighed (120.6 mg) and analyzed by GC. Linear product (R_t = 8.96 min), hexadecenes (peaks around 5.50 min) and mesitylene (at 2.85 min) were detected, and their relative percentage in the mixture was estimated using the previously calculated response factors:

	GC peak area	:	Response factor	=	Molar ratio	·	Molar mass	=	Mass ratio	=	**Mass percent**
mesitylene	61.05%	:	1.725	=	35.39	·	120.19	=	4253.5	=	**25.4%**
1-hexadecene	5.66%	:	1.222	=	4.63	·	224.43	=	1039.1	=	**6.2%**
n-hexadecylmesitylene	33.29%	:	1.000	=	33.29	·	344.34	=	11463.1	=	**68.4%**

Since the total mass of the sample was 120.6 mg, and the mass percentage of *n*-hexadecyl-mesitylene in it was found to be 68.4%, the yield of the linear product in this case is:

$$0.684 \cdot 120.6 \text{ mg} / (0.490 \text{ mmol} \cdot 344.34 \text{ g/mol}) \cdot 100\ \% = 49\ \%.$$

The fact that the yield estimated in this manner (49%) is reasonably close to the value found from the calibration curve (54%) confirmed that this method can be used for *estimation* of the linear product yield. Asuming that lower alkenes and corresponding *n*-alkylmesitylenes will have approximately the same response factors to mesitylene, the yields of linear products were estimated for cases when 1-tetradecanol (57%), 1-dodecanol (24%), 1-decanol (30%) and 1-nonanol (26%) were used as substrates.

EXPERIMENTAL SECTION – CHAPTER 5
FRIEDEL-CRAFTS REACTIONS OF CYCLOPROPANES IN HFIP

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1. General information, materials and general procedures (donor-acceptor cyclopropanes)

All arylation/cyclopropane opening 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 followed by staining with basic $KMnO_4$ solution and heating.

^{1}H-NMR spectra were recorded on a Bruker UltraShield 400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C-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 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.

High resolution mass spectrometry (HRMS) analysis was performed on MicroTOF-Q Bruker (ESI) and ThermoScientific Exactive Plus EMR/Trace 1300 GC (APPI) instruments.

Materials: All commercial materials were purchased from Sigma-Aldrich, Alfa Aesar and FluoroChem, and were used as received, without further purification. Triflic acid (TfOH) *ReagentPlus*®, ≥99% (CAS: 1493-13-6) was purchased from Sigma Aldrich, and HFIP (CAS: 920-66-1) from FluoroChem. Tris(pentafluorophenyl)borane $B(C_6F_5)$ was purchased from Alfa Aesar and used without precaution to exclude air or moisture. It is known to rapidly hydrate to $B(C_6F_5)•H_2O$ under such conditions.[226]

Preparation of Donor-Acceptor Cyclopropanes: Donor-acceptor cyclopropane diesters **C1a-C1j** were prepared via a two-step Knoevenagal/Corey-Chaykovsky sequence, according to unchanged literature procedures, in comparable yields to those reported and with corresponding analytical data.[227,228] Donor-acceptor cyclopropane **C1k**[229] was prepared by Corey-Chaykovsky cyclopropanation of *trans*-chalcone according to a literature procedure and with corresponding analytical data. Cyclopropanes **C1l-C1p** were prepared according to a two-step aldol condensation/Corey-Chaykovsky sequence, according to unchanged literature procedures, in comparable yields to those reported and with corresponding analytical data.

General Procedure L: A 10 mL Pyrex tube was charged with a stir bar, followed by the requisite cyclopropane (0.25 mmol), nucleophile (0.50 mmol), HFIP (0.125mL) and finally TfOH (2.2 µL, 10 mol%). The reaction was then stirred at ambient temperature until TLC showed disappearance of starting material (typically ca. 3 hours). At completion, the crude reaction mixture was concentrated *in vacuo* onto silica gel and purified by flash column chromatography over silica in the eluent system stated to give the desired ring-opened product.

General Procedure M: A 10 mL Pyrex tube was charged with a stir bar, followed by the requisite cyclopropane (0.25 mmol), nucleophile (0.50 mmol), HFIP or $MeNO_2$ (0.125 mL) and finally $B(C_6F_5)•H_2O$ (6.6 mg, 5 mol%). The reaction was then stirred at ambient temperature until TLC showed disappearance of starting material (typically ca. 3 hours). At completion, the crude reaction mixture was concentrated *in vacuo* onto silica gel and purified by flash column chromatography over silica in the eluent system stated to give the desired ring-opened product.

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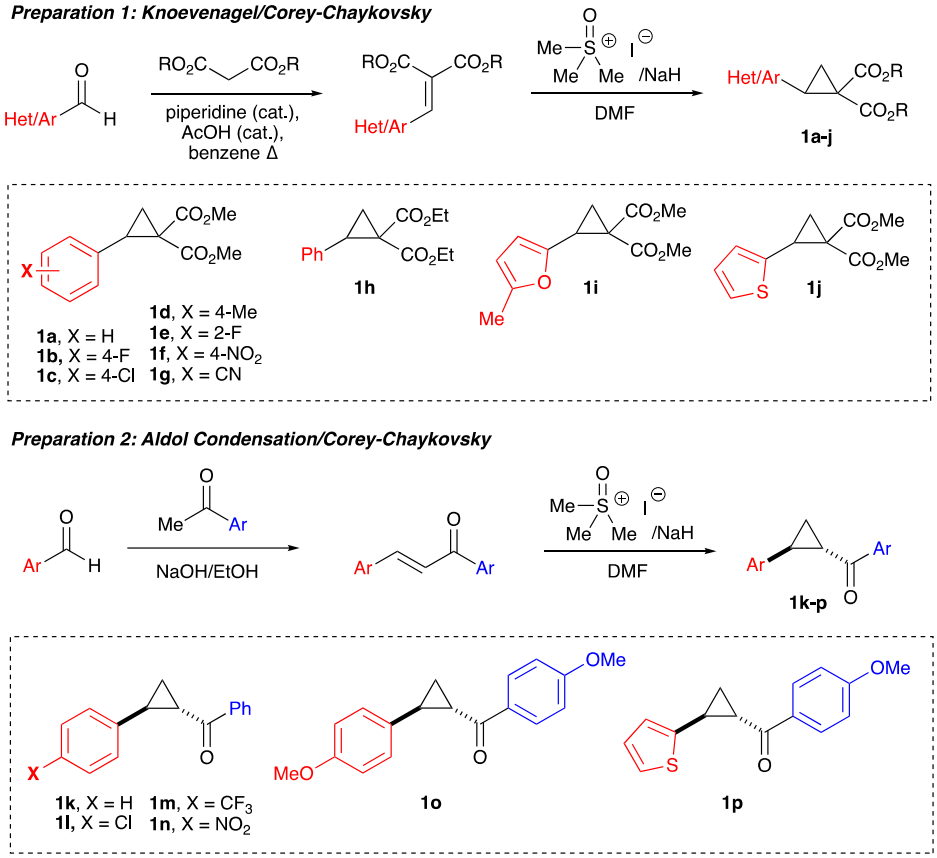
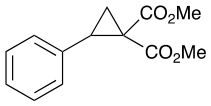
[227] M. K. Ghorai, R. Talukdar, D. P. Tiwari *Org. Lett.* **2014**, *16*, 2204.
[228] A. F. G. Goldberg, N. R. O'Connor, R. A. Craigll, B. M. Stolz *Org. Lett.* **2012**, *14*, 5314.
[229] J. A. Ciaccio, C. E. Aman *Synth. Commun.* **2006**, *36*, 1333.

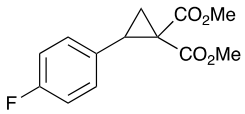
Synthetic overview and characterization data for cyclopropanes



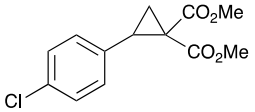
2. Characterization data for donor-acceptor cyclopropanes



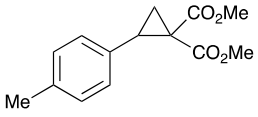
Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (C1a) was prepared *via* a two-step Knoevenagal/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[2] **Yield:** 1.37 g, 97%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.31-7.20 (5H, m), 3.81 (3H, s), 3.38 (3H, s), 3.25 (1H, t, J = 8.6 Hz), 2.22 (1H, dd, J = 8.0, 5.2 Hz), 1.77 (1H, dd, J = 9.3, 5.2 Hz).



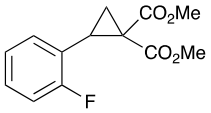
Dimethyl 2-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate (C1b) was prepared *via* a two-step Knoevenagal/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[2] **Yield:** 1.03 g, 82%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.16 (2H, dd, J = 8.6, 5.4 Hz), 6.96 (2H, t, J = 8.6 Hz), 3.79 (3H, s), 3.75 (3H, s), 3.19 (1H, t, J = 8.6 Hz), 2.15 (1H, dd, J = 8.0, 5.3 Hz), 1.74 (1H, dd, J = 9.3, 5.3 Hz); **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -116.8.



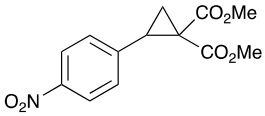
Dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (C1c) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[2] **Yield:** 0.126 g, 9%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 3.79 (3H, s), 3.40 (3H, s), 3.18 (1H, t, J = 8.8 Hz), 2.15 (1H, dd, J = 8.0, 5.6 Hz), 1.74 (1H, dd, J = 9.2, 5.2 Hz).



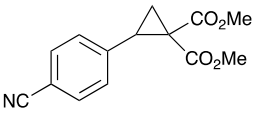
2-(*p*-Toluyl)cyclopropane-1,1-dicarboxylate (C1d) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[230] **Yield:** 0.380 g, 31%; **^{1}H NMR**: (400 MHz, $CDCl_3$) δ 7.07 (4H, s), 3.78 (3H, s), 3.38 (3H, s), 3.19 (1H, t, J = 8.8 Hz), 2.30 (3H, s), 2.17 (1H, dd, J = 8.4, 5.0 Hz), 1.72 (1H, dd, J = 9.6, 5.0 Hz).



2-(*o*-Fluorophenyl)cyclopropane-1,1-dicarboxylate (C1e) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[231] **Yield:** 0.270 g, 37%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.25–7.18 (1H, m), 7.10–6.97 (3H, m), 3.80 (3H, s), 3.39 (3H, s), 3.27 (1H, t, J = 8.6 Hz), 2.20 (1H, dd, J = 8.0, 5.2 Hz), 1.78 (1H, dd, J = 9.2, 5.2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –114.76 to –114.90 (1F, m).



Dimethyl 2-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (C1f) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[232] **Yield:** 0.408 g, 29%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.14 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.8 Hz), 3.81 (3H, s), 3.42 (3H, s), 3.28 (1H, t, J = 8.6 Hz), 2.22 (1H, dd, J = 7.6, 5.4 Hz), 1.83 (1H, dd, J = 9.2, 5.6 Hz).



Dimethyl 2-(4-cyanophenyl)cyclopropane-1,1-dicarboxylate (C1g) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[233]

Yield: 0.691g, 67%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.58 (2H, d, J = 8.2 Hz), 7.31 (2H, d, J = 8.2 Hz), 3.81 (3H, s), 3.41 (3H, s), 3.25 (1H, t, J = 8.5 Hz), 2.20 (1H, dd, J = 8.0, 5.5 Hz), 1.81 (1H, dd, J = 9.1, 5.4 Hz).

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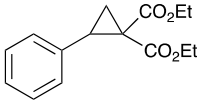
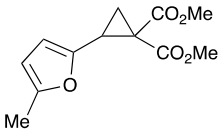
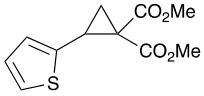


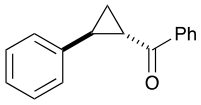
Diethyl 2-phenylcyclopropane-1,1-dicarboxylate (C1h) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[234] **Yield:** 0.850 g, 65%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.30-7.22 (5H, m), 4.23 (2H, q, J = 6.9 Hz), 3.86 (2H, q, J = 7.1 Hz), 3.24 (1H, t, J = 8.6 Hz), 2.20 (1H, dd, J = 8.0, 5.2 Hz), 1.73 (1H, dd, J = 9.2, 5.2 Hz), 1.32-1.29 (3H, m), 0.88 (3H, t, J = 7.1 Hz).



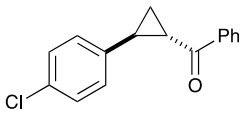
Dimethyl 2-(5-methylfuran-2-yl)cyclopropane-1,1-dicarboxylate (C1i) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[235] **Yield:** 1.12 g, 94%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 5.98 (1H, d, J = 3.1 Hz), 5.84 (1H, d, J = 2.3 Hz), 3.80 (3H, s), 3.56 (3H, s), 3.04 (1H, t, J = 8.6 Hz), 2.22 (3H, s), 2.04 (1H, ddd, J = 7.7, 5.0 Hz), 1.75 (1H, dd, J = 9.5, 5.0 Hz).



Dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (C1j) was prepared *via* a two-step Knoevenagel/Corey-Chaykovsky sequence according to a literature procedure and with corresponding analytical data.[2] **Yield:** 1.17g, 97%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.16 (1H, dd, J = 5.1, 0.6 Hz), 6.90 (1H, dd, J = 5.1, 3.5 Hz), 6.83 (1H, d, J = 3.5 Hz), 3.78 (3H, s), 3.48 (3H, s), 3.29 (1H, t, J = 8.5 Hz), 2.15 (1H, dd, J = 7.7, 5.2 Hz), 1.83 (1H, dd, J = 9.2, 5.2 Hz).

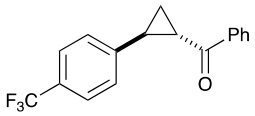


***trans*-Phenyl(2-phenylcyclopropyl)methanone (C1k)** was prepared by Corey-Chaykovsky cyclopropanation of *trans*-chalcone according to a literature procedure and with corresponding analytical data.[229] **Yield:** 0.829 g, 75%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.01-7.99 (2H, m), 7.58-7.54 (1H, m), 7.46 (2H, t, J = 7.5 Hz), 7.32 (2H, t, J = 7.6 Hz), 7.25-7.22 (1H, m), 7.19 (2H, dd, J = 8.0, 1.0 Hz), 2.91 (1H, ddd, J = 8.1, 5.1, 4.0 Hz), 2.71 (1H, ddd, J = 9.1, 6.5, 4.0 Hz).

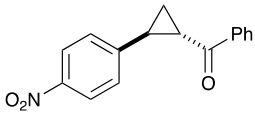


***trans*-(2-(4-Chlorophenyl)cyclopropyl)(phenyl)methanone (C1l)** was prepared *via* a two-step aldol condensation/Corey-Chaykovsky sequence, according to a literature procedure and with corresponding analytical data.[236] **Yield:** 0.726 g, 57%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.01 (2H, d, J = 7.4 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.49 (2H, t, J = 7.7 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.13 (2H, d, J = 8.4 Hz), 2.91-2.86 (1H, m), 2.72-2.67 (1H, m), 1.94 (1H, dt, J = 9.1, 4.6 Hz), 1.54 (1H, ddd, J = 8.0, 6.6, 4.3 Hz).

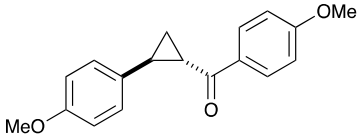
[234] R. Dey, P. Banerjee *Org. Lett.* **2017**, *19*, 304.
[235] Ivanova, Olga A.; Budynina, Ekaterina M.; Chagarovskiy, Alexey O.; Kaplun, Alexey E.; Trushkov, Igor V.; Melnikov, Mikhail Ya *Adv. Synth. Catal.* **2011,** *353*, 1125.



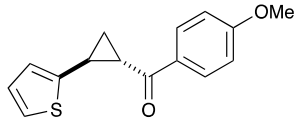
***trans*-Phenyl(2-(4-(trifluoromethyl)phenyl)cyclopropyl)methanone (C1m)** was prepared *via* a two-step aldol condensation/Corey-Chaykovsky sequence, according to a literature procedure and with corresponding analytical data.[236] **Yield:** 1.08 g, 74%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.98 (2H, d, J = 8.8 Hz), 7.11 (2H, d, J = 8.7 Hz), 6.94 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.7 Hz), 3.87 (3H, s), 3.80 (3H, s), 2.80-2.76 (1H, m), 2.65-2.60 (1H, m), 1.86 (1H, ddd, J = 9.1, 4.9, 4.2 Hz), 1.47 (1H, ddd, J = 7.9, 6.7, 4.1 Hz); **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -62.4.



***trans*-(2-(4-Nitrophenyl)cyclopropyl)(phenyl)methanone (C1n)** was prepared as a yellow solid *via* a two-step aldol condensation/Corey-Chaykovsky sequence, according to a literature procedure and with corresponding analytical data.[237] **Yield:** 0.765 g, 57%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.21 (2H, d, J = 8.8 Hz), 7.99 (2H, dd, J = 8.3, 1.1 Hz), 7.65 (1H, tt, J = 7.4, 1.4 Hz), 7.53 (2H, t, J = 7.7 Hz), 7.34 (2H, d, J = 8.8 Hz), 3.05 (1H, ddd, J = 8.3, 5.4, 4.0 Hz), 2.82 (1H, ddd, J = 9.0, 6.6, 4.0 Hz), 2.04 (1H, dt, J = 9.0, 5.0 Hz), 1.72 (1H, ddd, J = 8.2, 6.6, 4.6 Hz).



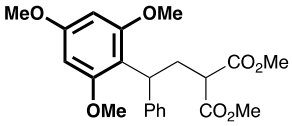
***trans*-(4-Methoxyphenyl)(2-(4-methoxyphenyl)cyclopropyl)-methanone (C1o)** was prepared *via* a two-step aldol condensation/Corey-Chaykovsky sequence, according to a literature procedure and with corresponding analytical data.[238] **Yield:** 0.801 g, 57%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.01 (2H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.5 Hz), 6.96 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.5 Hz), 3.89 (3H, s), 3.82 (3H, s), 2.80 (1H, dt, J = 8.2, 4.3 Hz), 2.67-2.62 (1H, m), 1.88 (1H, dt, J = 9.0, 4.5 Hz), 1.49 (1H, td, J = 7.1, 4.1 Hz).



***trans*-(4-Methoxyphenyl)(2-(thiophen-2-yl)cyclopropyl)methanone (C1p)** was prepared *via* a two-step aldol condensation/Corey-Chaykovsky sequence, according to a literature procedure.[239] **Yield:** 0.959 g, 74%; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.8 Hz), 7.12 (1H, dd, J = 4.9, 1.0 Hz), 6.97-6.92 (3H, m), 6.88 (1H, dt, J = 3.5, 0.5 Hz), 3.88 (3H, s), 2.91-2.82 (2H, m), 1.91 (1H, ddd, J = 9.0, 5.2, 4.0 Hz), 1.51 (1H, ddd, J = 8.1, 6.5, 4.0 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 196.3, 163.5, 145.0, 130.6, 130.4, 127.0, 124.0, 123.1, 113.8, 55.5, 29.6, 24.6, 19.8.

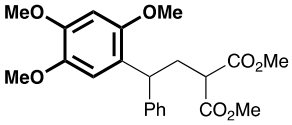
[236] P. Cotugno, A. Monopoli, F. Ciminale, A. Milella, A. Nacci *Angew. Chem. Int. Ed.* **2014**, *53*, 13563.
[237] L. A. Yanovskaya, V. A. Dombrovsky, O. S. Chizov, B. M. Zolotarev, O. A. Subbotin, V. F. Kucherov *Tetrahedron*, **1972**, *28*, 1565.
[238] L. Feng, H. Yan, C. Yang, D. Chen, W. Xia *J. Org. Chem.* **2016**, *81*, 7008.
[239] Paxton, R. J.; Taylor, R. J. K *Synlett*, **2007**, *4*, 633.

3. Characterization data for ring-opened products (donor-acceptor cyclopropanes)

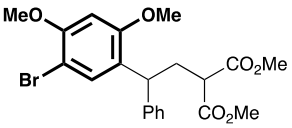


Dimethyl 2-(2-phenyl-2-(2,4,6-trimethoxyphenyl)ethyl)malonate (21a) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **21a** as a colourless liquid. Analytical data are in agreement with the literature.[240] **Yield:** 0.096 g, 95%; $\mathbf{R_f}$ = 0.23 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2955, 2839, 1751, 1732, 1603, 1589; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 7.4 Hz), 7.21 (2H, t, J = 7.6 Hz), 7.11 (1H, t, J = 7.3 Hz), 6.10 (2H, s), 4.63 (1H, dd, J = 10.9, 5.6 Hz), 3.78 (3H, s), 3.71 (3H, s), 3.70 (6H, s), 3.63 (3H, s), 3.26 (1H, dd, J = 9.4, 5.4 Hz), 2.92 (1H, ddd, J = 13.3, 11.6, 5.4 Hz), 2.74 (1H, ddd, J = 13.3, 9.4, 5.6 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.3, 170.0, 160.0, 159.4, 144.4, 127.7, 127.7, 125.4, 111.3, 91.1, 55.6, 55.2, 52.4, 52.3, 50.7, 37.0, 31.0.

(*R*)-Dimethyl 2-(2-phenyl-2-(2,4,6-trimethoxyphenyl)ethyl)malonate ((*R*)-21a)
Optical rotation: = +55.6 ($CHCl_3$, *c* 0.196); {lit.[240] +49.3 ($CHCl_3$, *c* 0.142).



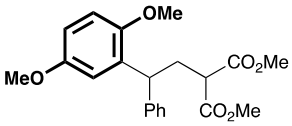
Dimethyl 2-(2-phenyl-2-(2,4,5-trimethoxyphenyl)ethyl)malonate (21b) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), 1,2,4-trimethoxybenzene (0.075 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-40% EtOAc in petroleum ether) gave **21b** as a colourless oil. **Yield:** 0.086 g, 85%; $\mathbf{R_f}$ = 0.14 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2953, 1751, 1732, 1514; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.31-7.26 (4H, m), 7.21-7.16 (1H, m), 6.75 (1H, s), 6.51 (1H, s), 4.39 (1H, t, J = 8.1 Hz), 3.88 (3H, s), 3.81 (3H, s), 3.75 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.32 (1H, dd, J = 7.6, 7.0 Hz), 2.73-2.56 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.0, 169.8, 151.6, 148.3, 143.8, 143.2, 128.4, 128.0, 126.3, 123.2, 112.4, 98.0, 56.9, 56.5, 56.2, 52.6, 52.5, 50.2, 40.8, 33.9; **HRMS:** (ESI^+) $[M+Na]^+$ $C_{22}H_{26}O_7Na$ Found: 425.1546, requires 425.1571 (+5.9 ppm).



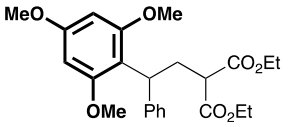
Dimethyl 2-(2-(5-bromo-2,4-dimethoxyphenyl)-2-phenylethyl)-malonate (21c) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), 1-bromo-2,4-dimethoxybenzene (0.072 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-35% EtOAc in petroleum ether) gave **21c** as a colourless oil. **Yield:**

[240] R. Talukdar, A. Saha, D. P. Tiwari, M. K. Ghorai *Tetrahedron* **2016**, *72*, 613.

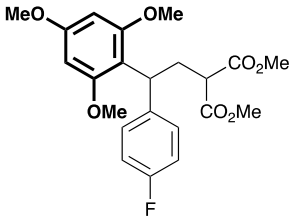
0.057 g, 51%; **R_f** = 0.21 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2953, 2845, 1751, 1732, 1599; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.33 (1H, s), 7.31-7.28 (2H, m), 7.25 (1H, d, *J* = 6.9 Hz), 7.22-7.17 (1H, m), 6.45 (1H, s), 4.32 (1H, t, *J* = 8.1 Hz), 3.89 (3H, s), 3.79 (3H, s), 3.73 (3H, s), 3.71 (3H, s), 3.29 (1H, t, *J* = 7.4 Hz), 2.69-2.54 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.9, 169.8, 157.4, 155.3, 143.0, 131.8, 128.5, 128.1, 126.5, 125.8, 102.1, 96.9, 56.5, 55.9, 52.7, 52.6, 50.2, 40.6, 33.8; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{21}H_{23}{}^{79}BrO_6Na$ Found: 473.0554, requires 473.0570 (+3.4 ppm).



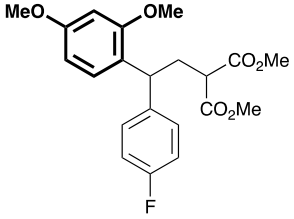
Dimethyl 2-(2-(2,5-dimethoxyphenyl)-2-phenylethyl)malonate (21d) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), 1,4-dimethoxybenzene (0.069 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **21d** as a colourless oil. **Yield:** 0.045 g, 48%; **R_f** = 0.42 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2955, 2842, 1743, 1737, 1604,; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.29 (2H, s), 7.28 (2H, s), 7.20 (1H, dq, *J* = 8.7, 4.3 Hz), 6.82 (1H, d, *J* = 3.0 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 6.72 (1H, dd, *J* = 8.8, 3.0 Hz), 4.43 (1H, t, *j* = 8.1 Hz), 3.76 (3H, s), 3.73 (3H, s), 3.73 (3H, s), 3.71 (3H, s), 3.33 (1H, t, *J* = 7.4 Hz), 2.72-2.58 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.0, 169.8, 153.8, 151.5, 143.2, 133.2, 128.4, 128.2, 126.4, 114.8, 111.9, 111.4, 56.2, 55.7, 52.6, 52.5, 50.2, 41.2, 33.8; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{21}H_{24}O_6Na$ Found: 395.1449, requires 395.1465 (+4.0 ppm).



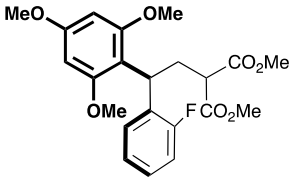
Diethyl 2-(2-phenyl-2-(2,4,6-trimethoxyphenyl)ethyl)malonate (21e) was prepared according to *General Procedure L* from cyclopropane **C1h** (0.066 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-25% EtOAc in petroleum ether) gave **21e** as a colourless liquid. **Yield:** 0.087 g, 81%; **R_f** = 0.35 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2940, 2839, 1748, 1730, 1605, 1592; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 7.5 Hz), 7.21 (2H, t, *J* = 7.6 Hz), 7.10 (1H, t, *J* = 7.3 Hz), 6.10 (2H, s), 4.64 (1H, dd, *J* = 10.7, 5.8 Hz), 4.25-4.04 (4H,m), 3.78 (3H, s), 3.71 (6H, s), 3.21 (1H, dd, *J* = 9.3, 5.4 Hz), 2.90 (1H, ddd, *J* = 13.4, 10.8, 5.4 Hz), 2.73 (1H, ddd, *J* = 13.4, 9.3, 5.8 Hz), 1.25 (3H, t, *J* = 7.2 Hz), 1.21 (3H, t, *J* = 7.2 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.1, 169.7, 160.1, 159.5, 144.7, 127.9, 127.8, 125.5, 111.5, 91.2, 61.3, 61.2, 55.7, 55.4, 51.2, 37.3, 31.2, 14.2, 14.1; **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{24}H_{31}O_7$ Found: 431.2063, requires 431.2064 (+0.3 ppm).



Dimethyl 2-(2-(4-fluorophenyl)-2-(2,4,6-trimethoxyphenyl)ethyl)-malonate (21f) was prepared according to *General Procedure L* from cyclopropane **C1b** (0.063 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **21f** as a colourless liquid. Analytical data are in agreement with the literature.[240] **Yield:** 0.081 g, 71%; **R_f** = 0.23 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2953, 2843, 1751, 1732, 1603, 1593; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.28-7.24 (2H, m), 6.91 (2H, t, J = 8.8 Hz), 6.12 (2H, s), 4.60 (1H, dd, J = 10.9, 5.6 Hz), 3.81 (3H, s), 3.73 (3H, s), 3.72 (6H, s), 3.64 (3H, s), 3.25 (1H, dd, J = 9.4, 5.4 Hz), 2.90 (1H, ddd, J = 13.3, 10.9, 5.4 Hz), 2.71 (1H, ddd, J = 13.3, 9.4, 5.6 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.3, 170.0, 161.1 (d, J = 242.8 Hz), 160.2, 159.4, 140.2 (d, J = 3.3 Hz), 129.2 (d, J = 7.8 Hz), 114.4 (d, J = 20.8 Hz), 111.2, 91.2, 55.7, 55.4, 52.6, 52.5, 50.8, 36.5, 31.3; **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -118.5.

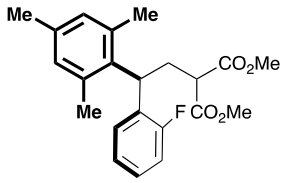


Dimethyl 2-(2-(2,4-dimethoxyphenyl)-2-(4-fluorophenyl)ethyl)-malonate (21g) was prepared according to *General Procedure L* from cyclopropane **C1b** (0.063 g, 0.25 mmol), 1,3-dimethoxybenzene (0.065 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **21g**, as the major regioisomer, as a colourless liquid. **Yield:** 0.061 g, 63%; **R_f** = 0.30 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2955, 2839, 1751, 1730, 1605, 1585, 1505; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ *(only data from the major regioisomer is reported)* 7.21 (2H, dd, J = 8.6, 5.5 Hz), 7.09 (1H, d, J = 8.4 Hz), 6.96 (2H, t, J = 8.7 Hz), 6.47 (1H, dd, J = 8.4, 2.4 Hz), 6.43 (1H, d, J = 2.4 Hz), 4.31 (1H, t, J = 8.1 Hz), 3.80 (3H, s), 3.75 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.29 (1H, t, J = 7.4 Hz), 2.67-2.54 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ *(only data from the major regioisomer is reported)* 169.9, 169.7, 161.3 (d, J = 244.0 Hz), 159.5, 158.0, 139.5 (d, J = 2.9 Hz), 129.4 (d, J = 7.9 Hz), 128.1, 123.9, 115.0 (d, J = 21.1 Hz), 104.3, 98.6, 55.4, 55.3, 52.5, 52.4, 50.1, 40.0, 33.9; **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -117.3 (major) and -118.3 (minor).

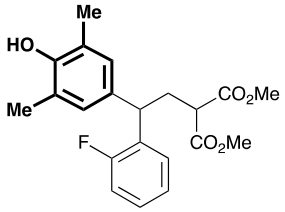


Dimethyl 2-(2-(2-fluorophenyl)-2-(2,4,6-trimethoxyphenyl)ethyl)-malonate (21h) was prepared according to *General Procedure L* from cyclopropane **C1e** (0.051 g, 0.20 mmol), 1,3,5-trimethoxybenzene (68.9 mg, 0.410 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 40 ºC for 4 h. Purification by flash column chromatography over silica (15-18% EtOAc in petroleum ether) gave **21h** as an off-white solid. **Yield:** 0.089 g, quantitative; **R_f** = 0.07 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.47–7.39 (m, 1H), 7.12–7.07 (m, 1H), 7.07–6.98 (m, 1H), 6.91–6.87 (m, 1H), 6.08 (s, 2H), 4.83 (dd, J = 11.2, 5.2 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.70 (6H), 3.61 (3H), 3.28 (dd, J = 8.8, 5.6 Hz, 1H),

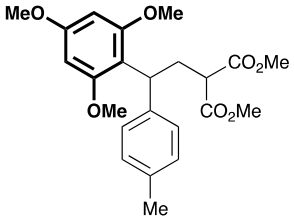
2.89 (ddd, *J* = 13.2, 11.2, 5.6 Hz, 1H), 2.65 (ddd, *J* = 13.6, 8.8, 5.2 Hz, 1H); **^{13}C NMR:** (100 MHz, $CDCl_3$) *δ* 170.4, 170.0, 161.0 (d, *J* = 244.5 Hz), 160.3, 159.6, 131.0 (d, *J* = 13.7 Hz), 129.7 (d, *J* = 4.5 Hz), 127.1 (d, *J* = 8.2 Hz), 123.2 (d, *J* = 3.3 Hz), 114.9 (d, *J* = 22.4 Hz), 110.1, 91.2, 55.8, 55.7, 55.4, 55.3, 52.5, 52.5, 50.6, 31.2 (d, *J* = 2.0 Hz), 30.8; **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –115.14 to –115.25 (m, 1F); **HRMS:** ($APPI^+$) $[M]^+$ $C_{22}H_{25}FO_7$ Found: 420.1578, requires 420.1579 -0.20 ppm).



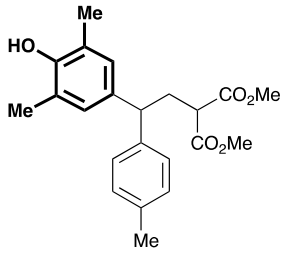
Dimethyl 2-(2-(2-fluorophenyl)-2-mesitylethyl)malonate (21i) was prepared according to *General Procedure L* from cyclopropane **C1e** (0.052 g, 0.20 mmol), mesitylene (56.8 µL, 0.408 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 50 ºC for 24 h. Purification by flash column chromatography over silica (3% EtOAc in petroleum ether) gave **21i** as a colourless oil. **Yield:** 0.068 g, 89%; **R_f** = 0.42 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) *δ* 7.32 (t, *J* = 7.6 Hz, 1H), 7.23–7.18 (m, 1H), 7.08 (td, *J* = 7.6, 0.8 Hz, 1H), 7.00–6.90 (m, 1H), 6.79 (s, 2H), 4.65 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.38 (t, *J* = 7.2 Hz, 1H), 2.91 (dt, *J* = 14.0 Hz, 7.2 Hz, 1H), 2.99–2.85 (m, 1H), 2.78–2.64 (m, 1H), 2.23 (br s, 9H); **^{13}C NMR:** (100 MHz, $CDCl_3$) *δ* 169.9, 169.9, 161.7 (d, *J* = 245.5 Hz), 137.3, 136.2, 134.7, 130.5 (m), 129.3, 129.2 (d, *J* = 2.3 Hz), 127.9 (d, *J* = 8.4 Hz), 123.6 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 22.4 Hz), 52.8, 52.7, 50.0, 37.5, 30.4, 21.3, 21.3, 20.8; **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –112.44 to –112.57 (m, 1F); **HRMS:** ($APPI^+$) $[M-H]^+$ $C_{22}H_{24}FO_4$ Found: 371.1654, requires 371.1653 (+0.10 ppm).



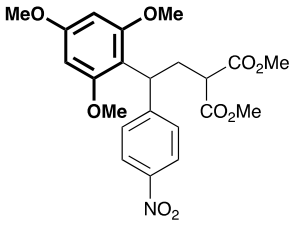
Dimethyl-2-(2-(2-fluorophenyl)-2-(3,5-dimethyl-4-hydroxophenyl)-ethyl)malonate (21j) was prepared according to *General Procedure L* from cyclopropane **C1e** (0.052 g, 0.21 mmol), 2,6-dimethylphenol (50.2 mg, 0.411 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 50 ºC for 24 h. Purification by flash column chromatography over silica (10% EtOAc in petroleum ether) gave **21j** as a pale yellow oil. **Yield:** 0.072 g, 93%; **R_f** = 0.07 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) *δ* 7.33-7.25 (m, 1H), 7.22-7.13 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.02-6.94 (m, 1H), 6.85 (s, 2H), 4.52 (s, 1H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.71(s, 3H), 3.70 (s, 3H), 3.29 (t, *J* = 7.4 Hz, 1H), 2.70-2.54 (m, 2H), 2.19 (s, 6H); **^{13}C NMR:** (100 MHz, $CDCl_3$) *δ* 169.8, 169.8, 160.7 (d, *J* = 244.0 Hz), 151.0, 133.9, 130.9 (d, *J* = 14.2 Hz), 128.4 (d, *J* = 4.2 Hz), 128.2, 128.1, 124.4 (d, *J* = 3.5 Hz), 123.2, 115.7 (d, *J* = 22.5 Hz), 52.7, 52.7, 50.1, 40.5 (d, *J* = 2.4 Hz), 33.8, 31.1, 16.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ (ppm): –116.27 to –116.47 (m, 1F); **HRMS:** ($APPI^+$) $[M-H]^+$ $C_{21}H_{22}FO_5$ Found: 373.1446, requires 373.1446 (+0.09 ppm).



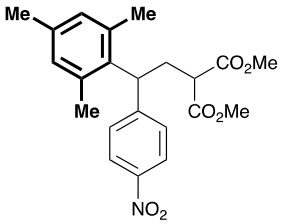
Dimethyl 2-(2-(*p*-tolyl)-2-(2,4,6-trimethoxyphenyl)ethyl)malonate (21k) was prepared according to *General Procedure L* from cyclopropane **C1d** (0.064 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.086 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (15% EtOAc in petroleum ether) gave **21k** as a colourless oil. with analytical data in agreement with the literature.[240] **Yield:** 0.114 g, quantitative; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 8.0 Hz), 7.02 (2H, d, J = 7.9 Hz), 6.09 (2H, s), 4.58 (1H, dd, J = 10.9, 5.7 Hz), 3.78 (3H, s), 3.71 (6H, s), 3.70 (3H, s), 3.62 (3H, s), 3.24 (1H, dd, J = 9.3, 5.5 Hz), 2.91 (1H, ddd, J = 13.4, 10.9, 5.5 Hz), 2.71 (1H, ddd, J = 13.4, 9.3, 5.7 Hz), 2.27 (3H, s).



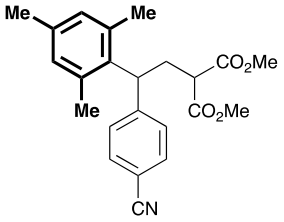
Dimethyl 2-(2-(4-hydroxy-3,5-dimethylphenyl)-2-(*p*-tolyl)ethyl)-malonate (21l) was prepared according to *General Procedure L* from cyclopropane **C1d** (0.059 g, 0.24 mmol), 2,6-dimethylphenol (0.059 g, 0.48 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 1 h. Purification by flash column chromatography over silica (10-15% EtOAc in petroleum ether) gave **21l** as a yellow oil. **Yield:** 0.085 g, 97%; **R_f** = 0.10 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.09 (s, 4H), 6.81 (s, 2H), 4.48 (s, 1H), 3.75 (t, J = 8.0 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.27 (t, J = 7.6 Hz, 1H), 2.58 (t, J = 7.6 Hz, 2H), 2.29 (s, 3H), 2.19 (s, 6H); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.0, 150.9, 141.0, 136.1, 135.3, 129.4, 128.0, 127.7, 123.1, 52.6, 50.2, 47.6, 34.8, 21.1, 16.2; **HRMS:** (APPI$^+$) $[M+H]^+$ $C_{22}H_{26}O_5$ Found: 371.1856, requires 371.1853 (+0.32 ppm).



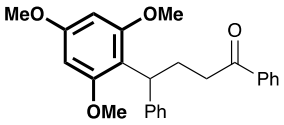
Dimethyl 2-(2-(4-nitrophenyl)-2-(2,4,6-trimethoxyphenyl)ethyl)-malonate (21m) was prepared according to *General Procedure L* from cyclopropane **C1f** (0.062 g, 0.22 mmol), 1,3,5-trimethoxybenzene (0.075 g, 0.45 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 50 ºC for 24 h. Purification by flash column chromatography over silica (20-25% EtOAc in petroleum ether) gave **21m** as a yellow oil. **Yield:** 0.092 g, 94%; **R_f** = 0.06 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.09 (s, 2H), 4.69 (dd, J = 11.2, 4.8 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.69 (s, 6H), 3.62 (s, 3H), 3.22 (dd, J = 9.6, 5.2 Hz, 1H), 2.90 (ddd, J = 13.2, 11.6, 5.2 Hz, 1H), 2.72 (ddd, J = 13.2, 9.6, 5.2 Hz, 1H); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.1, 169.8, 160.8, 159.3, 152.8, 146.0, 128.5, 123.1, 109.8, 91.1, 55.7, 55.4, 52.7, 52.6, 50.5, 37.0, 30.4; **HRMS:** (APPI$^+$) $[M]^+$ $C_{22}H_{25}NO_9$ Found: 447.1524, requires 447.1534 (+1.06 ppm).



Dimethyl 2-(2-mesityl-2-(4-nitrophenyl)ethyl)malonate (21n) was prepared according to *General Procedure L* from cyclopropane **C1f** (0.062 g, 0.22 mmol), mesitylene (60.2 µL, 0.433 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 50 ºC for 24 h. Purification by flash column chromatography over silica (5% EtOAc in petroleum ether) gave **21n** as a yellow oil. **Yield:** 0.085 g, 99%; $\mathbf{R_f}$ = 0.28 (petroleum ether/EtOAc 9:1); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.85 (s, 2H), 4.61 (dd, J = 10.4, 5.4 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.23 (dd, J = 9.2, 5.0 Hz, 1H), 3.02 (ddd, J = 13.6, 9.2, 6.0 Hz, 1H), 2.80–2.68 (m, 1H), 2.43–1.75 (m, 9H); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.8, 169.8, 151.4, 146.3, 137.3, 137.1, 134.4, 128.0, 123.6, 52.9, 52.8, 49.8, 41.6, 30.6, 21.2, 20.9; **HRMS:** (APPI$^+$) $[M]^+$ $C_{22}H_{25}NO_6$ Found: 399.1678, requires 399.1676 (+0.50 ppm).



Dimethyl 2-(2-(4-cyanophenyl)-2-mesitylethyl)malonate (21o) was prepared according to *General Procedure L* from cyclopropane **C1g** (0.065 g, 0.25 mmol), mesitylene (0.070 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 50 ºC for 3 h. Purification by flash column chromatography over silica (20% EtOAc in petroleum ether) gave **21o** as a colourless oil. **Yield:** 0.056 g, 60%; $\mathbf{R_f}$ = 0.44 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 8.4 Hz), 7.28 (2H, d, J = 8.0 Hz), 6.86 (2H, br s), 4.60 (1H, dd, J = 10.7, 5.7 Hz), 3.76 (3H, s), 3.63 (3H, s), 3.25 (1H, dd, J = 9.1, 5.2 Hz), 3.01 (1H, ddd, J = 14.1, 8.8, 5.5 Hz), 2.73 (1H, ddd, J = 13.8, 10.8, 5.2 Hz), 2.27 (3H, s), 2.11 (6H, br s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.6, 149.0, 137.2, 136.8, 134.3, 132.1, 130.7 (br), 127.8, 118.9, 109.7, 52.7, 52.6, 49.7, 41.5, 30.3, 21.1, 20.7; **HRMS:** (APPI$^+$) $[M]^+$ $C_{23}H_{25}NO_4$ Found: 379.1179, requires 379.1178 (+0.10 ppm).

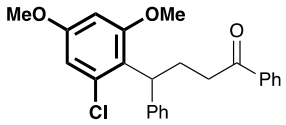


1,4-Diphenyl-4-(2,4,6-trimethoxyphenyl)butan-1-one (22a) was prepared according to *General Procedure L* from cyclopropane **C1k** (0.056 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-25% EtOAc in petroleum ether) gave **22a** as a white solid. **Yield:** 0.098 g, 98%.

10 x Scale-Up Procedure: The title compound was prepared according to *General Procedure A* from cyclopropane C**1k** (0.556 g, 2.50 mmol), 1,3,5-trimethoxybenzene (0.841 g, 5.00 mmol) and TfOH (11.1 µL, 5 mol%) in HFIP (1.25 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-25% EtOAc in petroleum ether) gave **22a** as a white solid. **Yield:** 0.971 g, 99%

$\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc 8:2); **mp:** 96-97 ºC; **IR ν_{max} / cm^{-1} (film):** 2933, 2834, 1682; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.91-7.89 (2H, m), 7.54 (1H, t, J = 7.4 Hz), 7.44 (2H, t, J = 7.6 Hz), 7.38 (2H, d, J = 7.5 Hz), 7.26 (2H, t, J = 7.6 Hz), 7.15 (1H, t, J = 7.3 Hz), 6.14 (2H, s),

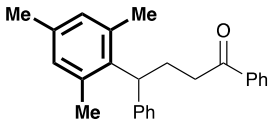
4.72 (1H, dd, *J* = 10.0, 6.2 Hz), 3.82 (3H, s), 3.70 (6H, s), 2.99 (1H, ddd, *J* = 16.2, 9.4, 6.7 Hz), 2.87 (1H, ddd, *J* = 15.9, 9.8, 5.7 Hz), 2.87 (1H, ddd, *J* = 15.9, 9.8, 5.7 Hz), 2.77-2.60 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.9, 159.8, 159.4, 145.3, 137.3, 132.7, 128.5, 128.1, 127.9, 127.7, 125.3, 112.9, 91.2, 55.6, 55.3, 38.8, 37.6, 26.7; **HRMS:** (ESI^+) $[M+Na]^+$ $C_{25}H_{26}O_4Na$ Found: 413.1690, requires 413.1723 (+8.0 ppm).



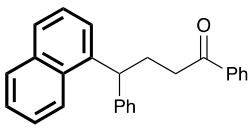
4-(2-Chloro-4,6-dimethoxyphenyl)-1,4-diphenylbutan-1-one (22b) was prepared according to <u>*General Procedure L*</u> from cyclopropane **C1k** (0.056 g, 0.25 mmol), 5-chloro-1,3-dimethoxybenzene (0.067 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave a 2:1 mixture of **22b** and **22b'** as a pale yellow oil. **Combined Yield:** 0.072 g, 71%

Repurification by careful column chromatography allowed partial separation of the regioisomers and the major regioisomer (as depicted) to be characterized.

Major regioisomer (22b): A pale yellow oil; **R_f** = 0.53 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 7.1 Hz), 7.55 (1H, t, *J* = 7.4 Hz), 7.44 (2H, t, *J* = 7.6 Hz), 7.36 (2H, d, *J* = 7.6 Hz), 7.27 (2H, t, *J* = 7.4 Hz), 7.17 (1H, t, *J* = 7.3 Hz), 6.56 (1H, d, *J* = 2.4 Hz), 6.33 (1H, d, *J* = 2.4 Hz), 4.82 (1H, dd, *J* = 9.7, 6.1 Hz), 3.79 (3H, s), 3.62 (3H, s), 3.03 (1H, ddd, *J* = 16.5, 9.8, 6.4 Hz), 2.87 (1H, ddd, *J* = 16.6, 9.7, 5.2 Hz), 2.80-2.65 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.3, 159.8, 159.1, 143.6, 137.0, 135.5, 132.8, 128.4, 128.0, 127.7, 125.6, 122.7, 106.1, 98.6, 55.5, 37.2, 25.7; **HRMS:** (ESI^+) $[M+Na]^+$ $C_{24}H_{23}{}^{35}ClO_3Na$ Found: 417.1236, requires 417.1228 (-1.9 ppm).

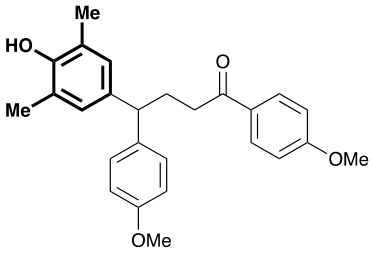


4-Mesityl-1,4-diphenylbutan-1-one (22c) was prepared according to <u>*General Procedure L*</u> from cyclopropane **C1k** (0.056 g, 0.25 mmol), mesitylene (0.070 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-5% EtOAc in petroleum ether) gave **22c** as a white solid. **Yield:** 0.078 g, 89%; **R_f** = 0.70 (petroleum ether/EtOAc 8:2); **mp:** 92-94 ºC; **IR ν_{max} / cm^{-1} (film):** 1688; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.89-7.87 (2H, m), 7.57 (1H, t, *J* = 7.4 Hz), 7.45 (2H, t, *J* = 7.6 Hz), 7.32-7.25 (4H, m), 7.21 (1H, t, *J* = 6.9 Hz), 6.87 (2H, s), 4.68 (1H, dd, *J* = 10.3, 5.3 Hz), 3.04 (1H, td, *J* = 13.6, 6.6 Hz), 2.95-2.83 (2H, m), 2.60-2.46 (1H, m), 2.31 (3H, s), 2.21 (6H, br s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.3, 144.1, 137.4, 137.2, 137.0, 135.8, 133.0, 130.4 (br), 128.6, 128.3, 128.1, 127.3, 125.6, 42.7, 36.8, 25.6, 21.5, 20.9; **HRMS:** (ESI^+) $[M+Na]^+$ $C_{25}H_{26}O_4Na$ Found: 365.1908, requires 365.1876 (-8.9 ppm).

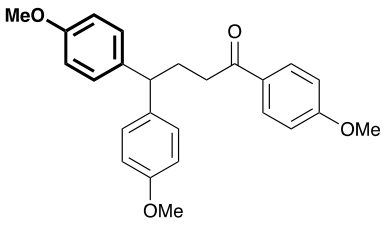


4-(Naphthalen-1-yl)-1,4-diphenylbutan-1-one (22d) was prepared according to <u>*General Procedure L*</u> from cyclopropane **C1k** (0.056 g, 0.25 mmol), naphthalene (0.064 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by

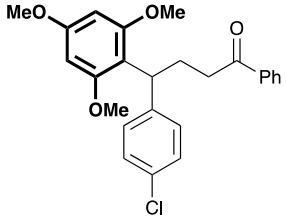
flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave a 2:1 regioisomeric mixture of **22d** and its regioisomer as a yellow oil. **Yield:** 0.072 g, 82%; $\mathbf{R_f}$ = 0.58 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 3053, 3026, 1680, 1597, 1578; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ *(only characteristic peaks reported)* 4.92 (2.3H, t, *J* = 7.7 Hz) *major regioisomer* and 4.25 (1H, t, *J* = 7.8 Hz) *minor regioisomer*; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{26}H_{22}ONa$ Found: 373.1533, requires 373.1563 (+8.1 ppm).



4-(4-Hydroxy-3,5-dimethylphenyl)-1,4-bis(4-methoxyphenyl)-butan-1-one (22e) was prepared according to *General Procedure L* from cyclopropane **C1o** (0.071 g, 0.25 mmol), 2,6-dimethylphenol (0.061 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-35% EtOAc in petroleum ether) gave **22e** as a yellow oil. **Yield:** 0.079 g, 78%; $\mathbf{R_f}$ = 0.26 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 3446 (br), 1667, 1599, 1572, 1510; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.9 Hz), 7.18 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.9 Hz), 6.86 (2H, s), 6.83 (2H, d, *J* = 8.7 Hz), 4.61 (1H, br s), 3.85 (3H, s), 3.82 (1H, t, *J* = 8.0 Hz), 3.77 (3H, s), 2.86 (2H, t, *J* = 7.5 Hz), 2.40 (2H, q, *J* = 7.6 Hz), 2.20 (6H, s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.1, 163.5, 158.0, 150.7, 137.4, 136.6, 130.4, 130.2, 128.8, 128.0, 123.1, 114.0, 113.7, 55.6, 55.3, 49.2, 36.9, 30.6, 16.2; **HRMS:** (ESI$^+$) $[M+K]^+$ $C_{26}H_{28}O_4K$ Found: 443.1635, requires 443.1619 (-3.5 ppm).

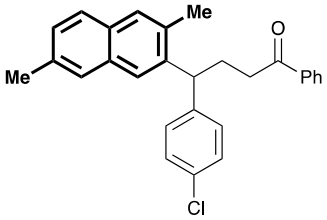


1,4,4-Tris(4-methoxyphenyl)butan-1-one (22f) was prepared according to *General Procedure L* from cyclopropane **C1o** (0.071 g, 0.25 mmol), anisole (0.054 mL g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-25% EtOAc in petroleum ether) gave **22f** as a white solid. **Yield:** 0.081 g, 83%; $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc 8:2); **mp:** 95-96 ºC; **IR ν_{max} / cm^{-1} (film):** 1672, 1595; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.9 Hz), 7.17 (4H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.9 Hz), 6.84 (4H, d, *J* = 8.7 Hz), 3.92 (1H, t, *J* = 7.9 Hz), 3.85 (3H, s), 3.77 (3H, s), 2.87 (2H, t, *J* = 7.5 Hz), 2.43 (2H, q, *J* = 7.6 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 198.8, 163.4, 158.0, 137.1, 130.4, 130.2, 128.8, 114.0, 113.7, 55.5, 55.3, 49.0, 36.7, 30.6; **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{25}H_{27}O_4$ Found: 391.1912, requires 391.1904 (-2.1 ppm).

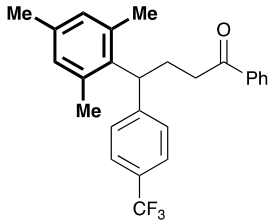


1-Phenyl-4-(4-chlorophenyl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (22g) was prepared according to *General Procedure L* from cyclopropane **C1l** (0.064 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over

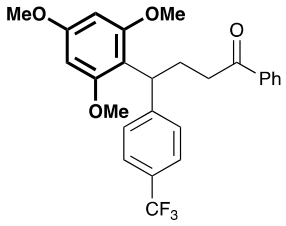
silica (0-30% EtOAc in petroleum ether) gave **22g** as a white solid. **Yield:** 0.100 g, 94%; $\mathbf{R_f}$ = 0.39 (petroleum ether/EtOAc 8:2); **mp:** 116-117 ºC; **IR ν_{max} / cm^{-1} (film):** 2839, 1688, 1593; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.3 Hz), 7.54 (1H, t, *J* = 7.3 Hz), 7.43 (2H, t, *J* = 7.7 Hz), 7.28 (2H, d, *J* = 7.5 Hz), 7.20 (2H, d, *J* = 8.5 Hz), 6.11 (2H, s), 4.64 (1H, dd, *J* = 10.0, 6.1 Hz), 3.81 (3H, s), 3.68 (3H, s), 2.95 (1H, ddd, *J* = 16.4, 9.0, 7.1 Hz), 2.83 (1H, ddd, *J* = 16.0, 9.5, 5.9 Hz), 2.70-2.53 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.7, 160.0, 159.3, 143.9, 143.9, 137.3, 132.8, 130.9, 129.4, 128.5, 128.2, 127.8, 112.4, 91.2, 55.7, 55.4, 38.2, 37.4, 26.4; **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{25}H_{26}{}^{35}ClO_4$ Found: 425.1530, requires 425.1514 (-3.7 ppm).



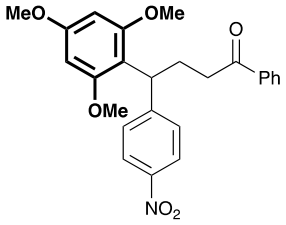
4-(4-Chlorophenyl)-4-(3,7-dimethylnaphthalen-2-yl)-1-phenylbutan-1-one (22h) was prepared according to *General Procedure L* from cyclopropane **C1l** (0.064 g, 0.25 mmol), 2,6-dimethylnaphthalene (0.078 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave a 3:1 regioisomeric mixture of **22h** and **22h'** as an off-white solid. **Yield:** 0.085 g, 82%; $\mathbf{R_f}$ = 0.67 (petroleum ether/EtOAc 8:2); **mp:** 129-132 ºC; **IR ν_{max} / cm^{-1} (film):** 1682; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ *(only characteristic peaks reported)* 4.82 (3.4H, t, *J* = 7.8 Hz), 2.52 (10H, s), 2.48 (10H, s) *major regioisomer* and 4.33 (1H, t, *J* = 7.8 Hz), 2.54 (3H, s), 2.35 (3H, s) *minor regioisomer*; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{28}H_{25}{}^{35}ClONa$ Found: 435.1502, requires 435.1486 (-3.6 ppm).



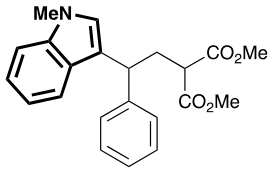
4-Mesityl-1-phenyl-4-(4-(trifluoromethyl)phenyl)butan-1-one (22i) was prepared according to *General Procedure L* from cyclopropane **C1m** (0.073 g, 0.25 mmol), mesitylene (0.070 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave **22i** as a white solid. **Yield:** 0.095 g, 93%; $\mathbf{R_f}$ = 0.70 (petroleum ether/EtOAc 8:2); **mp:** 129-130 ºC; **IR ν_{max} / cm^{-1} (film):** 1680, 1614; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.83 (2H, dd, *J* = 8.3, 1.2 Hz), 7.56-7.51 (3H, m), 7.42 (2H, t, *J* = 7.7 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 6.84 (2H, s), 4.65 (1H, dd, *J* = 10.5, 4.3 Hz), 3.01-2.94 (1H, m), 2.91-2.82 (2H, m), 2.55-2.47 (1H, m), 2.27 (3H, s), 2.14 (6H, br s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.9, 148.4, 137.0, 136.8, 136.3, 136.2, 133.0, 130.3, 128.5, 128.0, 127.9 (app. d, *J* = 32.2 Hz), 127.4, 125.1 (q, *J* = 3.5 Hz), 124.4 (q, *J* = 271.7 Hz), 42.6, 36.3, 25.4, 21.3, 20.8; **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -62.3; **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{26}H_{26}F_3O$ Found: 411.1943, requires 411.1930 (-3.2 ppm).



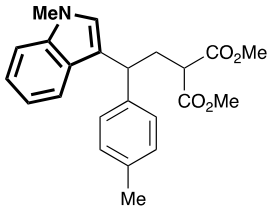
1-Phenyl-4-(4-(trifluoromethyl)phenyl)-4-(2,4,6-trimethoxyphenyl)-butan-1-one (22j) was prepared according to *General Procedure L* from cyclopropane **C1m** (0.073 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 16 h. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **22j** as a colourless oil. **Yield:** 0.097 g, 85%; $\mathbf{R_f}$ = 0.41 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2839, 1684, 1608, 1589; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.86-7.84 (2H, m), 7.54-7.50 (1H, m), 7.47-7.39 (6H, m), 6.09 (2H, s), 4.70 (1H, dd, *J* = 10.1, 6.0 Hz), 3.79 (3H, s), 3.65 (3H, s), 2.94 (1H, ddd, *J* = 16.4, 9.0, 7.1 Hz), 2.82 (1H, ddd, *J* = 16.7, 8.8, 5.3 Hz), 2.72-2.55 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.5, 160.1, 159.2, 149.5, 137.2, 132.7, 128.4, 128.1, 128.0, 127.4 (q, *J* = 32.0), 124.6 (q, *J* = 271.7 Hz), 124.5 (q, *J* = 3.4 Hz), 111.8, 91.0, 55.5, 55.2, 38.5, 37.1, 26.0; **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -62.1; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{26}H_{25}F_3O_4Na$ Found: 481.1604, requires 481.1597 (-1.5 ppm).



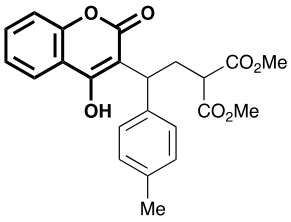
4-(4-Nitrophenyl)-1-phenyl-4-(2,4,6-trimethoxyphenyl)butan-1-one (22k) was prepared according to *General Procedure L* from cyclopropane **C1n** (0.067 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at 80 ºC for 3 h. Purification by flash column chromatography over silica (0-25% EtOAc in petroleum ether) gave **22k** as a yellow oil. **Yield:** 0.097 g, 89%; $\mathbf{R_f}$ = 0.21 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2837, 1682, 1593, 1512; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.07 (2H, d, *J* = 8.8 Hz), 7.86-7.83 (2H, m), 7.52 (1H, t, *J* = 7.4 Hz), 7.45 (2H, d, *J* = 8.5 Hz), 7.41 (2H, t, *J* = 7.7 Hz), 6.08 (2H, s), 4.73 (1H, dd, *J* = 10.2, 5.8 Hz), 3.79 (3H, s), 3.63 (6H, s), 2.95 (1H, dt, *J* = 16.9, 7.8 Hz), 2.82 (1H, ddd, *J* = 16.9, 8.3, 5.4 Hz), 2.71-2.56 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.3, 160.4, 159.2, 153.8, 145.8, 137.2, 132.9, 128.6, 128.5, 128.1, 123.0, 111.2, 91.0, 55.6, 55.4, 38.5, 36.8, 25.7; **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{25}H_{26}NO_6$ Found: 436.1765, requires 436.1755 (-2.3 ppm).



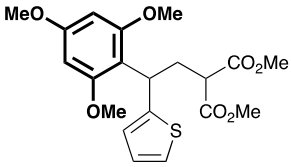
Dimethyl 2-(2-(1-methyl-1*H*-indol-3-yl)-2-phenylethyl)malonate (23a) was prepared according to *General Procedure M* from cyclopropane **C1a** (0.059 g, 0.25 mmol), 1-methylindole (0.062 mL, 0.50 mmol) and $B(C_6F_5)$•H_2O (13.2 mg, 10 mol%) in $MeNO_2$ (0.125 mL) and stirred at 80 ºC for 24 h. Purification by flash column chromatography over silica (10-25% EtOAc in petroleum ether) gave **23a** as a colourless oil. Analytical data are in agreement with the literature.[240] **Yield:** 0.062 g, 68%**; ^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 8.0 Hz), 7.36-7.28 (5H, m), 7.24-7.20 (2H, m), 7.07-7.03 (1H, m), 6.91 (1H, s), 4.25 (1H, t, *J* = 7.9 Hz), 3.78 (3H, s), 3.77 (3H, s), 3.70 (3H, s), 3.44 (1H, dd, *J* = 7.8, 6.9 Hz), 2.89-2.82 (1H, m), 2.65 (1H, ddd, *J* = 13.9, 8.7, 6.7 Hz).



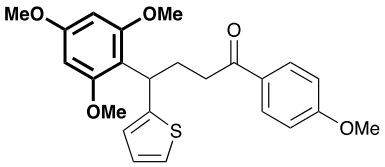
Dimethyl 2-(2-(1-methyl-1*H*-indol-3-yl)-2-(*p*-tolyl)ethyl)malonate (23b) was prepared according to *General Procedure M* from cyclopropane **C1d** (0.063 g, 0.25 mmol), 1-methylindole (0.062 mL, 0.50 mmol) and $B(C_6F_5)\bullet H_2O$ (6.6 mg, 5 mol%) in $MeNO_2$ (0.125 mL) and stirred at 80 ºC for 24 h. Purification by flash column chromatography over silica (10-30% EtOAc in petroleum ether) gave **23b** as an off-white solid. **Yield:** 0.081 g, 85%; $\mathbf{R_f}$ = 0.34 (petroleum ether/EtOAc 8:2); **mp:** 96-98 ºC; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 7.8 Hz), 7.24-7.19 (3H, m), 7.13 (2H, d, *J* = 7.9 Hz), 7.06 (1H, t, *J* = 7.4 Hz), 6.90 (1H, s), 4.21 (1H, t, *J* = 7.9 Hz), 3.77 (6H, s), 3.70 (3H, s), 3.43 (1H, dd, *J* = 8.1, 6.6 Hz), 2.85 (1H, dt, *J* = 14.1, 7.2 Hz), 2.62 (1H, ddd, *J* = 13.9, 8.9, 6.5 Hz), 2.34 (3H, s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.0, 169.9, 140.4, 137.3, 135.9, 129.2, 127.8, 127.2, 126.0, 121.7, 119.6, 118.9, 117.5, 109.1, 52.5, 52.4, 50.1, 40.2, 35.1, 32.7, 21.0; **HRMS:** ($APPI^+$) $[M]^+$ $C_{23}H_{25}NO_4$ Found: 379.1778, requires 379.1778 (+0.03 ppm).



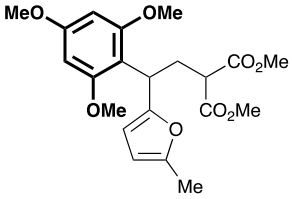
Dimethyl 2-(2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-(p-tolyl)ethyl)-malonate (23c) was prepared according to *General Procedure L* from cyclopropane **C1d** (0.063 g, 0.25 mmol), 4-hydroxycoumarin (0.049 g, 0.30 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (10-30% EtOAc in petroleum ether) gave **23c** as a white solid. **Yield:** 0.052 g, 50%; $\mathbf{R_f}$ = 0.21 (petroleum ether/EtOAc 7:3); **mp:** 152-154 ºC; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 7.9 Hz), 7.52 (1H, td, *J* = 7.8, 1.1 Hz), 7.34 (2H, d, *J* = 7.8 Hz), 7.27 (2H, app. d, *J* = 8.1 Hz), 7.14 (2H, d, *J* = 7.9 Hz), 4.51 (1H, dd, *J* = 9.6, 6.0 Hz), 3.76 (3H, s), 3.72 (3H, s), 3.51 (1H, dd, *J* = 8.6, 6.1 Hz), 2.96 (1H, ddd, *J* = 14.4, 9.3, 5.6 Hz), 2.82 (1H, ddd, *J* = 14.1, 8.3, 6.1 Hz), 2.32 (3H, s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.9, 170.1, 162.6, 161.0, 152.7, 137.3, 136.8, 132.0, 129.4, 127.7, 123.9, 123.4, 116.4, 116.1, 107.2, 53.1, 52.8, 49.8, 37.5, 29.6, 21.0.



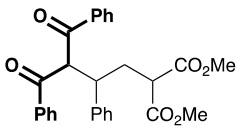
Dimethyl 2-(2-(thiophen-2-yl)-2-(2,4,6-trimethoxyphenyl)ethyl)-malonate (23d) was prepared according to *General Procedure M* from cyclopropane **C1j** (0.061 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and $B(C_6F_5)\bullet H_2O$ (6.6 mg, 5 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-35% EtOAc in petroleum ether) gave **23d** as a colourless liquid. Analytical data are in agreement with the literature.[240] **Yield:** 0.061 g, 60%; $\mathbf{R_f}$ = 0.29 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.04 (1H, dd, *J* = 4.9, 1.4 Hz), 6.86-6.83 (2H, m), 6.11 (2H, s), 4.85 (1H, dd, *J* = 10.3, 6.1 Hz), 3.79 (3H, s), 3.74 (6H, s), 3.71 (3H, s), 3.63 (3H, s), 3.25 (1H, dd, *J* = 9.2, 5.7 Hz), 2.90 (1H, ddd, *J* = 13.4, 10.4, 5.7 Hz), 2.76 (1H, ddd, *J* = 13.4, 9.2, 6.1 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.1, 169.8, 160.3, 148.6, 125.9, 123.7, 122.7, 110.6, 91.1, 55.6, 55.3, 52.4, 52.4, 50.5, 33.5, 32.9.



1-(4-Methoxyphenyl)-4-(thiophen-2-yl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (23e) was prepared according to *General Procedure M* from cyclopropane **C1p** (0.065 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and $B(C_6F_5)\bullet H_2O$ (6.6 mg, 5 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-20% EtOAc in petroleum ether) gave **23e** as a colourless oil. **Yield:** 0.099 g, 93%; $\mathbf{R_f}$ = 0.22 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2938;2835, 1672, 1599; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J = 8.9 Hz), 7.05 (app. t. J = 3.2 Hz), 6.89-6.86 (4H, m), 6.12 (2H, s), 4.89 (1H, dd, J = 9.3, 6.8 Hz), 3.84 (3H, s), 3.80 (3H, s), 3.72 (6H, s), 2.88 (1H, ddd, J = 15.9, .1, 6.8 Hz), 2.77 (1H, ddd, J = 15.6, 9.6, 5.7 Hz), 2.72-2.57 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.3, 163.2, 160.1, 159.3, 149.7, 130.4, 130.3, 126.0, 123.6, 122.5, 113.6, 112.1 91.2, 55.7, 55.5, 55.3, 37.1, 35.3, 29.1; **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{24}H_{26}O_5SNa$ Found: 449.1408, requires 449.1393 (-3.4 ppm).

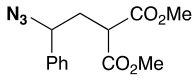


Dimethyl 2-(2-(5-methylfuran-2-yl)-2-(2,4,6-trimethoxyphenyl)-ethyl)malonate (23f) was prepared according to *General Procedure M* from cyclopropane **C1i** (0.060 g, 0.25 mmol), 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) and $B(C_6F_5)\bullet H_2O$ (6.6 mg, 5 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-35% EtOAc in petroleum ether) gave **23f** as a colourless liquid. **Yield:** 0.004 g, trace; $\mathbf{R_f}$ = 0.30 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.11 (2H, s), 5.82-5.80 (2H, m), 4.58 (1H, t, J = 8.0 Hz), 3.80 (3H, s), 3.72 (3H, s), 3.71 (6H, s), 3.60 (3H, s), 3.26 (1H, t, J = 7.5 Hz), 2.71 (2H, t, J = 7.8 Hz), 2.20 (3H, s); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.2, 169.8, 160.2, 159.6, 155.7 149.5, 108.9, 105.7, 105.0, 91.2, 55.7, 55.2, 52.4 (app. d, J = 3.1 Hz), 50.3, 32.0, 30.5, 13.6; **HRMS:** (APPI$^+$) $[M]^+$ $C_{21}H_{26}O_8$ Found: 406.1624, requires 406.1622 (+0.19 ppm).

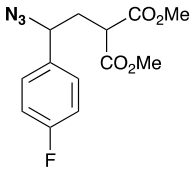


Dimethyl 2-(3-benzoyl-4-oxo-2,4-diphenylbutyl)malonate (24a) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), dibenzoylmethane (0.056 g, 0.25 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (10-30% EtOAc in petroleum ether) gave **24a** as a white solid. **Yield:** 0.089 g, 78%; $\mathbf{R_f}$ = 0.23 (petroleum ether/EtOAc 8:2); **mp:** 98-101 ^{o}C; **IR ν_{max} / cm^{-1} (film):** 1751, 1730, 1688, 1665; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.05 (2H, d, J = 7.3 Hz), 7.74 (2H, d, J = 7.3 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.47-7.40 (4H, m), 7.31-7.27 (2H, m), 7.25-7.23 (2H, m), 7.18 (2H, t, J = 7.5 Hz), 7.09 (1H, t, J = 7.2 Hz), 5.67 (1H, d, J = 10.3 Hz), 3.98 (1H, td, J = 10.4, 4.6 Hz), 3.76 (3H, d, J = 2.3 Hz), 3.50 (3H, d, J = 2.3 Hz), 3.16 (1H, dd, J = 9.1, 5.6 Hz), 2.40-2.35 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 194.2, 194.1, 169.5, 169.1, 139.2, 136.9, 136.7, 133.7 133.2, 128.9 (2C), 128.9, 128.6, 128.5, 128.5, 127.3, 64.5, 52.6, 52.4,

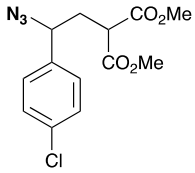
49.9, 44.7, 32.9; **HRMS:** (ESI$^+$) [M+Na]$^+$ $C_{28}H_{26}O_6Na$ Found: 481.1617, requires 481.1622 (+0.9 ppm).



Dimethyl 2-(2-azido-2-phenylethyl)malonate (24b) was prepared according to *General Procedure L* from cyclopropane **C1a** (0.059 g, 0.25 mmol), azidotrimethylsilane (0.066 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (10% EtOAc in petroleum ether) gave **24b** as a colourless liquid. Analytical data are in agreement with the literature.[241] **Yield:** 0.045 g, 65%; **R$_f$** = 0.66 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.42-7.35 (3H, m), 7.34-7.31 (2H, m), 4.55 (1H, t, J = 7.3 Hz), 3.75 (3H, s), 3.74 (3H, s), 3.54 (1H, t, J = 7.3 Hz), 2.34 (2H, dd, J = 7.7, 7.0 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.3, 169.2, 138.4, 129.0, 128.7, 126.9, 63.9, 52.8, 48.7, 35.3.

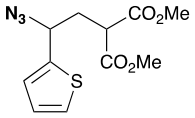


Dimethyl 2-(2-azido-2-(4-fluorophenyl)ethyl)malonate (24c) was prepared according to *General Procedure L* from cyclopropane **C1b** (0.063 g, 0.25 mmol), azidotrimethylsilane (0.066 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **24c** as a colourless liquid. Analytical data are in agreement with the literature.[241] **Yield:** 0.048 g, 65%; **R$_f$** = 0.65 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.30 (2H, dd, J = 8.7, 5.3 Hz), 7.08 (2H, t, J = 8.6 Hz), 4.54 (1H, t, J = 7.3 Hz), 3.75 (3H, s), 3.74 (3H, s), 3.52 (1H, t, J = 7.2 Hz), 2.30 (2H, t, J = 6.9 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.2, 169.1, 162.7 (d, J = 247.6 Hz), 134.3 (d, J = 3.0 Hz), 128.7 (d, J = 8.4 Hz), 116.0 (d, J = 21.8 Hz), 63.2, 52.8, 48.6, 35.4; **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -112.9.

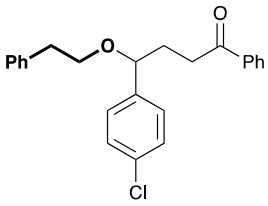


Dimethyl 2-(2-azido-2-(4-chlorophenyl)ethyl)malonate (24d) was prepared according to *General Procedure L* from cyclopropane **C1c** (0.067 g, 0.25 mmol), azidotrimethylsilane (0.066 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **24d** as a colourless liquid. **Yield:** 0.044 g, 56%; **R$_f$** = 0.60 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 2955, 2100, 1732; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.39 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.57 (1H, t, J = 7.3 Hz), 3.78 (3H, s), 3.76 (3H, s), 3.55 (1H, t, J = 7.3 Hz), 2.32 (1H, t, J = 7.3 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.2, 169.2, 137.1, 134.7, 129.3, 128.4, 63.3, 52.9, 48.7, 35.4; **HRMS:** (ESI$^+$) [M+Na]$^+$ $C_{13}H_{14}{}^{35}ClN_3O_4Na$ Found: 334.0560, requires 334.0565 (+1.6 ppm).

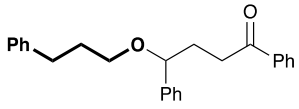
[241] K. L. Ivanov, E. V. Villemson, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur.-J.* **2015**, *21*, 4975.



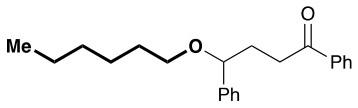
Dimethyl 2-(2-azido-2-(thiophen-2-yl)ethyl)malonate (24e) was prepared according to *General Procedure M* from cyclopropane **C1j** (0.061 g, 0.25 mmol), azidotrimethylsilane (0.066 mL, 0.50 mmol) and $B(C_6F_5)$•H_2O (6.6 mg, 5 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **24e** as a colourless liquid. Analytical data are in agreement with the literature.[241] **Yield:** 0.048 g, 68%; $\mathbf{R_f}$ = 0.60 (petroleum ether/EtOAc 8:2); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* = 5.1, 1.0 Hz), 7.05 (1H, dd, *J* = 3.4, 0.5 Hz), 7.01 (1H, dd, *J* = 5.0, 3.5 Hz), 4.81 (1H, t, *J* = 7.4 Hz), 3.76 (3H, s), 3.75 (3H, s), 3.58 (1H, t, *J* = 7.2 Hz), 2.43 (2H, t, *J* = 7.4 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.2, 169.1, 141.2, 127.0, 126.3, 126.1, 59.2, 52.9, 48.7, 35.6.



4-(4-Chlorophenyl)-4-phenethoxy-1-phenylbutan-1-one (24f) was prepared according to *General Procedure L* from cyclopropane **C1l** (0.064 g, 0.25 mmol), 2-phenylethanol (0.060 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave **24f** as an off-white solid. **Yield:** 0.085 g, 90%; $\mathbf{R_f}$ = 0.83 (petroleum ether/EtOAc 8:2); **mp:** 87-88 ºC; **IR ν_{max} / cm^{-1} (film):** 1680; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 8.3, 1.3 Hz), 7.61-7.57 (1H, m), 7.48 (2H, t, *J* = 7.6 Hz), 7.33-7.26 (4H, m), 7.23-7.19 (5H, m), 4.35 (1H, t, *J* = 6.5 Hz), 3.59 (1H, dt, *J* = 9.3, 6.8 Hz), 3.48 (1H, dt, *J* = 9.3, 6.9 Hz), 3.02 (2H, t, *J* = 7.2 Hz), 2.92-2.81 (2H, m), 2.11 (2H, q, *J* = 6.9 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.0, 141.1, 139.2, 137.1, 133.2, 133.1, 129.1, 128.7, 128.6, 128.4, 128.2, 127.9, 126.3, 80.6, 69.8, 36.5, 34.5, 32.7; **HRMS:** (ESI^+) $[M+K]^+$ $C_{24}H_{23}{}^{35}ClO_2K$ Found: 417.1054, requires 417.1018 (-8.7 ppm).



1,4-Diphenyl-4-(3-phenylpropoxy)butan-1-one (24g) was prepared according to *General Procedure L* from cyclopropane **C1k** (0.056g, 0.25 mmol), 3-phenylpropanol (0.068 mL, 0.50 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave **24g** as an off-white solid. **Yield:** 0.065 g, 73%; $\mathbf{R_f}$ = 0.83 (petroleum ether/EtOAc 8:2); **mp:** 76-77 ºC; **IR ν_{max} / cm^{-1} (film):** 1680; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* = 7.3 Hz), 7.58 (1H, t, *J* = 7.3 Hz), 7.48 (2H, t, *J* = 7.6 Hz), 7.41-7.36 (4H, m), 7.34-7.26 (3H, m), 7.20 (1H, d, *J* = 7.2 Hz), 7.16 (2H, d, *J* = 7.3 Hz), 4.38 (1H, dd, *J* = 7.6, 5.5 Hz), 3.41 (1H, dt, *J* = 9.3, 6.3 Hz), 3.31 (1H, dt, *J* = 9.3, 6.3 Hz), 3.13 (2H, td, *J* = 7.1, 2.6 Hz), 2.77-2.63 (2H, m), 2.28-2.14 (2H, m), 1.93-1.86 (2H, m); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.2, 142.7, 142.2, 137.2, 133.1, 128.7, 128.5, 128.4, 128.2, 127.7, 126.7, 125.8, 81.2, 68.2, 34.8, 32.8, 32.6, 31.6; **HRMS:** (ESI^+) $[M+Na]^+$ $C_{25}H_{26}O_2Na$ Found: 381.1829, requires 381.1825 (-1.1 ppm).



4-(Hexyloxy)-1,4-diphenylbutan-1-one (24h) was prepared according to *General Procedure L* from cyclopropane **C1k** (0.056g, 0.25 mmol), 1-hexanol (0.093 mL, 0.75 mmol) and TfOH (2.2 µL, 10 mol%) in HFIP (0.125 mL) and stirred at room temperature for 3 h. Purification by flash column chromatography over silica (0-5% EtOAc in petroleum ether) gave **24h** as a colourless liquid. **Yield:** 0.060 g, 74%; $\mathbf{R_f}$ = 0.84 (petroleum ether/EtOAc 8:2); **IR ν_{max} / cm^{-1} (film):** 1681; **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.98-7.96 (2H, m), 7.59-7.56 (1H, m), 7.47 (2H, t, J = 7.6 Hz), 7.39-7.27 (5H, m), 4.35 (1H, t, J = 6.6 Hz), 3.36 (1H, dt, J = 9.2, 6.7 Hz), 3.25 (1H, dt, J = 9.2, 6.6 Hz), 3.18-3.04 (2H, m), 2.19-2.14 (2H, m), 1.61-1.52 (2H, m), 1.37-1.22 (6H, m), 0.88 (3H, t, J = 7.0 Hz); **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.1, 142.7, 137.1, 132.9, 128.5, 128.4, 128.0, 127.4, 126.5, 81.0, 69.0, 34.7, 32.8, 31.7, 29.9, 25.9, 22.6, 14.0; **HRMS:** (APPI$^+$) $[M]^+$ $C_{22}H_{28}O_2$ Found: 324.2084, requires 324.2084 (+0.04 ppm).

4. General procedures for ring-opening of non-donor-acceptor cyclopropanes

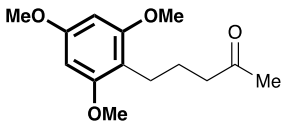
General Procedure N*: *Arylative Cyclopropane Ring-Opening

A 10 mL Pyrex tube was charged with a stir bar, followed by the requisite cyclopropane (0.25 mmol), nucleophile (0.25-0.75 mmol), HFIP (0.125-0.250 mL) and finally TfOH (2.2 µL, 10 mol%). The reaction was then heated at the requisite temperature for the necessary amount of time. At completion, the crude reaction mixture was concentrated *in vacuo* onto silica gel and purified by flash column chromatography over silica in the eluent system stated to give the desired ring-opened product.

General procedure O: Suzuki-Miyaura Cross Coupling for cyclopropane synthesis

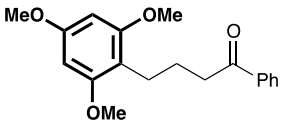
To a solution of cyclopropylboronic acid (0.286 g, 3.40 mmol, 1.30 equiv), bromoarene (2.6 mmol), tricyclohexyl phosphine (0.072 g, 0.30 mmol, 0.10 equiv) in toluene (10 mL) and water (0.5 mL) was added potassium phosphate (1.64 g, 7.70 mmol, 3.00 equiv) and $Pd(OAc)_2$ (28.6 mg, 5 mol%) in one portion. The mixture was heated to 100 °C for 3-16 h under Ar. After the reaction was cooled to ambient temperature, water was added and the mixture was extracted with EtOAc. The desired product was purified by flash column chromatography (10 % of EtOAc in petroleum ether).

5. Characterization data of ring-opened products (non-donor-acceptor cyclopropanes)

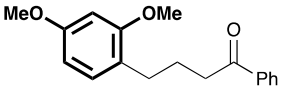


5-(2,4,6-Trimethoxyphenyl)pentan-2-one (25a) was prepared according to *General Procedure N* from cyclopropylmethyl ketone (0.025 mL, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in

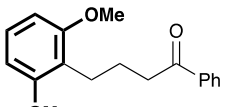
HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave **25a** as a pale-yellow liquid. **Yield:** 0.048 g, 76%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.11 (2H, s), 3.79 (3H, s), 3.77 (6H, s), 2.57 (2H, t, J = 7.3 Hz), 2.38 (2H, t, J = 7.5 Hz), 2.10 (3H, s), 1.75 (2H, quint. J = 7.4 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 209.9, 159.4, 158.9, 110.5, 90.5, 55.6, 55.4, 43.4, 29.7, 23.7, 21.7. **HRMS:** (ESI^+) $[M+H]^+$ $C_{14}H_{21}O_4$ Found: 253.1408, requires 253.1434.



1-Phenyl-4-(2,4,6-trimethoxyphenyl)butan-1-one (25b) was prepared according to *General Procedure N* from cyclopropylphenyl ketone (0.035 mL, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (5% EtOAc in petroleum ether) gave **25b** as a white solid. **Yield:** 0.053 g, 67%. **mp:** 84-85 °C. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.93-7.91 (2H, m), 7.52 (1H, dd, J = 8.3, 6.4 Hz), 7.43 (2H, t, J = 7.6 Hz), 6.11 (2H, s), 3.80 (3H, s), 3.71 (6H, s), 2.92 (2H, t, J = 7.4 Hz), 2.69 (2H, t, J = 7.1 Hz), 1.94 (2H, quint. J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.8, 159.4, 159.0, 137.5, 132.7, 128.5, 128.1, 110.6, 90.5, 55.6, 55.4, 38.0, 23.9, 21.7. **HRMS:** (ESI^+) $[M+H]^+$ $C_{19}H_{23}O_4$ Found: 315.1569, requires 315.1591.

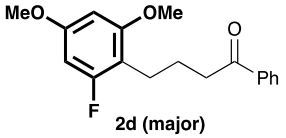


2c (major)

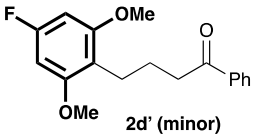


2c' (minor)

4-(2,4-Dimethoxyphenyl)-1-phenylbutan-1-one (25c) and **4-(2,6-Dimethoxyphenyl)-1-phenylbutan-1-one (25c')** were prepared according to *General Procedure N* from cyclopropylphenyl ketone (0.035 mL, 0.25 mmol) and 1,3-dimethoxybenzene (0.065 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-10% EtOAc in petroleum ether) gave **25c** and **25c'** as a colourless oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.068 g, 69%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.95 (2H, dd, J = 8.3, 1.2 Hz), 7.59-7.53 (1H, m), 7.48-7.44 (2H, m), 7.15 (0.4H, t, J = 8.3 Hz), 7.07 (0.7H, d, J = 7.9 Hz), 6.54 (0.8H, d, J = 8.3 Hz), 6.47-6.43 (1.3H, m), 3.83-3.82 (2H, m), 3.76-3.75 (4H, m), 2.98 (2H, q, J = 7.1 Hz), 2.80 (0.75H, t, J = 7.1 Hz), 2.69 (1.25H, t, J = 7.3 Hz), 2.08-1.98 (2H, m). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.6, 200.5, 159.2, 158.4, 137.3, 137.2, 132.8, 132.6, 130.2, 128.5, 128.4, 128.0, 126.9, 122.5, 118.2, 103.8, 103.5, 98.5, 55.5, 55.4, 55.2, 37.9, 28.9, 24.6, 23.5, 22.0. **HRMS:** (ESI^+) $[M+H]^+$ $C_{18}H_{21}O_3$ Found: 285.1468, requires 285.1485.



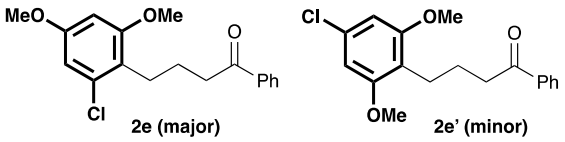
2d (major)



2d' (minor)

4-(2-Fluoro-4,6-dimethoxyphenyl)-1-phenylbutan-1-one (25d) and **4-(4-Fluoro-2,6-dimethoxyphenyl)-1-phenylbutan-1-one (25d')** were prepared according to *General Procedure N* from cyclopropylphenyl ketone (0.034 g, 0.25 mmol) and 1-fluoro-3,5-dimethoxybenzene (0.078 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **25d** and **25d'** as a colourless

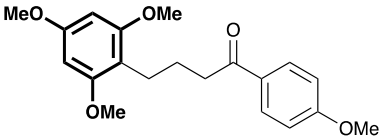
oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.062 g, 82%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 7.3 Hz), 7.53 (1H, t, J = 7.3 Hz), 7.44 (2H, t, J = 7.6 Hz), 6.26 (0.4H, s), 6.23 (0.8H, s), 6.21 (0.8H, s), 3.76 (1.5H, s), 3.70 (1.5H, s), 3.69 (3H, s), 2.93 (2H, app. dt, J = 11.6, 7.4 Hz), 2.71-2.69 (2H, m), 1.95 (2H, app. dquint, J = 15.5, 7.7 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.6 (major), 200.4 (minor), 162.6 (d, J = 240.8 Hz – major), 162.2 (d, J = 240.6 Hz – minor), 159.3 (d, J = 12.5 Hz), 158.9 (d, J = 12.5 Hz), 137.4, 137.3, 132.9, 132.8, 128.6, 128.5, 128.1, 113.5 (d, J = 3.5 Hz – minor), 109.6 (d, J = 19.8 Hz), 94.3 (d, J = 2.3 Hz – major), 92.9 (d, J = 28.1 Hz), 91.7 (d, J = 25.7 Hz), 55.7, 55.6, 37.9, 24.0, 23.6, 21.8, 21.5, 21.5. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -113.4 (minor), -116.2 (major). **HRMS:** (ESI^+) $[M+H]^+$ $C_{18}H_{18}FO_3$ Found: 303.1386, requires 303.1391.



4-(2-Chloro-4,6-dimethoxyphenyl)-1-phenylbutan-1-one (25e) and **4-(4-Chloro-2,6-dimethoxyphenyl)-1-phenylbutan-1-one (25e')** were prepared according to *General Procedure N* from cyclopropylphenyl ketone (0.034 g, 0.25 mmol) and 5-chloro-1,3-dimethoxybenzene (0.086 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **25e** and **25e'** as a colourless oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.055 g, 70%.

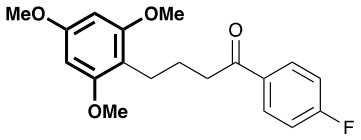
Major regioisomer (25e): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (2H, d, J = 7.2 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.6 Hz), 6.53 (1H, d, J = 2.3 Hz), 6.34 (1H, d, J = 2.3 Hz), 3.79 (3H, s), 3.70 (3H, s), 3.00 (2H, t, J = 7.4 Hz), 2.85 (2H, t, J = 7.3 Hz), 2.00 (2H, quint. J = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.4, 159.2, 158.8, 137.3, 135.2, 132.9, 128.6, 128.1, 121.0, 105.5, 97.5, 55.7, 55.6, 37.9, 25.7, 23.4. **HRMS:** (ESI^+) $[M+Na]^+$ $C_{18}H_{19}{}^{35}ClO_3Na$ Found: 341.0926, requires 341.0915.

Minor regioisomer (25e'): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.91 (2H, d, J = 7.1 Hz), 7.53 (1H, t, J =7.4 Hz), 7.44 (2H, t, J – 7.6 Hz), 6.50 (2H, s), 3.70 (6H, s), 2.91 (2H, t, J = 7.3 Hz), 2.70 (2H, t, J = 7.2 Hz), 1.93 (2H, quint. J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 200.4, 158.6, 137.3, 132.7, 132.3, 128.4, 128.0, 116.6, 104.4, 55.7, 37.7, 23.3, 21.7. **HRMS:** (ESI^+) $[M+H]^+$ $C_{18}H_{20}{}^{35}ClO_3$ Found: 319.1090, requires 319.1095.

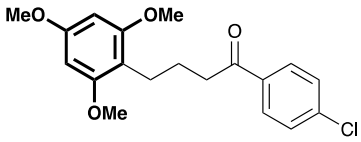


1-(4-Methoxyphenyl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (25f) was prepared according to *General Procedure N* from cyclopropyl 4-methoxyphenylmethanone (0.044 g, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **25f** as a colourless oil. **Yield:** 0.046 g, 61%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.9 Hz), 6.90 (2H, d, J = 8.9 Hz), 6.11 (2H, s), 3.86 (3H, s), 3.80 (3H, s), 3.71 (6H, s), 2.87 (2H, t, J = 7.4 Hz), 2.67 (2H, t, J = 7.2 Hz), 1.91 (2H, quint. J = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.5, 163.2, 159.4, 159.0, 130.6, 130.4, 113.6, 110.8, 90.5, 55.6,

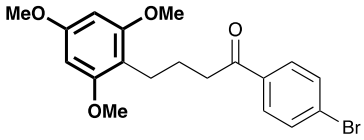
55.5, 55.4, 37.8, 24.2, 21.8. **HRMS:** (ESI$^+$) $[M+Na]^+$ $C_{20}H_{24}O_5Na$ Found: 367.1524, requires 367.1516.



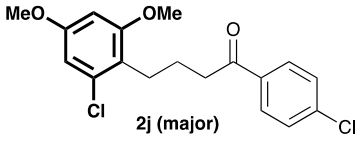
1-(4-Fluorophenyl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (25g) was prepared according to *General Procedure N* from cyclopropyl 4-fluorophenylketone (0.036 mL, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **25g** as a colourless oil. **Yield:** 0.080 g, 98%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.96-7.91 (2H, m), 7.12-7.07 (2H, m), 6.10 (2H, s), 3.80 (3H, s), 3.71 (6H, s), 2.88 (2H, t, J = 7.4 Hz), 2.67 (2H, t, J = 7.1 Hz), 1.92 (2H, quint. J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.2, 165.6 (d, J = 253.7 Hz), 159.5, 159.0, 133.9 (d, J = 2.6 Hz), 130.7 (d, J = 9.3 Hz), 115.6 (d, J = 21.9 Hz), 110.6, 90.5, 55.6, 55.5, 37.9, 23.9, 21.7. **^{19}F NMR:** (376 MHz, $CDCl_3$) δ -106.3. **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{19}H_{22}O_4F$ Found: 333.1485, requires 333.1497.

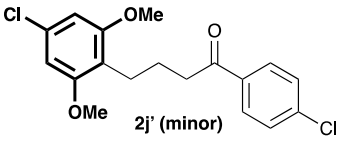


1-(4-Chlorophenyl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (25h) was prepared according to *General Procedure N* from cyclopropyl 4-chlorophenylketone (0.045 g, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **25h** as a white solid. **Yield:** 0.079 g, 91%. **mp:** 88-89 °C. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 8.5 Hz), 7.40 (2H, d, J = 8.4 Hz), 6.10 (2H, s), 3.80 (3H, s), 3.70 (6H, s), 2.88 (2H, t, J = 7.3 Hz), 2.67 (2H, t, J = 7.0 Hz), 1.92 (2H, quint., J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.5, 159.5, 159.0, 139.0, 135.8, 129.6, 128.8, 110.5, 90.5, 55.6, 55.4, 37.9, 23.8, 21.6. **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{19}H_{22}O_4{}^{35}Cl$ Found: 349.1191, requires 349.1201.



1-(4-Bromophenyl)-4-(2,4,6-trimethoxyphenyl)butan-1-one (25i) was prepared according to *General Procedure N* from cyclopropyl 4-bromophenylketone (0.050 g, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (0-15% EtOAc in petroleum ether) gave **25i** as a white solid. **Yield:** 0.068 g, 69%. **mp:** 96-97 °C. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 6.10 (2H, s), 3.80 (3H, s), 3.70 (6H, s), 2.87 (2H, t, J = 7.3 Hz), 2.67 (2H, t, J = 7.1 Hz), 1.91 (2H, quint. J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.7, 159.5, 159.0, 136.2, 131.8, 129.7, 127.8, 110.5, 90.5, 55.6, 55.4, 37.9, 23.8, 21.6. **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{19}H_{22}O_4{}^{79}Br$ Found: 393.0676, requires 393.0696.



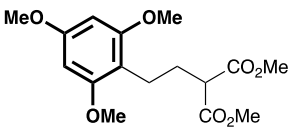


4-(2-Chloro-4,6-dimethoxyphenyl)-1-(4-chlorophenyl)butan-1-one (25j) and **4-(4-Chloro-2,6-dimethoxyphenyl)-1-**

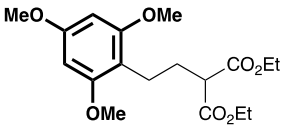
(4-chlorophenyl)butan-1-one (25j') were prepared according to *General Procedure N* from cyclopropyl 4-chlorophenyl ketone (0.045 g, 0.25 mmol) and 5-chloro-1,3-dimethoxybenzene (0.086 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **25j** and **25j'** as a colourless oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.066 g, 74%.

Major regioisomer (25j): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.6 Hz), 7.41 (2H, d, J = 8.6 Hz), 6.50 (1H, d, J = 2.4 Hz), 6.32 (1H, d, J = 2.4 Hz), 3.77 (3H, s), 3.68 (3H, s), 2.93 (2H, t, J = 7.3 Hz), 2.81 (2H, t, J = 7.3 Hz), 1.97 (2H, quint. J = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.1, 159.2, 158.9, 139.3, 135.6, 135.2, 129.6, 128.9, 120.8, 105.6, 97.5, 55.7, 55.6, 37.9, 25.7, 23.3. **HRMS:** (ESI^+) $[M+K]^+$ $C_{18}H_{18}{}^{35}Cl_2O_3K$ Found: 391.0273, requires 391.0265.

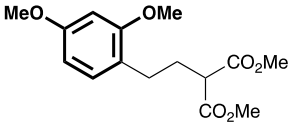
Minor regioisomer (25j'): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.5 Hz), 7.43 (2H, d, J = 8.5 Hz), 6.53 (2H, s), 3.72 (6H, s), 2.90 (2H, t, J = 7.3 Hz), 2.71 (2H, t, J = 7.2 Hz), 1.94 (2H, quint. J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 199.1, 158.6, 139.1, 132.4, 129.4, 128.7, 116.5, 106.9, 104.4, 55.7, 37.7, 23.2, 21.7. **HRMS:** (ESI^+) $[M+H]^+$ $C_{18}H_{19}{}^{35}Cl_2O_3$ Found: 353.0702, requires 353.0706.



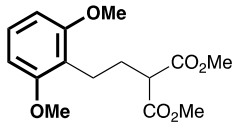
Dimethyl 2-(2,4,6-trimethoxyphenethyl)malonate (26a) was prepared according to *General Procedure N* from dimethyl cyclopropane-1,1-dicarboxylate (0.034 g, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (10-30% EtOAc in petroleum ether) gave **26a** as a colourless liquid. **Yield:** 0.079 g, 98%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.09 (2H, s), 3.78 (3H, s), 3.75 (6H, s), 3.70 (6H, s), 3.31 (1H, t, J = 7.5 Hz), 2.63 (2H, t, J = 7.1 Hz), 2.08 (2H, q, J = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.2, 159.7, 159.0, 109.3, 20.4, 55.6, 55.4, 52.4, 51.2, 28.5, 20.1. **HRMS:** (ESI^+) $[M+H]^+$ $C_{16}H_{23}O_7$ Found: 327.1413, requires 327.1438.



Diethyl 2-(2,4,6-trimethoxyphenethyl)malonate (26b) was prepared according to *General Procedure N* from diethyl cyclopropane-1,1-dicarboxylate (0.044 mL, 0.25 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (25% EtOAc in petroleum ether) gave **26b** as a colourless liquid. **Yield:** 0.063 g, 71%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.10 (2H, s), 4.16 (4H, app. qq, J = 10.5, 7.1 Hz), 3.79 (3H, s), 3.76 (6H, s), 3.28 (1H, t, J = 7.5 Hz), 2.64 (2H, t, J = 7.2 Hz), 2.06 (2H, q, J = 7.3 Hz), 1.25 (6H, t, J = 7.1 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.8, 159.6, 159.0, 109.6, 90.4, 61.2, 55.6, 55.4, 51.7, 28.4, 20.2, 14.2. **HRMS:** (ESI^+) $[M+Na]^+$ $C_{18}H_{26}O_7Na$ Found: 377.1552, requires 377.1571.

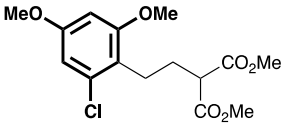


2m (major)

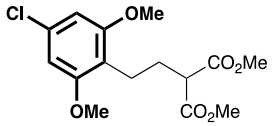


2m' (minor)

Dimethyl 2-(2,4-dimethoxyphenethyl)-malonate (26c) and **Dimethyl 2-(2,6-dimethoxyphenethyl)malonate (26c')** were prepared according to *General Procedure N* from dimethyl cyclopropane-1,1-dicarboxylate (0.034 g, 0.25 mmol) and 1,3-dimethoxybenzene (0.065 mL, 0.50 mmol) in HFIP (0.125mL) and stirred at 100 °C. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **26c** and **26c'** as a colourless oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.057 g, 77%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.15 (0.4H, dd, J = 9.9, 6.8 Hz), 7.02 (0.6H, d, J = 8.0 Hz), 6.55-6.42 (2H, m), 3.81-3.79 (7H, m), 3.75-3.73 (5H, m), 3.38 (1H, app. q, J = 7.9 Hz), 2.75 (0.8H, t, J = 7.1 Hz), 2.61 (1.2H, t, J = 7.4 Hz), 2.25-2.12 (2H, m). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.1, 170.0, 161.0, 159.4, 158.4, 157.0, 130.4, 130.1, 127.2, 121.2, 116.8, 107.8, 106.2, 103.8, 103.5, 101.5, 98.5, 55.5, 55.4, 55.2, 52.4, 52.3, 51.2, 51.1, 29.1, 28.1, 27.2, 20.4. **HRMS:** (ESI^+) $[M+Na]^+$ $C_{15}H_{20}O_6Na$ Found: 319.1138, requires 319.1152.



2n (major)

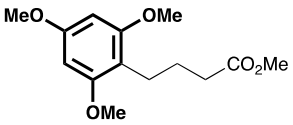


2n' (minor)

Dimethyl 2-(2-chloro-4,6-dimethoxyphen-ethyl)malonate (26d) and **Dimethyl 2-(4-chloro-2,6-dimethoxyphenethyl)malonate (26d')** were prepared according to *General Procedure N* from dimethyl cyclopropane-1,1-dicarboxylate (0.034 g, 0.25 mmol) and 5-chloro-1,3-dimethoxybenzene (0.086 g, 0.50 mmol) in HFIP (0.125mL) and stirred at 100 °C. Purification by flash column chromatography over silica (0-30% EtOAc in petroleum ether) gave **26d** and **26d'** as a colourless oil (ca. 2:1 mixture of regioisomers). **Yield:** 0.046 g, 56%.

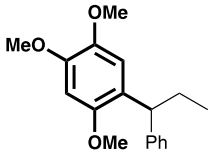
Major regioisomer (26d): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.52 (1H, d, J = 2.4 Hz), 6.35 (1H, d, J = 2.4 Hz), 3.79 (3H, s), 3.78 (3H, s), 3.75 (6H, s), 3.38 (1H, t, J = 7.5 Hz), 2.79 (2H, t, J = 7.5 Hz), 2.14 (2H, q, J = 7.5 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 169.8, 159.0, 158.9, 135.1, 119.7, 105.5, 97.3, 55.6, 55.5, 52.4, 51.2, 27.8, 24.0. **HRMS:** (ESI^+) $[M+H]^+$ $C_{15}H_{20}{}^{35}ClO_6$ Found: 331.0958, requires 331.0943.

Minor regioisomer (26d'): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.53 (2H, s), 3.79 (6H, s), 3.73 (6H, s), 3.32 (1H, t, J = 7.5 Hz), 2.69 (2H, t, J = 7.1 Hz), 2.11 (2H, q, J = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 170.0, 158.6, 132.7, 115.3, 104.4, 55.7, 55.4, 51.1, 27.9, 20.2.

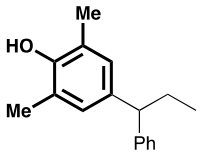


Methyl 4-(2,4,6-trimethoxyphenyl)butanoate (26e) was prepared according to *General Procedure N* from methyl cyclopropanecarboxylate (0.025 g, 0.025 mmol) and 1,3,5-trimethoxybenzene (0.084 g, 0.50 mmol) in 1,2-DCE (0.125 mL) and stirred at 100 °C. Purification by flash column chromatography over silica (10% EtOAc in petroleum ether) gave **26e** as a colourless oil. **Yield:** 0.010 g, 15%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.11 (2H, s), 3.80 (3H, s), 3.77 (6H, s), 3.64 (3H, s), 2.61 (2H, t, J = 7.2 Hz), 2.28 (2H, t, J = 7.8 Hz), 1.80 (2H, quint. J =

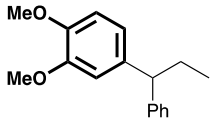
7.5 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 174.7, 159.5, 159.0, 110.4, 90.5, 55.7, 55.4, 51.4, 33.8, 24.7, 21.8. **HRMS:** (ESI^+) $[M+H]^+$ $C_{14}H_{21}O_5$ Found: 269.1388, requires 269.1384.



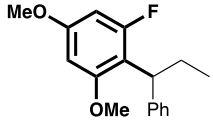
1,2,4-Trimethoxy-5-(1-phenylpropyl)benzene (27a) was prepared according to *General Procedure N* from cyclopropylbenzene (0.031 mL, 0.25 mmol) and 1,2,4-trimethoxybenzene (0.075 mL, 0.50 mmol) in HFIP (0.0125 mL) and stirred at 80 °C. Purification by flash column chromatography over silica (1% EtOAc petroleum ether) allowed for partial separation of **27a** from excess nucleophile to provide an analytical sample of **27a** in 90% purity. **Yield (NMR relative to CH_2Br_2):** 79 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.28-7.27 (4H, m), 7.16 (1H, app. dd, *J* = 8.3, 4.3 Hz), 6.80 (1H, s), 6.52 (1H, s), 4.25 (1H, t, *J* = 7.8 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.76 (3H, s), 2.08-1.96 (2H, m), 0.92 (3H, t, *J* = 7.4 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 151.5, 147.7, 145.4, 143.1, 128.1, 128.0, 125.7, 125.4, 112.2, 98.2, 56.8, 56.7, 56.1, 44.7, 28.0, 12.7. **HRMS:** ($APCI^+$) $[M]^+$ $C_{18}H_{22}O_3$ Found: 286.1577, requires 286.1563.



2,6-Dimethyl-4-(1-phenylpropyl)phenol (27b) was prepared according to *General Procedure N* from cyclopropylbenzene (0.031 mL, 0.25 mmol) and 2,6-dimethylphenol (0.061g, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (2% EtOAc in petroleum ether) gave **27b** as a yellow oil. **Yield:** 0.041 g, 68 %. **^{1}H NMR:** (400 MHz, $CDCl_3$): δ 7.35-7.19 (5H, m), 6.90 (2H, s), 4.51 (1H, s), 3.72 (1H, t, *J* = 7.7 Hz), 2.26 (6H, s), 2.08 (2H, quint, *J* = 7.3 Hz), 0.95 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$): δ 150.4, 145.9, 136.9, 128.4, 128.3, 127.9, 125.9, 122.8, 52.6, 28.8, 16.1, 13.0. **HRMS:** (ESI^-) $[M-H]^-$ $C_{17}H_{19}O$ Found: 239.1440, requires: 239.1441.

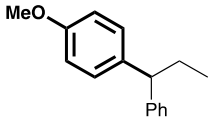


1,2-Dimethoxy-4-(1-phenylpropyl)benzene (27c) was prepared according to *General Procedure N* from cyclopropylbenzene (0.132 mL, 1.00 mmol) and 1,2-dimethoxybenzene (0.252 mL, 0.500 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by filtration through Celite (CH_2Cl_2) followed by bulb-to-bulb distillation under vacuum (3 mm Hg, 60.4 °C), gave **27c** as a yellow oil. **Yield:** 0.045 g, 70 %. **^{1}H NMR**: (400 MHz, $CDCl_3$): δ 7.32-7.15 (5H, m), 6.82 (2H, s), 6.76 (1H, s), 3.87 (3H, s), 3.86 (3H, s), 3.76 (1H, t, *J* = 7.9 Hz), 2.07 (2H, quint, *J* = 7.5 Hz), 0.92 (3H, t, *J* = 7.5 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$): δ 148.8, 147.3, 145.4, 137.9, 128.4, 128.0, 127.8, 126.1, 119.8, 111.5, 111.2, 55.9, 52.9, 28.8, 12.9. **HRMS:** ($APCI^+$) $[M]^+$ $C_{17}H_{20}O_2$ Found: 256.1455, requires 256.1456.

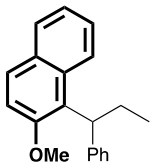


1-Fluoro-3,5-dimethoxy-2-(1-phenylpropyl)benzene (27d) was prepared according to *General Procedure N* from cyclopropylbenzene (0.031 mL, 0.25 mmol) and 1-fluoro-3,5-dimethoxybenzene (0.067 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Attempted purification could not separate the product regioisomers from excess nucleophile (ca. 2:1 mix of regioisomers). **Yield (NMR relative**

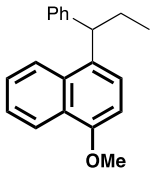
to CH_2Br_2): 83 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.38-7.36 (0.7H, m), 7.30-7.23 (2.3H, m), 7.20-7.11 (2.0H, m), 6.30-6.29 (2H, m), 3.81 (4H, s), 3.79-3.78 (2H, m), 2.23-2.01 (2H, m), 0.94-0.86 (3H, m).



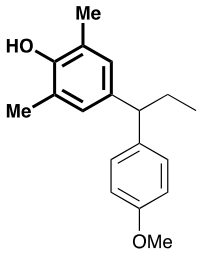
1-Methoxy-4-(1-phenylpropyl)benzene (27e) was prepared according to *General Procedure N* from cyclopropylbenzene (0.031 mL, 0.25 mmol) and anisole (0.054 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Attempted purification by flash column chromatography over silica (100 % petroleum ether) gave **27e** as a colourless liquid (ca. 3:1 mix of regioisomers), however not all anisole could be removed from the product. **Yield (NMR relative to CH_2Br_2):** 93 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.36-7.12 (7H, m), 7.01-6.93 (0.62H, m), 6.87-6.83 (1.35H, m), 3.85 (1.5H, s), 3.80 (2.5H, s), 3.79-3.73 (1H, m), 2.11-2.02 (2H, m), 0.92 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 157.8, 145.6, 137.4, 128.8, 128.3, 127.8, 125.9, 113.7, 55.1, 52.4, 28.8, 12.8. **HRMS:** (APCI$^+$) $[M]^+$ $C_{16}H_{18}O$ Found: 226.1356, requires 226.1352.



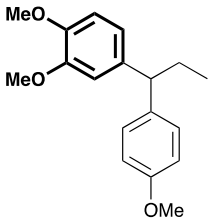
2-Methoxy-1-(1-phenylpropyl)naphthalene (27f) was prepared according to *General Procedure N* from cyclopropylbenzene (0.033 mL, 0.25 mmol) and 2-methoxynaphthalene (0.079 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (100% petroleum ether) gave **27f** as an off-white solid. **Yield:** 0.065 g, 94 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.78-7.71 (3H, m), 7.39-1.16 (8H, m), 4.00 (1H, t, *J* = 7.9 Hz), 3.95 (3H, s), 2.26-2.12 (2H, m), 1.02 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 157.4, 145.3, 140.4, 133.2, 129.3, 129.1, 128.4, 128.1, 127.4, 126.9, 126.1, 125.9, 118.7, 105.7, 55.3, 53.1, 28.5, 12.9. **HRMS:** (ESI$^+$) $[M+H]^+$ $C_{20}H_{21}O$ Found: 277.1578, requires 277.1587.



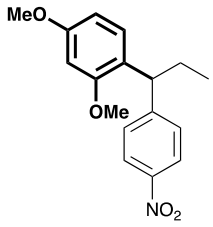
1-Methoxy-4-(1-phenylpropyl)naphthalene (27g) was prepared according to *General Procedure N* from cyclopropylbenzene (0.033 mL, 0.25 mmol) and 1-methoxynaphthalene (0.072 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (100% petroleum ether) gave **27g** as a colourless oil (ca. 4:1 mix of regioisomers). **Yield:** 0.065 g, 94 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) (*only data for the major regioisomer are reported*) δ 8.29 (1H, s), 7.79 (1H, d, *J* = 8.5 Hz), 7.45-7.34 (8H, m), 6.88 (1H, d, *J* = 7.7 Hz), 4.10-4.03 (1H, m), 4.07 (3H, s), 2.32-2.26 (2H, m), 1.04 (3H, t, *J* = 6.7 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) (*only data for the major regioisomer are reported - one carbon resonance is not observed/overlaps with other resonances*) δ 155.3, 145.3, 142.1, 133.2, 128.4, 128.1, 127.7, 127.3, 126.0, 125.3, 120.1, 120.0, 103.9, 55.5, 53.6, 28.5, 12.9. **HRMS:** (ESI$^+$) $[M+K]^+$ $C_{20}H_{20}KO$ Found: 315.1159, requires 315.1146.



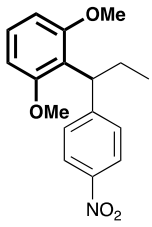
4-(1-(4-Methoxyphenyl)propyl)-2,6-dimethylphenol (27h) was prepared according to *General Procedure N* from cyclopropane S3 (0.037 mg, 0.25 mmol) and 2,6-dimethylphenol (0.061 g, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (2% EtOAc in petroleum ether) gave **27h** as a yellow oil. **Yield:** 0.034 g, 50 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.7 Hz), 6.84 (2H, d, *J* = 4.7 Hz), 6.83 (2H, d, *J* = 4.2 Hz), 4.461 (1H, s) 3.79 (3H, s) 3.62 (1H, t, *J* = 7.8 Hz), 2.22 (6H, s), 2.0 (2H, quint, *J* = 7.6 Hz), 0.89 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 157.7, 150.3, 138.0, 137.3, 128.7, 127.9, 122.7, 113.7, 55.2, 51.7, 29.0, 16.1, 12.9. **HRMS:** ($APCI^+$) $[M+H]^+$ $C_{18}H_{23}O_2$ Found: 271.1642, requires 271.1614.



1,2-Dimethoxy-4-(1-(4-methoxyphenyl)propyl)benzene (27i) was prepared according to *General Procedure N* from cyclopropane S3 (0.037 g, 0.25 mmol) and 1,2-dimethoxybenzene (0.063 mL, 0.50 mmol) in HFIP (0.125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (1-7% EtOAc in petroleum ether) gave **27i** as a colourless liquid. **Yield:** 0.035 g, 49 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 8.7 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 6.80 (2H, d, *J* = 2.7 Hz), 6.74 (1H, s), 3.86 (6H, d, *J* = 3.8 Hz), 3.80 (2H, s), 3.71 (1H, t, *J* = 7.8 Hz), 2.03 (2H, quint, *J* = 7.6 Hz), 1.28 (1H, s), 0.91 (3H, t, *J* = 7.4 Hz). **^{13}C NMR:** (400 MHz, $CDCl_3$) δ 157.8, 148.8, 147.2, 138.3, 137.6, 128.7, 119.6, 113.7, 111.3, 111.1, 55.9, 55.8, 55.2, 52.0, 29.0, 12.9. **HRMS:** (ESI^+) $[M+Na]^+$ $C_{18}H_{22}O_3Na$ Found: 309.1464, requires 309.1461.



3h (major)



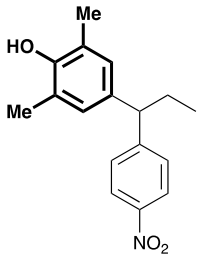
3h' (minor)

2,4-Dimethoxy-1-(1-(4-nitrophenyl)propyl)benzene (27j) and **1,3-dimethoxy-2-(1-(4-nitrophenyl)propyl)-benzene (27j')** were prepared according to *General Procedure N* from cyclopropane S2 (0.041 g, 0.25 mmol) and 1,3-dimethoxybenzene (0.065 mL, 0.50 mmol) in HFIP (0.0125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (100 % petroleum ether) gave **27j** and **27j'** as a colourless oil (a ca. 3:1 mix of regioisomers). **Yield:** 0.024 g, 32 %.

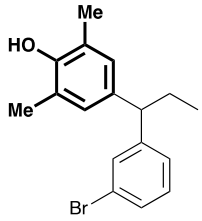
Major Regioisomer (27j): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09 (2H, d, *J* = 8.7 Hz), 7.36 (2H, d, *J* = 8.7 Hz), 7.13 (1H, d, *J* = 8.4 Hz), 6.48 (1H, dd, *J* = 8.4, 2.4 Hz), 6.41 (1H, d, *J* = 2.4 Hz), 4.23 (1H, t, *J* = 7.8 Hz), 3.79 (3H, s), 3.72 (3H, s), 2.09-1.96 (2H, m), 0.90 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 159.6, 158.1, 153.9, 146.1, 128.9, 127.8, 124.3, 123.5, 104.2, 98.8, 55.5, 55.4, 45.1, 27.6, 12.7. **HRMS:** ($APCI^+$) $[M]^+$ $C_{17}H_{19}NO_4$ Found: 301.1304, requires 301.1309.

Minor Regioisomer (27j'): ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 8.9 Hz), 7.50 (2H, dd, *J* = 8.9, 0.6 Hz), 7.16 (1H, t, *J* = 8.3 Hz), 6.53 (2H, d, *J* = 8.3 Hz), 4.67 (1H, t, *J* = 7.9

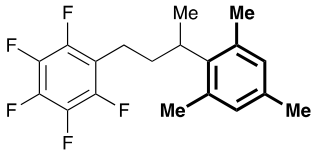
Hz), 3.73 (6H, s), 2.26-2.17 (2H, m), 0.87 (3H, t, *J* = 7.4 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 158.5, 153.8, 145.6, 128.7, 128.0, 122.8, 119.8, 104.4, 55.6, 41.4, 24.1, 12.7.



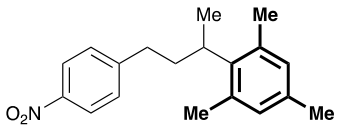
2,6-Dimethyl-4-(1-(4-nitrophenyl)propyl)phenol (27k) was prepared according to *General Procedure N* from cyclopropane S2 (0.041 g, 0.25 mmol) and 2,6-dimethylphenol (0.061 g, 0.50 mmol) in HFIP (0.0125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (100 % petroleum ether) gave **27k** and **27k'** as a yellow oil (a ca. 3:1 mix of regioisomers). **Yield:** 0.043 g, 60 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) (*only data for the major regioisomer are reported*) δ 8.13 (2H, d, *J* = 8.7 Hz), 7.37 (2H, d, *J* = 8.7 Hz), 6.80 (2H, s), 4.51 (1H, s), 3.76 (1H, t, *J* = 7.8 Hz), 2.21 (6H, s), 2.08-2.01 (2H, m), 0.90 (3H, t, *J* = 7.4 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) (*only data for the major regioisomer are reported*) δ 153.7, 150.9, 134.9, 128.9, 128.6, 127.9, 123.7, 123.2, 52.4, 28.4, 16.0, 12.7. **HRMS:** ($APCI^+$) $[M]^+$ $C_{17}H_{19}NO_3$ Found: 285.1353, requires 285.1359.



2,6-Dimethyl-4-(1-(3-bromophenyl)propyl)phenol (27l) was prepared according to *General Procedure N* from cyclopropane (0.147 g, 0.750 mmol) and 2,6-dimethylphenol (0.091 g, 0.75 mmol) in HFIP (0.0125 mL) and stirred at room temperature. Purification by flash column chromatography over silica (10% EtOAc in petroleum ether) gave **27l** as a yellow oil. **Yield:** 0.233 g, 97 %. **^{1}H NMR:** (400 MHz, $CDCl_3$) 7.44 (1H, br s), 7.36-7.34 (1H, m), 7.21-7.17 (2H, m), 6.88 (2H, s), 4.64 (1H, s), 3.68 (1H, t, *J* = 7.8 Hz), 2.27 (6H, s), 2.06 (2H, quint. *J* = 7.4 Hz), 0.95 (3H, t, *J* = 7.3 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) 150.7, 148.4, 136.0, 130.9, 130.0, 129.1, 128.0, 126.5, 123.1, 122.6, 52.3, 28.7, 16.2, 12.9. **HRMS:** ($APCI^+$) $[M]^+$ $C_{17}H_{19}{}^{79}BrO$ Found: 318.0620, requires 318.0614.

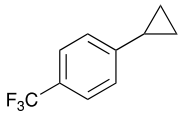


1,2,3,4,5-Pentafluoro-6-(3-mesitylbutyl)benzene (28a) was prepared according to *General Procedure O* from (cyclopropylmethyl)-pentafluorobenzene **S5** (60.2 mg, 0.244 mmol, 90% pure), mesitylene (67.9 µL, 0.488 mmol) and TfOH (2.2 µL, 0.025 mmol) in 0.125 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (100% petroleum ether) gave **28a** as an off-white solid. **Yield:** 0.082 g, 88%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 6.84 (2H, s), 3.31 (1H, sext, *J* = 7.6 Hz), 2.74–2.62 (1H, m), 2.62–2.50 (1H, m), 2.40 (3H, s), 2.35–2.28 (3H, s), 2.26 (3H, s), 2.18–2.04 (1H, m), 2.04–1.89 (1H, m), 1.37 (3H, d, *J* = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 145.1 (dm, *J* = 244.0 Hz), 139.5 (dm, *J* = 249.6 Hz), 137.5 (dm, *J* = 244.9 Hz), 138.6, 136.3 (br), 135.4, 131.4 (broad), 130.5, 129.4 (br), 115.6 (td, *J* = 18.7, 3.6 Hz), 35.0, 35.0, 21.6 (br, 2C), 21.4 (br), 20.7, 19.1. **^{19}F NMR:** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ –143.4 (2F, dd, *J* = 22.4, 8.4 Hz), –157.2 (1F, t, *J* = 20.6 Hz), 162.0 (2F, dq, *J* = 21.1, 10.8 Hz). **HRMS:** ($APCI^+$) $[M+H]^+$ $C_{19}H_{20}F_5$ found 342.1416; requires 342.1407.

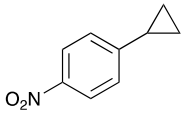


1,3,5-Trimethyl-2-(4-(4-nitrophenyl)butan-2-yl)benzene (28b) was prepared according to *General Procedure O* from 1-cyclopropylmethyl-4-nitrobenzene **S6** (45.3 mg, 0.256 mmol), mesitylene (71.1 µL, 0.511 mmol) and TfOH (2.3 µL, 0.026 mmol) in 0.125 mL of HFIP (24 h, 100 °C). Purification by flash column chromatography over silica (100% petroleum ether) gave **28b** as a yellow oil (mixture of two regioisomers in the ratio 4:1, according to the ^{1}H NMR spectrum). Only data for the major regioisomer is reported. **Yield:** 0.068 g, 88%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 6.81 (2H, s), 3.21 (1H, sext, *J* = 7.6 Hz), 2.72–2.53 (2H, m), 2.34 (3H, s), 2.24 (3H, s), 2.20–2.07 (4H, s), 2.07–1.97 (1H, m), 1.32 (3H, d, *J* = 7.2 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 150.7, 146.4, 138.9, 136.4, 131.4, 129.3, 129.3, 123.7, 36.7, 34.7, 34.4, 21.6, 20.8, 19.2.

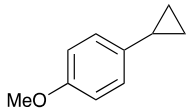
6. Preparation of non-commercial monosubstituted cyclopropanes



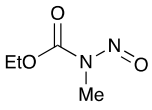
1-Cyclopropyl-4-(trifluoromethyl)benzene (S1) was prepared according to General Procedure B with corresponding analytical data.[242] **Yield:** 96 %. **^{1}H NMR**: (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 1.98-1.95 (m, 1H), 1.09-1.05 (m, 2H), 0.79-0.76 (m, 2H).



1-Cyclopropyl-4-nitrobenzene (S2) was prepared according to General Procedure B with corresponding analytical data.[243] **Yield:** 74 %. **^{1}H NMR**: (400 MHz, $CDCl_3$): δ 8.12 (d, *J*=8.9 Hz, 2H), 7.18 (d, *J*=8.9 Hz, 2H), 2.05-1.99 (m, 1H), 1.16-1.13 (m, 2H), 0.88-0.81 (m, 2H).



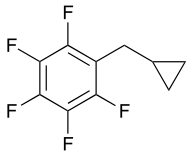
1-Cyclopropyl-4-methoxybenzene (S3) was prepared according to General Procedure B with corresponding analytical data.[244] **Yield**: 20 %. **^{1}H NMR**: (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 3.81 (s, 3H), 1.89-1.86 (m, 1H), 0.93-0.91 (m, 2H), 0.65-0.63 (m, 2H).



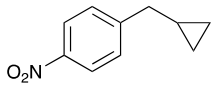
Ethyl *N*-methyl-*N*-nitrosocarbamate (S4) was prepared according to a literature procedure with corresponding spectral data.[245] To stirring ethyl *N*-methylcarbamate (0.41 g, 4.00 mmol), a solution of H_3PO_4 (0.340 g, 3.44 mmol) in H_2O (0.34 mL) was added carefully. Then, a solution of $NaNO_2$ (0.340 g, 4.90 mmol) in H_2O (0.79 mL) was added slowly, over 1 h, under stirring, and the reaction mixture stirred at room temperature for 16 h. The mixture was extracted with toluene (2 x 5 mL) and used as a crude solution for the preparation of

[242] Y-Y. Zhou, C. Uyeda, *Angew. Chem. Int. Ed.*, 2016, *55*, 3171-3175.
[243] G. A. Somorjai, *J. Am. Chem. Soc*., 2016, *138*, 8533-8537.
[244] L. Ackermann, A. R. Kapdi and C. Schulzke, *Org. Lett*., 2010, *12*, 2298-2301;
[245] F. Shroeder, Ruethi, F. WO2015059290 (A1), 2015.

the following cyclopropanes (**S5** and **S6**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 4.56 (2H, q, *J* = 7.2 Hz), 3.16 (3H, s), 1.47 (3H, t, *J* = 7.2 Hz).



(Cyclopropylmethyl)pentafluorobenzene (S5): In a 100 mL round bottom flask, allyl pentafluorobenzene (766 µL, 5.00 mmol) was dissolved in 5 mL of toluene, together with 2.5 mL of 40% KOH(aq) solution and $Pd(acac)_2$ (30 mg, 0.10 mmol) and cooled to 0 °C. Then, 10 mL of crude ethyl *N*-methyl-*N*-nitrosocarbamate **S4** in toluene solution was added, the reaction mixture stirred at 0 °C for 1 h, and then at ambient temperature for 16 h. At completion, the organic layer was decanted, dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The crude residue was filtered through a celite plug and concentrated to give **S4** as a yellow oil, which was used without further purification. **Yield:** 0.621 g, 56%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 2.61 (2H, d, *J* = 6.8 Hz), 1.05–0.89 (1H, m), 0.50 (2H, d, *J* = 7.6 Hz), 0.25 (2H, d, *J* = 4.4 Hz). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 145.2 (dm, *J* = 243.0 Hz), 139.7 (dm, *J* = 249.5 Hz), 137.6 (dm, *J* = 248.4 Hz), 117.3, 115.2 (td, *J* = 19.4, 3.7 Hz), 27.2, 11.0, 4.9. **^{19}F NMR:** (376.5 MHz, $CDCl_3$, CF_3CO_2H - ext. std.) δ –143.1 (2F, dd, *J* = 22.5, 8.4 Hz), –157.0 (1F, t, *J* = 21.0 Hz), –161.9 (2F, dq, *J* = 21.0, 10.8 Hz). **HRMS:** (ESI) *m/z* for $C_{10}H_7F_5$ ($[M+H]^+$) calculated 222.0462; found 222.0454.



1-Cyclopropylmethyl-4-nitrobenzene (S6) was prepared from 4-nitrobenzyl chloride (346 mg, 2.01 mmol), potassium cyclopropyltrifluoroborate (452 mg, 3.05 mmol), $Pd_2(dba)_3$ (94 mg, 0.10 mmol), RuPhos (100 mg, 0.21 mmol) and K_2CO_3 (556 mg, 4.02 mmol). The reactants were dissolved in a degassed mixture of toluene/water (19:1, mL/mL) under an argon atmosphere. The reaction was stirred for 9 h at 120 °C. After cooling to room temperature, the reaction mixture was filtered through celite and $MgSO_4$, and the solvent was removed under reduced pressure. Purification by automated flash column chromatography over silica (with a mixture of petroleum ether and ethyl acetate) gave **S6** as a pale yellow oil. **Yield:** 0.225 g, 63%. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 2.65 (d, *J* = 6.8 Hz, 2H), 1.06–0.93 (m, 1H), 0.63–0.51 (m, 2H), 0.24 (q, J = 5.2 Hz, 2H). Spectral data are in agreement with the literature.[246]

7. Hammett analysis data

Standard Procedure for 1H NMR Time Course Experiments

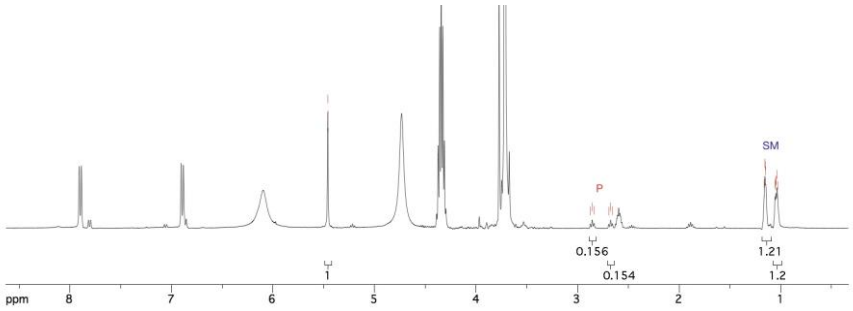
A screw-top NMR tube containing capillaries of external standard C_6D_6 and tetrachloroethane was charged with a 1 M solution of the requisite cyclopropane (0.50 mmol) in HFIP (0.500 mL) followed by 1,3,5-trimethoxybenzene (1.0 mmol, 0.168 g). After introduction to

[246] V. Colombel, F. Rombouts, D. Oehlrich, G. A. Molander *J. Org. Chem.* **2012**, *77*, 2966.

the NMR probe, this sample was heated at 77 °C and allowed to rest at this temperature for 5 min. The sample was then locked and shimmed. After removing the NMR tube, TfOH (4.4 μL, 10 mol%) was added to the mixture, the tube capped, inverted 3 times, reintroduced into the machine and acquisition begun after 120 seconds. The reaction was then followed by ^{1}H NMR over time (ns = 4, 300 s/36 experiments or every 600s/24 experiments). Conversion to product was calculated relative to the internal standard as below and plotted between 2-10% conversion to determine initial rates.

$$c_{\text{product}} = \frac{\text{Average product integration}}{\text{Average product integration} + \text{Average cyclopropane integration}} \cdot c_0$$

Average initial rates were determined via the average of at least 3 congruent values – the values being given below.



Initial rates	**Ph**	**p-F**	**p-Cl**	**p-Me**	**p-MeO**
Run 1	0.000286082	0.000225879	0.000411375	0.000385802	0.000230652
Run 2	0.000481448	0.000209991	0.000211763	0.000434392	0.000172799
Run 3	0.000242146	0.000221579	0.000243308	0.000331549	0.00030776
Run 4	0.000264584	0.000287866	0.000127467	-	0.000256576
Run 5	0.000322052	-	0.000385617	-	0.000242874
Run 6	0.000333308	-	0.000218328	-	-
Run 7	0.000429073	-	-	-	-
Run 8	0.000292829	-	-	-	-
Average	0.00033144	0.000236329	0.00026631	0.000383914	0.000242132
log k_{obs}	-3.479594916	-3.62648358	-3.574613259	-3.4157659	-3.615947344
log (k_{obs}/KH)	0	-0.146888664	-0.095018343	0.063829016	-0.136352428

8. DFT Calculations

DFT calculations were performed using Gaussian 16 A03.[1] The ωB97X-D exchange-correlation functional [2] and the def2-TZVP basis set [3] was used in all calculations. The SMD solvent model [4] was used with parameters adapted for HFIP. An absolute Gibbs energy of solvation for the proton of -267 kcal/mol was included in calculations involving charged species.

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Reaction energies for all reactions modelled according to Path B. All values are Gibbs energies in kcal/mol, calculated using ωB97X-D/def2-TZVP with an SMD solvation correction.

Arene	Ketone	Protonated Cyclopropane	Transition State	Intermediate	Enol	Product
1,3,5-trimethoxybenzene	-C(=O)Me	4.37	32.25	1.23	-0.09	-12.66
1,3,5-trimethoxybenzene	$-C(=O)OCH_3$	10.74	43.14	20.89	14.17	-13.07
1,3,5-trimethoxybenzene	$-(C(=O)OCH_3)_3$	10.21	33.45	2.99	0.03	-12.64
1,4-dimethoxybenzene	-C(=O)Me	4.37	37.49	17.63	-1.06	-15.02
1,3,5-trimethoxybenzene	-(C(=O)Ph	7.52	32.92	0.01	0.69	-12.94
1,3,5-trimethoxybenzene	-(C(=O)Ph-F)	8.23	34.00	1.48	1.73	-12.22
1,3,5-trimethoxybenzene	-(C(=O)Ph-OMe)	5.71	33.55	0.76	1.68	-12.51
1,3,5-trimethoxybenzene	-(C(=O)Ph-Cl)	8.75	33.88	-0.13	0.31	-12.53
1,3,5-trimethoxybenzene	-(C(=O)Ph-Me)	7.07	33.88	1.65	2.74	-11.73
1,2,3-trimethoxybenzene	-(C(=O)Ph	7.52	36.41	10.10	-1.92	-14.61
1,2,4-trimethoxybenzene	-(C(=O)Ph	7.52	33.71	5.20	-1.56	-14.30

Sample Input File

%nproc=8
%mem=4000MB
%chk=TS.chk
#wb97xd scrf=(SMD,solvent=generic,read) def2tzvp freq

Transition state - TMB plus MVK

1 1
C,-0.6083978893,0.0093030874,-1.5287832584
C,-1.5383033942,-0.8855814596,-0.9809255084
C,-0.5216755045,1.3088109006,-0.9946604833
H,-0.1634669627,-0.2056374392,-2.4910289034
C,-2.2785091037,-0.5528803305,0.1447664484
O,-1.6164358589,-2.0732330925,-1.5995938361
C,-1.2518454133,1.6658483416,0.1198162327
O,0.3506369088,2.1177385057,-1.6168641608
C,-2.1188236137,0.7236013993,0.6822448269
H,-2.9640901569,-1.2563454706,0.5869233666
C,-2.4926799262,-3.065415725,-1.081101858
H,-1.1812443815,2.6413843474,0.5769074489
C,0.5514599301,3.4290543023,-1.1067699894
O,-2.7798636091,1.1459706971,1.770419731

H,-2.3814901999,-3.9275630883,-1.7345252451
H,-2.212277047,-3.3412768212,-0.061967864
H,-3.5294757355,-2.7225855528,-1.1045078299
H,1.3023356964,3.8844023442,-1.7483724641
H,-0.3709497979,4.0121048125,-1.1541398035
H,0.9191015574,3.3988357366,-0.0784862186
C,-3.6955466689,0.2694813636,2.4132934283
H,-4.0972935619,0.8295211601,3.2545766487
H,-4.5094844946,-0.0098654303,1.740592916
H,-3.1889307964,-0.6258322577,2.7811447536
C,1.2567397218,-0.7901142688,-0.5132309731
H,1.8039498357,-0.0599181029,-1.090982152
H,1.0797071639,-1.7564758397,-0.9651924766
C,1.1813864651,-0.6543798846,0.9319258493
H,0.4352955019,-1.2750238438,1.416212896
H,1.1785708813,0.360207151,1.3135694927
C,2.5353022382,-1.329106747,0.9085913315
H,2.5636695438,-2.4034887871,1.0279936529
C,3.7085453335,-0.6689046172,0.7195621555
O,4.820559006,-1.402126798,0.743996041
C,3.882259886,0.7922323201,0.5116178298
H,5.6048042111,-0.8575558027,0.6052340146
H,2.9400813002,1.3313539058,0.4598741006
H,4.4752011844,1.198741522,1.3351378923
H,4.4369677504,0.9627884622,-0.4144400324

stoichiometry=C3H2O1F6
eps=17.8
solventname=2-propanol
epsinf=1.89
molarvolume=94.1
rsolv=2.82
SurfaceTensionAtInterface=23.23
ElectronegativeHalogenicity=0.6
HBondAcidity=0.57
hbondbasicity=0.25
density=0.158

Vuk VUKOVIĆ

Synergistic Effect of Acids and HFIP on Friedel-Crafts Reactions of Alcohols and Cyclopropanes

Résumé

L'activation catalytique d'alcools vers la formation déshydrative de liaisons chimiques sans pré-activation est devenue un intérêt de recherche majeur au cours des deux dernières décennies. Dans cette thèse, l'effet synergique particulier des acides forts en tant que catalyseurs dans l'hexafluoroisopropanol (HFIP) comme solvant de diverses classes de carbocations instables dans la chimie de Friedel-Crafts a été étudié. Il a été constaté que pour la première fois, les réactions de Friedel-Crafts d'alcools benzyliques primaires fortement désactivés, catalysées par un acide, se déroulaient facilement, en raison des phénomènes d'agrégation induits par l'acide dans HFIP. Une stratégie similaire a été utilisée pour l'activation d'alcools propargyliques, comme nouvelle voie d'accès sélectif aux allènes et indènes portant la fonction CF_3, à partir des mêmes composés de départ. De plus, ce système catalytique a été appliqué avec succès pour les réactions de Friedel-Crafts de cyclopropanes de type non activés et donneur-accepteur. Enfin, il a été découvert que le HFIP pouvait atténuer le réarrangement de carbocation classique dans les alkylations de Friedel-Crafts, permettant l'accès aux produits avec chaînes alkyle linéaires en une seule étape à partir d'alcools aliphatiques linéaires.

Mots clés : hexafluoroisopropanol (HFIP), catalyse par des acides de Brønsted, agrégation dans les solvants, alkylations de Friedel-Crafts, activation des alcools, ouverture des cyclopropanes

Résumé en anglais

The catalytic activation of alcohols towards dehydrative bond formation in the absence of pre-activation has become a major research interest over the past two decades. In this thesis, the peculiar synergistic effect of strong acids as catalysts in hexafluoroisopropanol (HFIP) as solvent on various classes of unstable carbocations in Friedel-Crafts chemistry was investigated. It was found that for the first time, Brønsted acid catalyzed Friedel-Crafts reactions of highly electronically deactivated primary benzylic alcohols proceeded smoothly due to the acid-induced aggregation phenomena in HFIP. A similar strategy was used for the activation of propargylic alcohols as a new route to selectively access CF_3-substituted allenes and indenes from the same starting compounds. Furthermore, this catalytic system was succesfully applied for Friedel-Crafts reactions of unactivated and donor-acceptor cyclopropanes. Finally, it was discovered that HFIP can mitigate against classical carbocation rearrangement in Friedel-Crafts alkylations, allowing access to linear alkyl chain products in a single step from linear alkyl alcohols.

Keywords: hexafluoroisopropanol (HFIP), Brønsted acid catalysis, aggregation in solvents, Friedel-Crafts alkylations, alcohol activation, cyclopropane opening