# UNIVERSITÉ DE STRASBOURG

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**Laboratoire de Catalyse Chimique**

**Institut de Science et d'Ingénierie Supramoléculaires**

# THÈSE

présentée par :

Shaofei ZHANG

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# Reactivity of Alcohols and Epoxides by Brønsted Acid Catalysis in Hexafluoroisopropanol (HFIP)

**THÈSE dirigée par:**

| | |
|---|---|
| **Prof. MORAN Joseph** | Directeur de thèse, Université de Strasbourg |

**MEMBRES du jury:**

| | |
|---|---|
| **Prof. GULDER Tanja** | Rapporteur, Universität Leipzig |
| **Prof. AMGOUNE Abderrahmane** | Rapporteur, Université Claude Bernard, Lyon 1 |
| **Dr. DONNARD Morgan** | Examinateur, Université de Strasbourg |

# Reactivity of Alcohols and Epoxides by Brønsted Acid Catalysis in Hexafluoroisopropanol (HFIP)

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ABNO** | 9-Azabicyclo[3.3.1]nonane *N*-oxyl |
| **acac** | Acetylacetonate |
| **Ac** | Acetyl |
| **AcO** | Acetate |
| **AcOH** | Acetic acid |
| **aq.** | aqueous |
| **Ar** | Aryl/Arene |
| **Bu** | Butyl |
| **Bn** | Benzyl |
| **BINAP** | 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl |
| **BINOL** | 1,1′-Bi-2-naphthol |
| **B(pin)$_2$** | Bis(pinacolato)diboron |
| **Cbz** | Benzyloxycarbonyl |
| **Cf.** | Confer/conferatur |
| **cod/COD** | 1,3-Cyclooctadiene |
| **Cy** | Cyclohexyl |
| **CSA** | Camphorsulfonic acid |
| **Cp** | Cyclopentadienyl |
| ***m*-CPBA** | *Meta*-chloroperbenzoic acid |
| **DCE** | 1,2-dichloroethane |
| **DCM** | Dichloromethane |
| **DFT** | Density Functional Theory |
| **Diglyme** | 2-Methoxyethyl ether |
| **DMF** | Dimethyl formamide |
| **DMSO** | Dimethyl sulfoxide |
| **DIBAL-H** | Diisobutylaluminum hydride |
| **DMPU** | *N, N*′-Dimethylpropyleneurea |
| **DMFU** | Dimethylfumarate |
| **DPPH** | 2,2-Diphenyl-1-picrylhydrazyl |
| **dppb** | 2-Dicyclohexylphosphino-2’, 6’-dimethoxybiphenyl |
| **equiv.** | Equivalent |

| | |
|---|---|
| **Et** | Ethyl |
| **EWG** | Electron withdrawing group |
| **ESI** | Electrospray Ionization |
| **FC** | Friedel-Crafts/ Flash column chromatography |
| **g** | Gram(s) |
| **HBD** | H-Bond Donating |
| **HOMO** | Highest occupied molecular orbital |
| **HRMS** | High-resolution mass spectrometry |
| **HMBC** | Heteronuclear multiple-bond correlation spectroscopy |
| **HFIP** | Hexafluoroisopropanol |
| **IBX** | 2-Iodoxybenzoic acid |
| ***i*Pr** | Isopropyl |
| **L** | Ligand |
| **LUMO** | Lowest unoccupied molecular orbital |
| ***m*** | *Meta* |
| **Me** | Methyl |
| **Mes** | Mesitylene |
| **mg** | Milligram |
| **mol%** | Molar percent |
| **M.S.** | Molecular sieve |
| **mmol** | Millimole |
| **m.p.** | Melting point |
| **mL** | Milliliter |
| **Nu** | Nucleophile |
| ***o*** | *ortho* |
| **OTf** | Triflate |
| **OMs** | Mesylate |
| ***p*** | *para* |
| **PMHS** | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| **ppm** | Parts per million |
| **Pr** | Propyl |
| **ref** | Reference |

| | |
|---|---|
| **rt** | Room temperature |
| **s** | Second(s) |
| ***t*** | *tert* |
| **TEPO** | Triethylphosphine oxide |
| **TFA** | Trifluoroacetic acid |
| **THF** | Tetrahydrofuran |
| **TMP** | Trimethylolpropane |
| **Tol** | Tolyl |
| **Ts** | *p*-Toluenesulfonyl, tosyl |
| ***p*-TsOH** | *p*-Toluenesulfonic acid |
| **TS** | Transition state |
| **µ** | Micro |
| **X** | Halide |

# ACKNOWLEDGEMENTS

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# RESUME

## 1) Introduction

Les époxydes et les alcools aliphatiques primaires représentent tous deux des substrats de base en chimie de synthèse, les premiers servant en particulier de point d'entrée vers des molécules densément fonctionnalisées pour la chimie médicinale et la chimie des matériaux. Ces deux classes de précurseurs facilement disponibles ont été employées dans une myriade de transformations, mais leur arylation directe reste encore très difficile, surtout dans le cas de réactions intermoléculaires.

Dans le cas de l'arylation directe des époxydes, les stratégies d'arylation basées sur la catalyse des acides de Lewis ou de Brønsted, la catalyse des métaux de transition ou la photocatalyse souffrent d'un accès difficile aux produits ramifiés. Pour les époxydes substitués par des groupements alkyles, le couplage croisé avec des halogénures d'aryle ou des acides arylboroniques conduit à des composés linéaires,[1] à l'exception d'un seul exemple rapporté par le groupe de Weix dans lequel le produit ramifié est accessible par un intermédiaire iodohydrine.[2] Pour les oxydes de styrène, on trouve davantage d'exemples d'arylation sélective pour obtenir les produits ramifiés,[3] mais les substrats qui portent des groupements fortement attracteurs d'électrons restent totalement absents. Dans le cas de l'arylation déshydratante des alcools aliphatiques primaires, en raison de la stabilité de leur liaison carbone-oxygène, seuls deux exemples ont été rapportés dans la littérature avec de faibles rendements (<10%).[4] Dans les deux cas, la substitution entre en compétition avec l'élimination, l'isomérisation ultérieure de l'alcène formé et finalement des réactions d'hydroarylation, ce qui donne un mélange complexe d'isomères. Pour contourner ce problème, des stratégies ont été conçues sur la base du couplage croisé de Kumada-Corriu,[5] du couplage électrophile croisé,[6] de l'hydrodéfluorination[7] ou de

[1] (a) X.-Y. Lu, C.-T. Yang, J.-H. Liu, Z.-Q. Zhang, X. Lu, X. Lou, B. Xiao, Y. Fu, *Chem. Commun*. **2015**, *51*, 2388; (b) M. Parasram, B. J. Shields, O. Ahmad, T. Knauber, A. G. Doyle, *ACS Catal.* **2020**, *10*, 5821.
[2] Y. Zhao, D. J. Weix, *J. Am. Chem. Soc*. **2014**, *136*, 48.
[3] X.-Y. Lu, L.-Y. Yan, J.-S. Li, J.-M. Li, H.-p. Zhou, R.-C. Jiang, C.-C. Liu, R. Lu, R. Hu, *Chem. Commun*. **2020**, *56*, 109.
[4] (a) O.Sieskind, P. Albrecht, *Tetrahedron Lett.* **1993**, *34*, 1197; (b) A. R. A. S. Deshmukh, V.K. Gumaste, B.M. Bhawal, *Catal. Lett*. **2000**, *64*, 247.
[5] T. Hatakeyama, Y. Fujiwara, Y. Okada, T. Itoh, T. Hashimoto, S. Kawamura, K. Ogata, H. Takaya, M. Nakamura, *Chem. Lett*. **2011**, *40*, 1030.
[6] S. Kim, M. J. Goldfogel, M. M. Gilbert, D. J. Weix, *J. Am. Chem. Soc*. **2020**, *142*, 9902.
[7] J. Zhu, M. Pérez, C. B. Caputo, D. W. Stephan, *Angew. Chem. Int. Ed*. **2016**, *55*, 1417.

l'activation C-H.[8] Cependant, elles nécessitent toutes une pré-activation des substrats. Par conséquent, une stratégie idéale pour l'arylation sélective des époxydes et des alcools aliphatiques primaires reste un défi à relever.

L'un des principaux avantages de la fonctionnalisation par ouverture des époxydes est que, en plus de la construction d'une liaison C-C ou C-hétéroatome, un alcool est généré qui peut être utilisé pour d'autres fonctionnalisations. Cependant, cet alcool est rarement utilisé pour installer directement une seconde liaison C-C en une seule étape. Une diarylation déshydratante des époxydes offrirait un accès rapide aux 1,1,2-triaryléthanes, des structures dont les applications vont des sciences de la vie aux précurseurs de matières premières. Les méthodes actuelles de préparation de ces structures, telles que l'hydrogénation des triaryléthènes,[9] les couplages croisés orthogonaux de Suzuki-Miyaura[10] ou la diarylation des alcènes,[11] nécessitent soit une synthèse en plusieurs étapes pour la préparation de différents partenaires de couplage croisé, soit l'utilisation de conditions de réaction sophistiquées sous atmosphère inerte. De plus, dans le cas spécifique des alcènes substitués par des alkyles, un groupe directeur est généralement nécessaire pour faciliter la transformation.

## 2) Résultats et discussions

### a) Monoarylation et diarylation d'époxides dans l'HFIP.

Nous avons entrepris de remédier à ces limitations concernant la réactivité des époxydes et des alcools aliphatiques primaires en nous appuyant sur notre expertise en matière de réactivité grâce au solvant hexafluoroisopropanol (HFIP). L'association d'un catalyseur acide de Lewis ou de Brønsted avec le HFIP est connue pour promouvoir des transformations avec des alcools, des alcènes et des cyclopropanes plutôt peu réactifs grâce la formation d'un réseau de liaisons hydrogène entre les molécules de HFIP.[12] Nous avons émis l'hypothèse que, suite à l'ouverture intermoléculaire de l'époxyde par un arène nucléophile, le motif arène nouvellement installé pourrait permettre un déplacement intramoléculaire de l'alcool résultant pour générer un ion phénonium intermédiaire

[8] A. S. S. Wilson, M. S. Hill, M. F. Mahon, C. Dinoi, L. Maron, *Science* **2017**, *358*, 1168.
[9] P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855.
[10] C. M. Crudden, C. Ziebenhaus, J. P. G. Rygus, K. Ghozati, P. J. Unsworth, M. Nambo, S. Voth, M. Hutchinson, V. S. Laberge, Y. Maekawa, D. Imao, *Nat. Commun*. **2016**, *7*, 11065.
[11] P. Gao, L.-A. Chen, K. M. Brown, *J. Am. Chem. Soc*. **2018**, *140*, 10653.
[12] V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun*. **2020**, *56*, 11548.

(Schéma 1). De là, une addition nucléophile intermoléculaire par un second partenaire arène fournirait un accès direct aux 1,1,2-triaryléthanes.

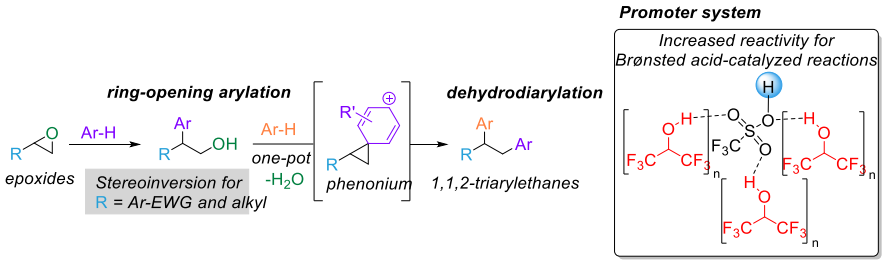
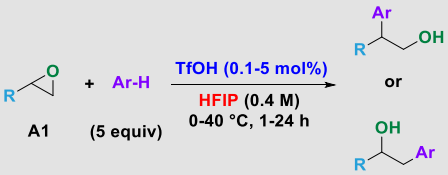



**Schéma 1.** Stratégie envisagée pour la synthèse de 1,1,2-triaryléthanes.

Nous avons commencé nos recherches en étudiant la monoarylation d'oxydes de styrène fortement déficients en électrons, qui sont notoirement difficiles à fonctionnaliser. Après une large étude des conditions de réaction, notamment des catalyseurs acides de Lewis et de Brønsted, nous avons découvert que la réaction entre l'oxyde de (pentafluorophényl)éthylène **A1** et le *m*-xylène (5 équiv.) fournissait le produit ciblé avec un rendement de 97% à température ambiante en 6 heures en conduisant la réaction dans HFIP (0,4 M) en présence de TfOH (5 mol%) comme catalyseur (Schéma 2). Une réactivité similaire a pu être obtenue en utilisant le système $Bi(OTf)_3/nBu_4NPF_6$ au lieu du TfOH dans des conditions de réaction identiques (rendement de 96%). L'utilisation de solvants plus courants (dichlorométhane, 1,2-dichloroéthane, toluène et nitrométhane) a conduit à une diminution significative du rendement (<55%), soulignant le rôle critique du HFIP dans cette transformation.

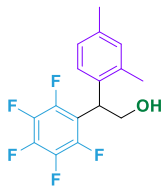
Avec des conditions optimisées en main, nous avons d'abord exploré le champ d'application de la réaction à partir de l'oxyde de styrène **A1** en testant divers nucléophiles aryles et hétéroaryles. La transformation est compatible avec une large gamme d'arènes mono- à tétrasubstituées, incorporant des substituants électrodonneurs ou attracteurs, pour donner les produits correspondants **A2-A27** avec des rendements de 42-97%. L'encombrement stérique présenté par les différents groupes fonctionnels sur le nucléophile n'a pas entravé la réactivité puisque des rendements presque quantitatifs ont pu être obtenus (jusqu'à 98 %). L'utilisation du 1,3,5-triéthylbenzène comme nucléophile a permis d'obtenir non seulement le produit de monoarylation **A8**, mais aussi le produit de diarylation **A69** dans un rapport de 1:1,25, validant ainsi notre hypothèse sur la diarylation des dérivés époxydes. De plus, la réaction n'est pas limitée aux nucléophiles riches en électrons, mais a pu être étendue au benzène (**A17**), au fluorobenzène (**A18**) et au bromobenzène (**A19**) avec de bons rendements. Pour certains arènes, des mélanges de

*Optimized conditions*

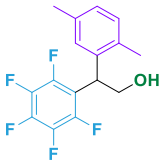



A1

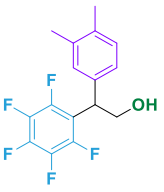
*Scope of (hetero)arenes*



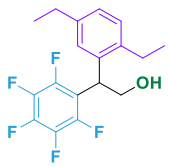

A2
(97%, *p/o/m* 70:15:15)



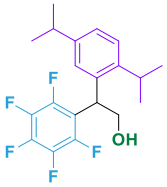

A3
(86%)



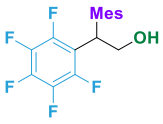

A4
(84%, *p/o* 67:33)



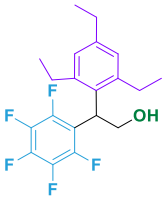

A5
(60%)



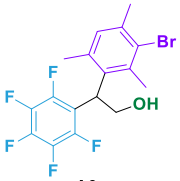

A6
(76%)



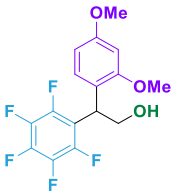

A7
(98%)



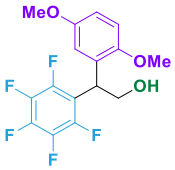

A8
(98%)[a]



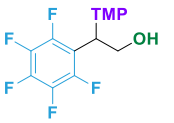

A9
(76%)



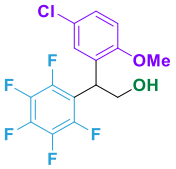

A10
(98%, *p/o* 88:12)



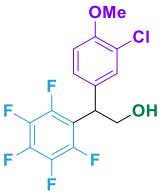

A11
(98%)



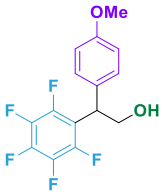

A12
(97%)



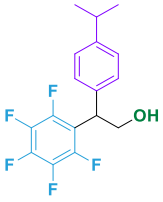

A13
(62%)



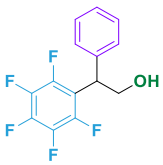

A14
(87%)



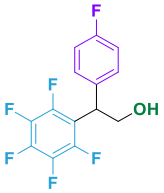

A15
(95%, *p/o* 60:40)



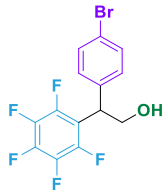

A16
(70%, *p/o* 65:35)



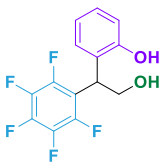

A17
(82%)
(90%)[b]



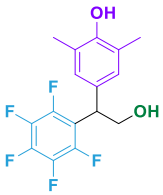

A18
(53%, *p/o* 62:38)



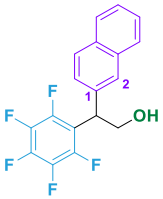

A19
(69%, *p/o* 80:20)



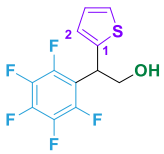

A20
(42%)
(80%)[c]



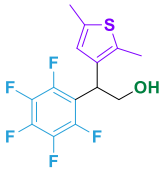

A21
(80%, *p/o* 80:20)



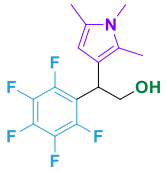

A22
(88%, *1/2* 76:24)



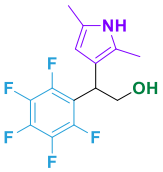

A23
(95%, *1:2* 60:40)



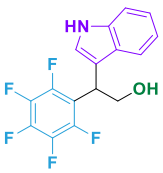

A24
(70%)



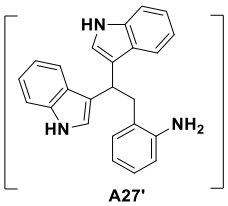

A25
(98%)



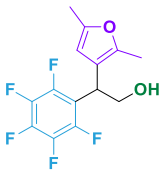

A26
(74%)




A27
(86%)[d]

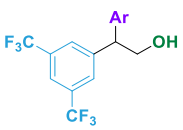



A27'

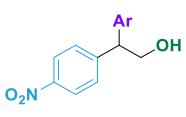



A28
(-)

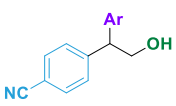
*Scope of epoxides*



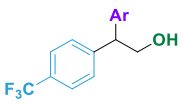

A29 (Ar = *p*-Xylene, 90%)
A30 (Ar = Mes, 92%)
A31 (Ar = Ph, 72%)




A32 (Ar = *p*-Xylene, 72%)
A33 (Ar = Mes, 94%)
A34 (Ar = TMP, 84%)
A35 (Ar = Ph, 74%)




A36 (Ar = *p*-Xylene, 68%)
A37 (Ar = Mes, 79%)
A38 (Ar = Ph, 46%)




A39 (Ar = *p*-Xylene, 52%)
A40 (Ar = Mes, 69%)
A41 (Ar = Ph, 56%)

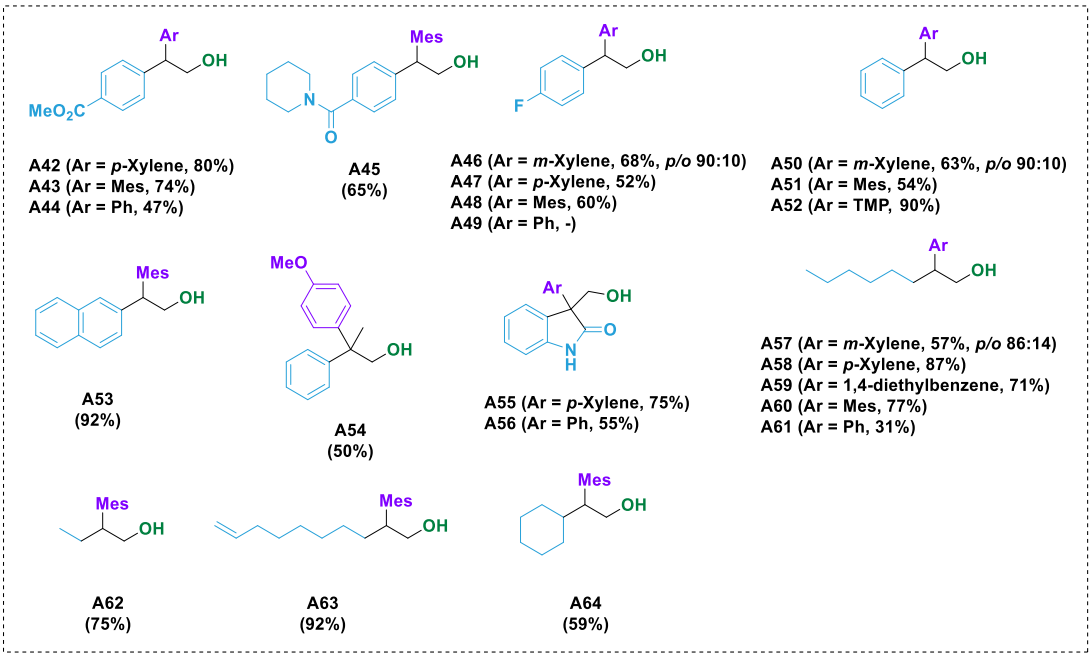



**Schéma 2.** Monoarylation d'époxydes. [a] A 0 °C. [b] [C] = 0.2 M. [c] En utilisant $Bi(OTf)_3/nBu_4NPF_6$ (5mol%) comme promoteur. [d] En présence de TfOH (0.1 mol%).Mes = 1,3,5-triméthylphényle. TMP = 1,3,5-triméthoxyphényle.

régioisomères favorisant le *para*-produit ont été observés, typiques des alkylations de Friedel-Crafts. Les hétéroarènes tels que les thiophènes, les pyrroles et les indoles ont été tolérés dans les conditions de réaction pour fournir les composés **A23-A27** avec des rendements élevés. Les furanes se sont en revanche décomposés dans les conditions de réaction acides.

Nous avons ensuite examiné l'influence de la substitution de l'époxyde, en utilisant des arènes de nucléophilie différente. Les oxydes de styrène désactivés incorporant des groupement électroattracteurs (trifluorométhyle, ester, amide, nitrile et nitro) ont fourni les produits avec des rendements bons à élevés (46-94%) indépendamment du nucléophile employé. La réaction a été également compatible avec des oxydes de styrène moins déficients en électrons ainsi que des alkyles sans chute notable des rendements.

Encouragés par ces résultats, nous avons porté notre attention sur la diarylation d'époxydes en un pot (Schéma 3). Pour optimiser la formation de 1,1,2-triaryléthanes, nous avons étudié la réaction de l'oxyde de (pentafluorophényl)éthylène **A1** avec le *m*-xylène, qui servirait de nucléophile pour les deux étapes. Après l'accomplissement de la première étape à 20 °C, nous avons constaté que la simple augmentation de la température à 80 °C était suffisante pour déclencher la seconde arylation, permettant d'obtenir le

produit de diarylation **4ab** avec un rendement de 76 %. Une série d'arènes nucléophiles riches en électrons portant des fonctionnalités alkyle, méthoxy, halogénure et hydroxy a été examinée en réaction avec l'oxyde de styrène **1a**, donnant les produits diarylés dans des rendements de 40-80% (**A65**-**A74**). Dans certains cas (**A66** et **A73**), un mélange de régioisomères a été obtenu, ce qui résulte de la régiosélectivité obtenue lors de la première arylation de l'oxyde de styrène (voir **A2** et **A21** dans le Schéma 2). Bien que des arènes faiblement nucléophiles comme le benzène puissent être employées dans la première étape, ils ne sont pas des nucléophiles compétents pour la seconde étape, car l'intermédiaire phényl éthanol est resté intact même à des températures de réaction allant jusqu'à 140 °C. Des oxiranes diversement substitués (groupements alkyles et aryles) ont également subi la diarylation pour produire les 1,1,2-triaryléthanes et 1,2-diaryléthanes correspondants avec de bons rendements (**A75**-**A94**, jusqu'à 92%). L'oxyde de styrène a conduit à des rendements plus modestes pour la diarylation (**A84** et **A85**). Dans ce cas, l'intermédiaire alcool semble se déshydrater rapidement pour générer le styrène correspondant, qui s'oligomérise ensuite. En général, une comparaison des rendements du Schéma 2 avec ceux du Schéma 3 révèle que les rendements obtenus pour la diarylation sont limités par l'arylation initiale par ouverture de cycle, la déshydroarylation ultérieure étant très efficace. Dans le cas d'oxiranes substitués par des alkyles portant des groupements électroattracteurs, notamment des fragments pentafluorobenzyle et perfluoro, où la régiosélectivité de la première étape était inversée, la diarylation a pu également être réalisée facilement avec des rendements de 82 et 75 %, respectivement (**A93** et **A94**). Notamment, deux arènes différentes peuvent être installées dans cette réaction de diarylation de manière séquentielle en jouant sur leur nucléophilie. Par exemple, en utilisant le benzène comme premier nucléophile suivi d'une seconde arène, nous avons pu générer des 1,1,2-triaryléthanes avec trois unités aryles différentes avec des rendements modérés à élevés (**A95**-**A102**). La disposition des groupes aryles a été vérifiée par des analyses de RMN 2D HMBC (1H-13C) dans le cas du composé **A95**. Nous avons également observé la formation d'un régioisomère comme produit mineur provenant d'une addition nucléophile en position terminale, qui résulte vraisemblablement d'un encombrement stérique pour l'intermédiaire phénonium. Enfin, dans les cas où les rendements étaient modérés (**A95**, **A99** et **A102**), nous avons remarqué que l'isolement de l'intermédiaire phényl éthanol avant de réengager les conditions de réaction améliorait significativement les rendements (rendements de 66-81% en deux étapes).

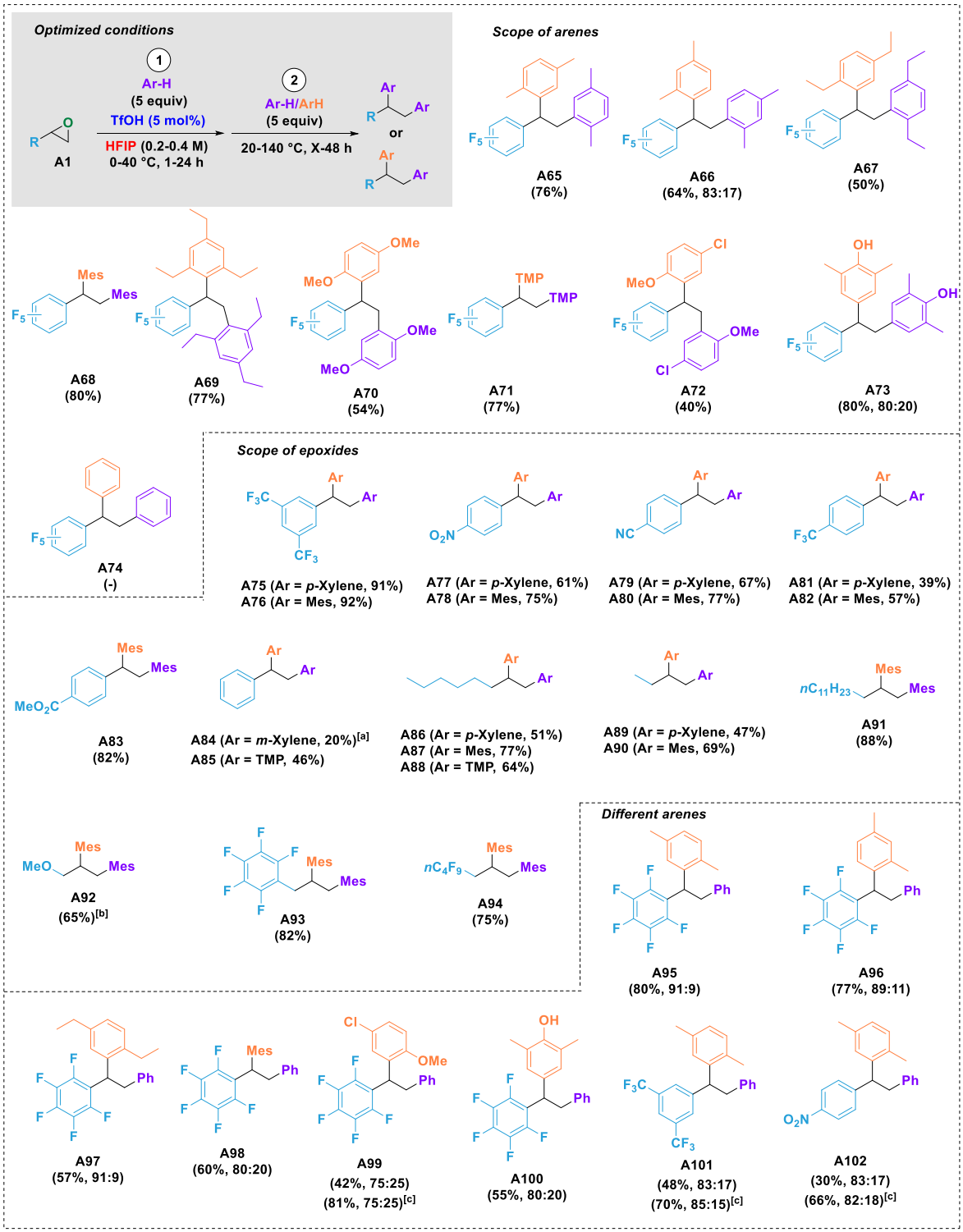



**Schéma 3.** Diarylation d'époxides. [a] Rendement determiné par $^{1}$H RMN en utilisant l'hexaméthyldisiloxane comme référence. [b] Produit de triarylation obtenu comme composé minoritaire. [c] Rendement sur deux étapes.

**b) Catalyse par des acides boroniques dans HFIP.**

Au cours de cette thèse, nous nous sommes également intéressés à un sujet indépendant portant sur l'utilisation des acides boroniques comme acides de Lewis dans HFIP. Les acides boroniques sont apparus comme une classe prometteuse de catalyseurs qui permettent la substitution nucléophile déshydratant des alcools, le réarrangement de Beckmann des oximes, et diverses réactions impliquant soit des acides carboxyliques soit des époxydes dans des conditions douces.[13] Des études approfondies du mécanisme catalytique ont été réalisées dans le cas des acides carboxyliques, alors que peu de preuves mécanistiques existent pour les réactions avec des alcools et des oximes. Les systèmes catalytiques d'acide arylboronique requis pour les réactions impliquant les alcools et les oximes (**B1**-**B3**, Schéma 4) sont sensiblement plus électrophiles que ceux utilisés pour l'activation des acides carboxyliques, les premiers nécessitant soit de multiples groupements électroattracteurs, soit des acides boroniques cationiques, soit une complexation avec des diols hautement désactivés électroniquement. Un autre paramètre critique dans ces réactions est le solvant. Notre groupe, ainsi que de nombreux autres, ont souligné l'effet favorable des solvants tels que HFIP sur les réactions catalysées par les acides de Brønsted et de Lewis grâce à la formation d'un réseau de liaisons hydrogène.[14] Dans le cas de l'HFIP, nous avons souligné que le rôle des catalyseurs était d'augmenter de manière significative l'acidité de ce réseau, qui est la véritable espèce catalytiquement active.

Nos réflexions sur la réactivité des acides arylboroniques ont débuté lors de nos investigations sur l'ouverture de cyclopropanes non activés par des arènes nucléophiles catalysée par le TfOH dans l'HFIP (Schéma 4).[13] Nous avons été intrigués par la réactivité du système catalytique **B3** généralement utilisés pour l'activation d'alcools et d'oximes, car il est capable de déclencher l'ouverture de cycle du phénylcyclopropane pour générer le produit **7**. Compte tenu de l'absence d'un groupe fonctionnel OH dans le substrat et de l'absence de paires de Lewis frustrées, nous avons supposé qu'il serait peu probable que cette réaction présente une catalyse par un acide covalent ou de Lewis. Un mécanisme plausible impliquerait la catalyse par un acide de Brønsted, qui serait généré par la coordination de l'ester boronate (**B3**) avec HFIP. En effet, la présence de2,6-di-*tert*-butylpyridine, une base de Brønsted volumineuse couramment utilisée pour distinguer la

[13] S. Zhang, D. Lebœuf, J. Moran, *Chem. Eur. J.* **2020**, *26*, 9883.
[14] D. G. Hall, *Chem. Soc. Rev*. **2019**, *48*, 3475.

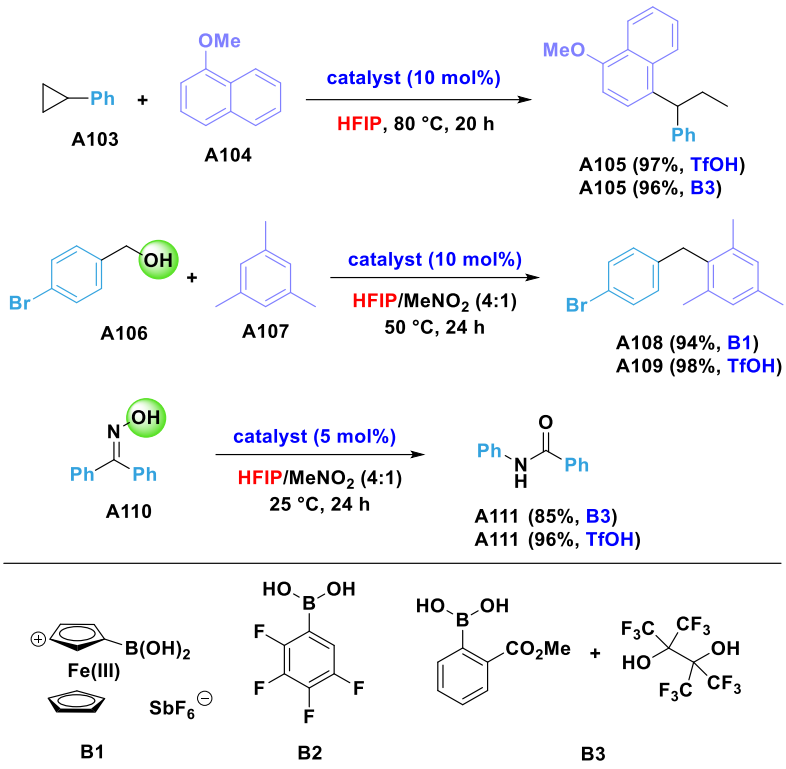



**Schéma 4.** Comparaison acide de Brønsted/acide boronique dans HFIP.

catalyse de type acide de Lewis de celle de Brønsted, a complètement arrêté la réaction, ce qui est cohérent avec une catalyse d'acide de Brønsted. Ces observations nous ont conduit à nous demander si certaines réactions catalysées par des acides boroniques précédemment rapportées pouvaient également être le résultat d'une catalyse par des acides de Brønsted. Nous avons donc réétudié une série de réactions catalysées par des acides boroniques avec des alcools et des oximes.

Nous avons observé la même tendance que pour la réaction précédente. Nous avons alors examiné plusieurs acides boroniques et de Brønsted à l'aide de la méthode de Gutmann-Beckett, ce qui a révélé que des acides de Brønsted forts sont très probablement produits par **B1** et **B3** dans HFIP (Figure 1). Une autre caractéristique intéressante est que, selon le solvant utilisé (toluène vs HFIP/$MeNO_2$), l'acidité relative et absolue des systèmes catalytiques à base d'acide boronique peut être complètement modifiée. Par exemple, **B2** est plus acide que **B1** dans le toluène, mais ce phénomène est inversé dans le HFIP/$MeNO_2$. De plus, dans HFIP/$MeNO_2$, **B1** et **B3** présentent une acidité comprise entre celle du TFA et celle du TfOH. Sur la base de ces résultats, nous pensons que les transformations avec des acides boroniques impliquent une activation du substrat par les acides de Brønsted, plutôt que les mécanismes typiques des acides covalents ou de Lewis. L'interaction entre le HFIP et l'acide boronique, vraisemblablement par assemblage

covalent, crée un acide de Brønsted fort qui est probablement la véritable espèce catalytiquement active dans ces réactions.

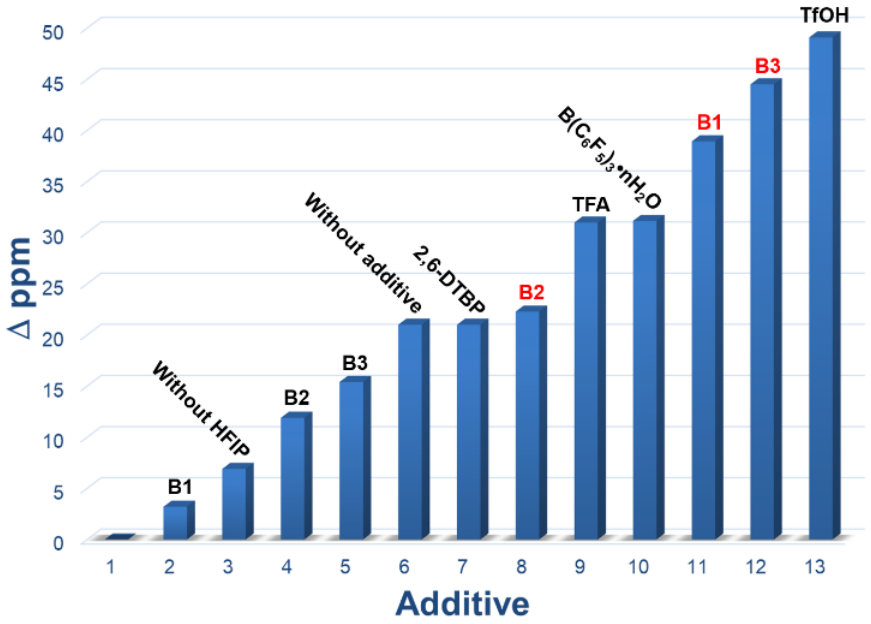



**Figure 1.** Méthode de Gutmann-Beckett montrant l'influence d'un additif (3 équiv.) sur l'oxyde de triéthylphosphine (TEPO) (1 'quiv.) dans HFIP/$MeNO_2$ (4:1) exprimé comme les variations du déplacement chimique observé par $^{31}P$ RMN par rapport à la référence (TEPO) dans le toluène-$d_8$. Les valeurs pour B1, B2 et B3 (en noir) sont les références dans le toluene-$d_8$ seul.

### 3) Conclusion générale

Dans la première partie, nous avons pu démontrer la versatilité de la combinaison de HFIP avec TfOH dans plusieurs réactions inédites, ce qui laisse entrevoir tout son potentiel pour son exploitation dans de nouvelles transformations. Nous avons ainsi décrit la préparation efficace de dérivés de phényl éthanols suivant une réaction de monoarylation d'époxydes. La transformation a également pu être étendue à la synthèse de 1,1,2-triaryléthanes à partir de ces mêmes époxydes. Le mécanisme de réaction s'est avéré être stéréospécifique, comme le confirment nos expériences mécanistiques et les calculs DFT (non présentés ici). Cette vaste expansion (150 exemples) de la réaction de Friedel-Crafts ne nécessite pas de catalyseur coûteux ni de précautions particulières et permet à l'utilisateur de réimaginer la réactivité des alcools aliphatiques primaires et des époxydes.

Pour la seconde partie, notre étude a mis en lumière le mode d'activation pour la catalyse par des acides boroniques, en montrant que la catalyse par un acide de Brønsted plutôt

qu’une activation par l'acide de Lewis ou une activation covalente, est probablement responsable de la réactivité observée dans presque tous les exemples représentatifs étudiés. Plus précisément, les catalyseurs **B1** et **B3** produisent des acides de Brønsted forts en présence de HFIP. Dans l'avenir, ces connaissances devraient être utiles pour la conception rationnelle de catalyseurs de deuxième génération pour la substitution nucléophile déshydratante ou pour les réarrangements d'oxime, qu'ils soient ou non basés sur le bore. Enfin, ce travail met en garde contre le fait qu'un large éventail d'expériences de contrôle est nécessaire pour exclure un rôle catalytique des acides de Brønsted, en tenant compte des nombreux rôles importants joués par le solvant.

# 1. General Introduction

## 1.1. HFIP: a solvent with unique properties

1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP; [$(CF_3)_2CHOH$]) is a versatile solvent with a wide range of applications in organic chemistry, material science and biology, due to its unique fundamental properties compared with other fluorinated and non-fluorinated solvents.[15]

The two trifluoromethyl groups in HFIP create significant differences in its physical and chemical properties when compared to its non-fluorinated analog isopropanol. For instance, the thermal stability of HFIP allows it to be used as a solvent for high temperature reactions. Its miscibility with both water and most common polar organic solvents makes HFIP an excellent solvent or additive for many reactions.[16] In addition, the low boiling point of HFIP (bp = 58°C) enables its easy recovery by distillation after the reaction is completed, counterbalancing its initial cost.[17]

Fluorinated alcohols also exhibit specific properties in organic synthesis. In the case of HFIP, the presence of two electron-withdrawing trifluoromethyl groups confers a high acidity to the hydrogen of the hydroxyl group with a p$K_a$ value of 9.3 in aqueous solution.[16] The acidity scale for HFIP, reported in 1981 by Carre,[18] shows a similar range

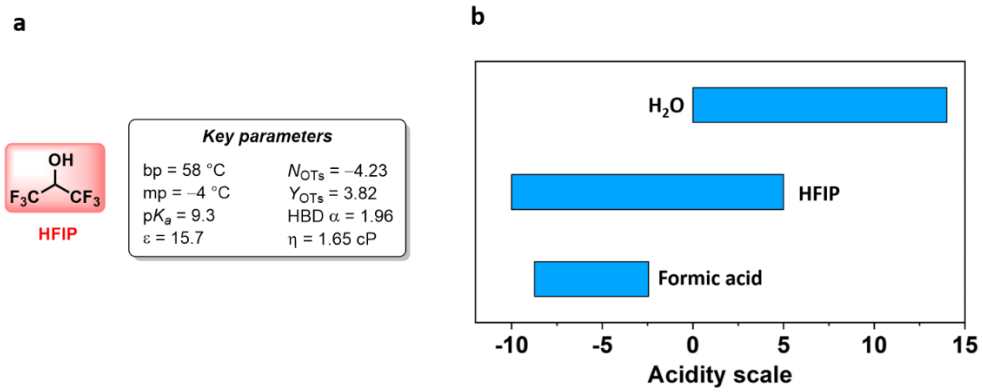
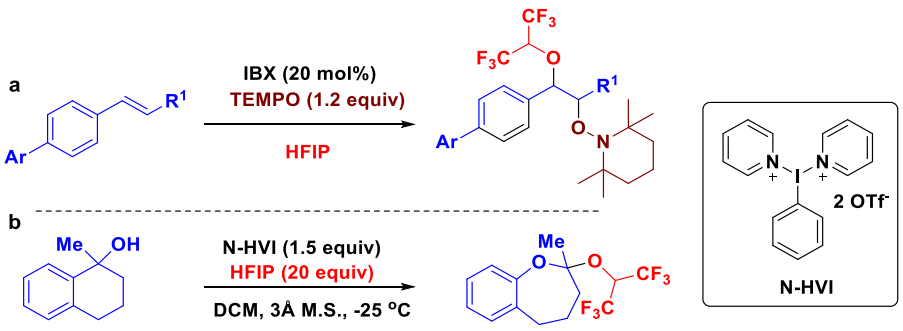



*Figure 1.1.* ***a****: Structure and key parameters of HFIP;* ***b****: Acidity scale.*

[15] J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18.
[16] I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088.
[17] S. J. Brenek, S. Caron, E. Chisowa, M. P. Delude, M. T. Drexler, M. D. Ewing, R. E. Handfield, N. D. Ide, D. V. Nadkarni, J. D. Nelson, M. Olivier, H. H. Perfect, J. E. Phillips, J. J. Teixeira, R. M. Weekly, J. P. Zelina, *Org. Process Res. Dev.* **2012**, *16*, 1348.
[18] B. Carre, J. Devynck, *Analytica Chimica Acta*, **1981**, *131*, 141.

of acidities as the one for water but shifted towards a more acidic regime in the range of acidities of formic acid (b: see Figure 1.1). In fact, the more acidic this range of acidities is for a solvent, the higher is the ion-pair dissociation constants for strong electrolytes. The means that for Brønsted acid-catalyzed reaction, the catalytic efficiency is different in HFIP compared to water due to a different concentration of the dissociated proton.

Using an alcohol as a solvent, which is a nucleophile, also carries the risk of forming side products in transformations that involve other nucleophilic species. However, owing to the negative inductive effect of the trifluoromethyl groups, HFIP exhibits a low nucleophilicity compared to *i*PrOH. In 1976, Schleyer and co-workers[19] compared the nucleophilicity using a solvent nucleophilicity scale (*N*), which is a common way to evaluate the nucleophilicity of a given solvent. Specifically, they examined $N_{OTs}$, which is the nucleophilic parameter of a solvent defined from rate data for methyl tosylate: $N_{OTs} = \log(K/K_0)_{MeOTs}-0.3Y_{OTs}$ ($K$: rate constant of solvolysis of MeOTs; $K_0$: rate constant of solvolysis of MeOTs in aqueous EtOH (80%); $Y$: Solvent ionizing power). $N_{OTs}$ were found to be equal to 0.2 in *i*PrOH, but only measured -4.23 in HFIP.[17,20] In this scale, higher values of the $N_{OTs}$ parameter imply a higher nucleophilicity of the solvent. Thus, the low nucleophilicity of HFIP helps limit undesirable side reactions, although a few exceptions in the literature can be found where HFIP acts as a nucleophile with a highly reactive carbocation, but only in cases where a nucleophile stronger than HFIP is absent.




*Scheme 1.1. HFIP act as nucleophile.*

As an example, in 2016, Donohoe and co-authors reported a method for the stereoselective metal-free *syn*-dihydroxylation of electron-rich olefins by using HFIP as a nucleophile and solvent to generate the target product (a: see Scheme 1.1).[21] Another

[19] F. L. Schadt, T. W. Bentley, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1976**, *98*, 7667.
[20] T. W. Bentley, G. E. Carter, *J. Org.Chem.* **1983**, *48*, 579.
[21] I. Colomer, R. C. Barcelos, K. E. Christensen, T. J. Donohoe, *Org. Lett.* **2016**, *18*, 5880.

example was reported by the group of Wengryniuk, which demonstrated that HFIP can be used as a nucleophile for the formation of medium-sized cyclic ethers through ring-expansion (b: see Scheme 1.1).[22]

However, probably the most important property of HFIP that made it such an appealing solvent in synthesis is its hydrogen-bond donating ability (HBD). In addition to enhancing its acidity, the electron-withdrawing trifluoromethyl groups also make HFIP a strong hydrogen-bond donor (HBD $\alpha = 1.96$).[16,23] In particular, a stable complex of HFIP with THF (**a**: see Figure 1.2) was reported in 1964 by Lindsey. Due to the strong solvating power of HFIP through hydrogen-bond donation, the boiling point of the complex (100 °C) is far higher than that of either component.[24] An X-ray structure of HFIP molecules (**b**: see Figure 1.2) was reported by Berkessel's group, showing infinite helices of hydrogen-bonded aggregates,[25] which is now commonly used as a basic model for density functional theory (DFT) calculations of the solvent effect. However, in the liquid state, the degree of self-association of HFIP is low and the value of the dimerization constant is 0.13 $dm^3mol^{-1}$. Thus, harnessing the hydrogen-bond donating ability of HFIP by the formation of an H-bond network between molecules of HFIP rarely exceeds aggregates larger than a trimer complex (**c**: see Figure 1.2).[25]

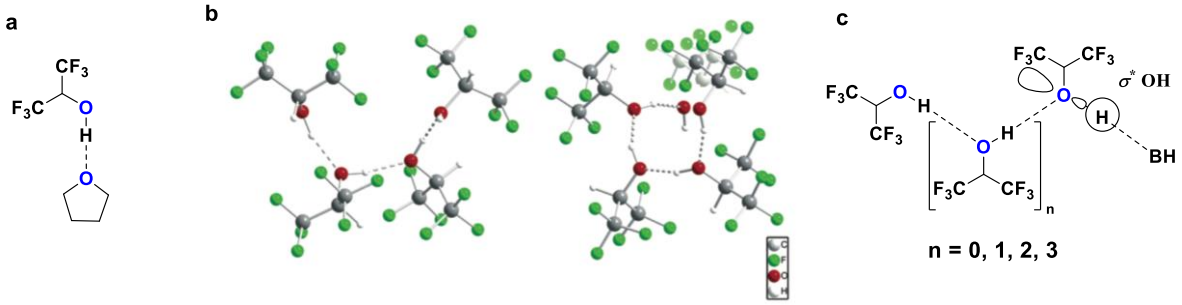



*Figure 1.2. **a**: Complex of HFIP and THF; **b**: Aggregation-induced H-bonding enhancement of HFIP; **c**: HFIP X-ray structure.*

HFIP aggregates have been shown on numerous occasions to promote chemical reactivity. The best-known example is the epoxidation of olefins by hydrogen peroxide (**a**: see Figure 1.3), which is several orders of magnitude faster in HFIP than in other solvent such as

[22] B. T. Kelley, J. C. Walters, S. E. Wengryniuk, *Org. Lett.* **2016**, *18*, 1896.
[23] (a) D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. Bonnet-Delpon, *J. Org. Chem.* **2011**, *76*, 1126; (b) V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun.* **2020**, *56*, 11548.
[24] W. J. Middleton, R. V. Lindsey, *J. Am. Chem. Soc.* **1964**, *86*, 4948.
[25] A. Berkessel, J. A. Adrio, *J. Am. Chem. Soc*. **2006**, *128*, 13412.

1,4-dioxane. To rationalize this observation, a mechanism involving a spiro-bicyclic transition state for oxygen transfer from $H_2O_2$ to the olefin was proposed by Berkessel and co-workers[255] based on experimental and theoretical investigations (**b**: see Figure 1.3). The kinetic analysis on the epoxidation of cyclooctene indicated that the reaction is clearly first order in hydrogen peroxide and olefin and 2nd-3rd order in HFIP. On the basis of this data, they proposed that supramolecular dimers or trimers of HFIP were involved in the transition state, which serve to enhance its hydrogen-bond donating ability. The participation of higher order HFIP aggregates in the transition state was also invoked by Kirchner and co-workers (**c**: see Figure 1.3).[26] They proposed a cluster of three HFIP molecules around $H_2O_2$ as the main factor for the effective decrease of the reaction barrier in the rate determining step.

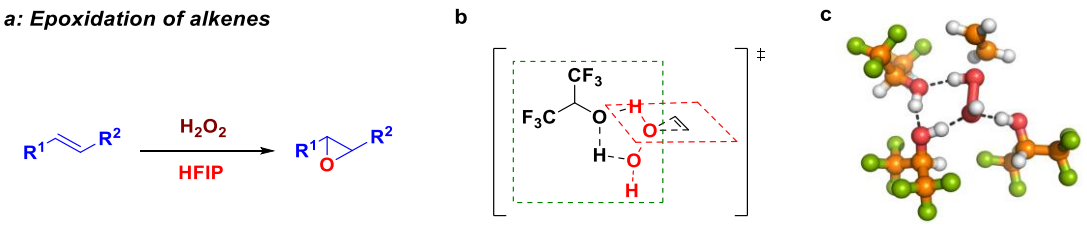
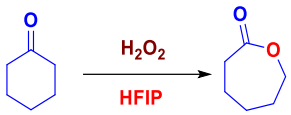



*Figure 1.3.* ***a****: Epoxidation of alkenes in HFIP;* ***b****: Spiro-bicyclic intermediate in HFIP-assisted olefin epoxidation;* ***c****: HFIP-promoted epoxidation of ethylene.*

The strong hydrogen-bond donating ability of HFIP has many beneficial effects in several reactions. As an example, during the study of triflic acid-catalyzed Friedel-Crafts alkylation of highly deactivated benzyl alcohols in HFIP reported by our group,[27] a catalytically active H-bond aggregates, generated from the H-bond between HFIP and TfOH, was highlighted based on the experimental results.




*Scheme 1.2. Baeyer-Villiger oxidation of ketones in HFIP.*

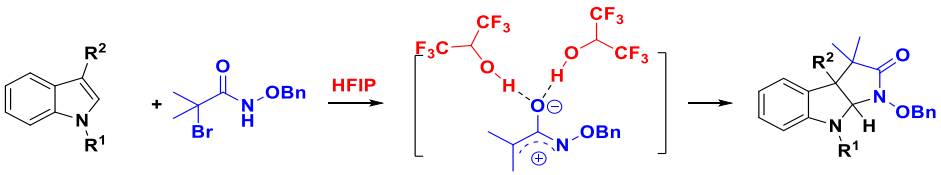
HFIP also has the advantage of being redox stable, which makes it a solvent of choice for electrochemistry and photoredox processes, as well as transformations involving highly

[26] O. Hollóczki, A. Berkessel, J. Mars, M. Mezger, A. Wiebe, S. R. Waldvogel, B. Kirchner, *ACS Catal.* **2017**, *7*, 1846.
[27] V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew.Chem. Int. Ed.* **2017**, *56*, 3085.

oxidizing reaction conditions. For example, the Baeyer-Villiger oxidation of ketones reactions occurred smoothly in HFIP in the absence of catalyst (Scheme 1.2).[28]

Recently, the use of HFIP was advertised in many studies, playing an important role as either reaction medium or additive to promote the generation of radical or cationic intermediates. This can be explained by its relatively high dielectric constant ($\varepsilon$ = 15.7) as well as its low nucleophilicity. Based on these properties, HFIP is considered as an ideal solvent for generating and stabilizing cationic species. In 2009, a series of α-vinyl arylmethyl cations were generated and studied in the presence of HFIP as a solvent by Schepp and co-workers.[29] Their investigations showed that laser irradiation of cinnamyl acetate gave a transient signal with a maximum absorption at 380 nm in HFIP and a first order decay of cations with a rate constant of 7.0 $\times 10^4$ $s^{-1}$, while no distinct transient species was detected in TFE. The rate constant increased after addition of the nucleophile. The study of the lifetimes of various carbocation in fluorinated solvent and $MeNO_2$ was also reported by Warkentin and co-workers;[30] the experimental results indicated that the lifetime of carbocation is much longer in HFIP and TFE than in $MeNO_2$. As an example, the lifetimes of the 2-propyl cation are 0.05 ns in $MeNO_2$, but 0.14 ns in HFIP and TFE.

The [3+2] cycloaddition of indole with α-halohydroxamate (Scheme 1.3), which was independently reported by Wu[31] and Jeffrey[32] in 2015, emphasized that HFIP strongly participates to the stabilization of the key azaoxyallyl cation intermediate. It was demonstrated by mechanistic experiments as well as by DFT calculations that the stronger the H-bond donating ability of the solvent, the lower the transition-state energy.




*Scheme 1.3. [3+2]-Cycloaddition of indoles with α-haloamides.*

With respect to all the properties of HFIP presented above, it is clear that HFIP can be considered as a solvent of choice for acid-catalyzed reactions. The enhanced acidity of

[28] K. Neimann; R. Neumann, *Org. Lett.* **2000**, 2, 2861.
[29] G. Hallett-Tapley, F. L. Cozens, N. P. Schepp, *J. Phys. Org. Chem.* **2009**, *22*, 343.
[30] J. P. Pezacki, D. Shukla, J. Lusztyk, J. Warkentin, *J. Am. Chem. Soc.* **1999**, *121*, 6589.
[31] M. C. DiPoto, R. P. Hughes, J. Wu, *J. Am. Chem. Soc.* **2015**, *137*, 14861.
[32] A. Acharya, D. Anumandla, C. S. Jeffrey, *J. Am. Chem. Soc.* **2015**, *137*, 14858.

HFIP as well as its strong H-bond donating ability led to a high catalytic efficiency and less undesired reactions owing to its low nucleophilicity. As most acid-catalyzed reactions are likely to generate cations during the catalytic cycle, the ability of HFIP to extend their lifetime is particularly useful.

## 1.2. Lewis acids and Brønsted acids as catalysts

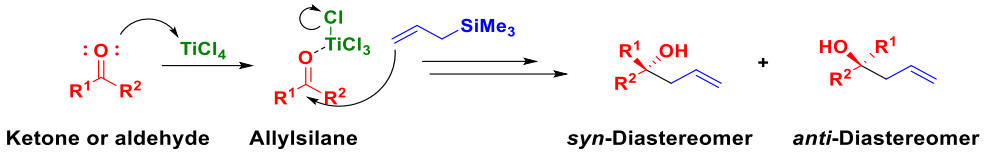
Because of their unique properties and reactivity, Lewis and Brønsted acids have been widely employed as catalysts in organic synthesis. Most of them can be handled in the open air without special precautions as they are chemically stable and display shelf-stability for long periods of time, making them simple but ubiquitous for the development of new catalytic processes.

### 1.2.1. Lewis acids as catalysts

During the last decades, the utilization of Lewis acids as catalysts was reported in numerous reactions such as aldol, allylation, cycloaddition, Diels-Alder, Friedel-Crafts, Mannich, Michael, transfer hydrogenation, cross-coupling reactions, etc.[33] The definition of a Lewis acid was proposed in 1923 by Gilbert Newton Lewis as "any species that, because of the presence of an incomplete electronic grouping, can accept the nonbonding electron pair, thus forming a dative or coordination bond."[34] Based on this definition, most of the metal salts can be considered as Lewis acids. Two categories are encountered: *i.* σ-Lewis acids, which preferentially activate a substrate by association with a lone pair of an electronegative atom; *ii.* π-Lewis acids, which preferentially activated a substrate by association with a π-electron bond (see Figure 1.3). The key property of a Lewis acid catalyst in organic synthesis is to decrease the LUMO energy and thus favor nucleophilic addition *via* activation of the C=X (X= O, S or N) bond or the π-bond. An example is the Sakurai reaction, where a strong Lewis acid is necessary for the reaction between a ketone and an allyl silane. The active species is formed by a coordination between the oxygen of the ketone with the metal of the Lewis acid ($TiCl_4$) in order to trigger the nucleophilic addition of the allylsilane to afford the desired allylic alcohol (see Scheme 1.4).[35]

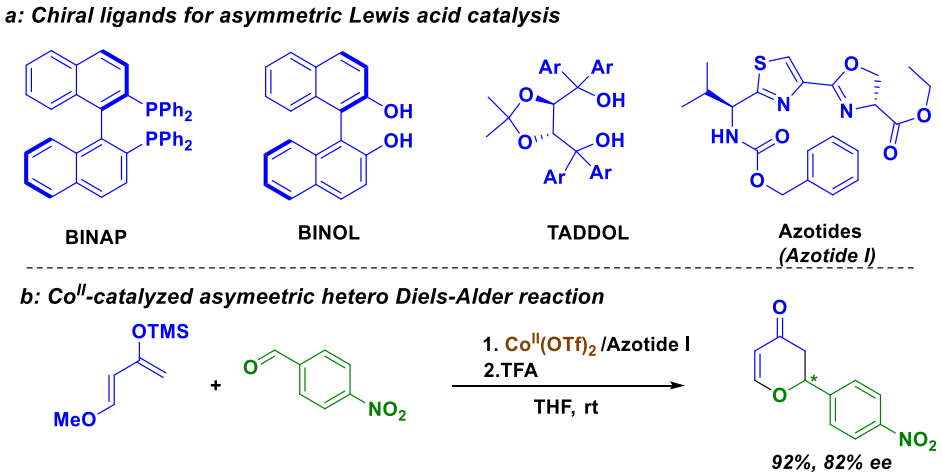
[33] (a) A. Corma, H. Carcia, *Chem. Rev.* **2003**, *103*, 4307; (b) H. Yamamoto, *Lewis acids in organic synthesis*; Wiley-VCH, **2000**. ISBN: 978-3527295791.
[34] G. N. Lewis, *Valency and Structure of Atoms and Molecules*; Wiley: New York, **1923**.
[35](a) A. Hosomi, H. Sakurai, *Tetrahedron Letters.* **1976**, *17*, 1295; (b) A. Hosomi, M. Endo, H. Sakurai, *Chem. Lett.* **1976**, *5*, 941. (c) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 1673;(d) Y. Shingo, F. Kunihiko; W. Reiko, K. Motomu, S. Masakatsu, *J. Am. Chem. Soc.* **2002**, *124*, 6536.


*Figure 1.3. σ and π-Lewis acid.*




*Scheme 1.4. Sakurai allylation.*[35]

At early stages, easily available Lewis acids such as metal salts and main group Lewis acids have been widely applied to organic reactions. With the in-depth investigations of Lewis acid catalysis, Lewis acids have been notably employed as an efficient tool for the asymmetric catalysis in the presence of chiral ligands, such as BINAP, BINOL, TADDOL and azotides. Asymmetric Lewis acid catalysis has been broadly used in Mannich-type reactions,[36] ene reaction,[37] Michael addition[38] and hetero Diels-Alder reaction.[39] For example, Diness and co-workers recently reported a strategy for the synthesis of azotides and their evaluation as ligands in the cobalt (II) catalyzed asymmetric hetero Diels-Alder reactions.[39] The prepared azotide **I** shows high enantioselectivity (82% ee) with 92% yield.




*Scheme 1.5. Asymmetric Lewis acid catalysis.*

[36] M. Mauro; K. Anne; J. Karsten; G. Nicholas; J. K. Anker, *Chem. Eur. J.* **2003**, *9*, 2359.
[37] D. A. Evans, S. J. Miller, T. Lectkalb, *J. Am. Chem. Soc.* **1993**, *115*, 6460.
[38] D. A. Evans, M. C. Willis, J. N. Johnston, *Org. Lett.* **1999**, *1*, 865.
[39] C. B. Jacobsen, D. S. Nielsen, M. Meldal, F. Diness, *J. Org. Chem.* **2019**, *84*, 6940.

### 1.2.2. Brønsted acids as catalyst

In the same vein, Brønsted acids act as efficient catalysts, which are mostly environmentally friendly and applicable to large-scale synthesis. They have therefore received considerable attention in modern organic synthesis. Like Lewis acids, Brønsted acids have several advantages: they are generally readily available, easy to handle, and usually not air- or moisture-sensitive. Acids such as $H_2SO_4$, HCl, etc. are frequently used in industrially relevant processes. The definition of Brønsted acids was proposed by Johannes Nicolaus Brønsted in 1923[40] as follows: "an acid is any hydrogen-containing species able to dissociate protons in aqueous solution." The early applications of Brønsted acid catalysts in organic synthesis were for hydrolysis or formation of esters, acetals, etc.[41] After many decades of investigations, Brønsted acids are broadly employed as catalysts for many organic reactions such as Diels-Alder, Friedel-Crafts, or aza-Henry reaction, as well as for asymmetric synthesis. Strictly speaking, based on the definition of a Lewis acid, a proton is the smallest possible Lewis acid, meaning that Brønsted acids have a similar activation mode for reactions which are also catalyzed by Lewis acids. In theory, a plethora of carbonyl reactions can be promoted by a catalytic amount of a strong Brønsted acid (Figure 1.4).[42]

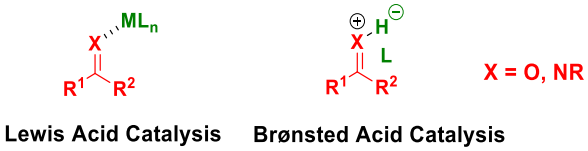



*Figure 1.4. Lewis-acid catalysis and Brønsted-acid catalysis.*

An acid with an acidity greater than that of pure sulfuric acid was defined by Gillespie as a superacid.[43] Superacids are commonly employed as catalysts in petrochemistry and in the study of various carbocations such as the mixture $FSO_3H/SbF_5$ (1:1) which is called "magic acid"[44] and $HSbF_6{\cdot}HF/SbF_5$ which is a common superacid employed in many transformations. Recent examples of its use in organic synthesis include

[40] J. N. Brønsted, *Recl. TraV. Chim. Pays Bas* **1923**, *42*, 718.
[41] (a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; (b) C. H. Cheon, H. Yamamoto, *Chem. Commun*. **2011**, *47*, 3043.
[42] P. M. Pihko, *Angew. Chem. Int. Ed*. **2004**, *43*, 2062.
[43] R. J. Gillespie, T. E. Peel, *Adv. Phys. Org. Chem*. **1971**, *9*, 1.
[44] (a) G. A. Olah, C. U. Pittman, *J. Am. Chem. Soc.* **1966**, *88*, 3310; (b) A. Commeryas, G. A. Olah *J. Am. Chem. Soc*. **1969**, *91*, 2929; (c) G. A. Olah, G. K. S. Prakash, M. Barzaghi, K. Lammertsma, R. Von, P. Schleyer, J. A. People, *J. Am. Chem. Soc*. **1986**, *108*, 1032.

trifluoromethylthiolation,[45] fluorination,[46] chlorofluorination of aromatic amines,[47] and cellulose depolymerization.[48] Another common superacid is triflic acid ($CF_3SO_3H$ or TfOH) which has been employed as a catalyst for various transformation, such as Friedel-Crafts alkylation[49], cationic cascade polycyclization,[50] hydroarylation of 1, 3-dienes[51] and others.[52] The term superacid does not only apply to Brønsted acids but also to Lewis acids with an acidity stronger than $H_0$ = -12, that of monomeric $SbF_5$ in the gas phase.

Chiral Brønsted acids are another important class of organocatalysts which have been widely used in asymmetric synthesis to activate, for instance, carbonyl compounds,[53] alkenes and alkynes.[54] The pathway with respect to their activation can be generalized in Figure 1.5 and conceptually differentiated into two limiting cases, which differ in the extent to which a proton is transferred from the catalyst to the substrate. In the first limiting case, hydrogen bond catalysis, the active species can be formed by hydrogen bonding of the electronegative part (O, N) of the substrate with one or more protons from the catalyst. Common examples of hydrogen-bonding catalysts include monofunctional thioureas, [55] bifunctional thioureas, [56] or α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-

[45] L. J. C. B. Milandou, H. Carreyre, S. Alazet, G. Greco, A. Martin-Mingot, C. N. Loumpangou, J.-M. Ouamba, F. Bouazza, T. Billard, S. Thibaudeau *Angew. Chem. Int. Ed*. **2017**, *56*, 169.
[46] A. Martin-Mingot, G. Compain, F. Liu, M.-P. Jouannetaud, C. Bachmann, G. Frapper, S. Thibaudeau, *J. Fluor. Chem*. **2012**, *134*, 56.
[47] A. L. Darz, U. Castelli, N. Mokhtari, A. Martin-Mingot, J. Marrot, F. Bouazza, O. Karam, S. Thibaudeau, *Tetrahedron*, **2016**, *72*, 674.
[48] A. Martin-Mingot, K. D. O. Vigier, F. Jérôme, S. Thibaudeau, *Org. Biomol. Chem*. **2012**, *10*, 2521.
[49] V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085.
[50] C. Theunissen, B. Métayer, N. Henry, G. Compain, J. Marrot, A. M. Mingot, S. Thibaudeau, G. Evano, *J. Am. Chem. Soc.* **2014**, *136*, 12528.
[51] Z. Liu, G. Li, T. Yao, J. Zhang, L. Liu, *Adv. Synth. Catal.* **2021**, *363*, 2740.
[52] (a) A. A. Golushko, M. A. Sandzhieva, A. Y. Ivanov, I. A. Boyarskaya, O. V. Khoroshilova, A. Y. Barkov, A. V. Vasilyev *J. Org. Chem*. **2018**, *83*, 10142; (b) S. Saulnier, S. V. Lozovskiy, A. A. Golovanov, A. Y. Ivanov, A. V. Vasilyev, *Eur. J. Org. Chem*. **2017**, *36*, 3635; (c) S. Saulnier, A. A. Golovanov, A. V. Vasilyev, *RSC Adv*. **2016**, 6, 103546.
[53] (a)S. E. Denmark, T. M. Willson, *J. Am. Chem. Soc.* **1989**, *111*, 3475; (b) S. E. Denmark, E. J. Weber, T. M. Wilson, T. M. Willson, *Tetrahedron* **1989**, *45*, 1053; (c) G. E. Keck, S. M. Dougherty, K. A. Savin, *J. Am. Chem. Soc.* **1995**, *117*, 6210; (d) D. Kampen, B. List, *Synlett* **2006**, 2589; (e) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48. (f) D. M. Sedgwick, M. Grayson, S. Fustero, P. Barrio, *Synthesis*, **2018**, *50*, 1935.
[54] (a) I. Fleming, A. Barbero, D. Walter, *Chem. Rev*. **1997**, *97*, 2063; (b) K. Miura, T. Hondo, T. Nakagawa, T. Takahashi, A. Hosomi, *Org. Lett.* **2000**, *2*, 385: (c) K. Miura, A. Hosomi, *Synlett* **2003**, 143; (c) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 10204; (d) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer, A. Davis, *Org. Lett.* **2005**, *7*, 1047; (e) Z. Li, J. Zhang, C. Brouwer, C.-G. Yang, N. W. Reich, C. He, *Org. Lett.* **2006**, *8*, 4175.
[55] (a) D. P. Curran, L. H. Kuo, *J. Org. Chem*. **1994**, *59*, 3259; (b) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; (c) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, 1919; (d) G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, *126*, 4102.
[56] (a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*. **2003**, *125*, 12672; (b) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett*. **2004**, *45*, 9185; (c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; (d) X. Xu, T. Yabuta, P. Yuan, Y. Takemoto, *Synlett* **2006**, 137.

dioxolane-4,5-dimethanol (TADDOL) derivatives.[57] In the second limiting case, known as Brønsted acid catalysis, a weakly Brønsted basic atom of the substrate can be protonated the catalyst, such as chiral phosphoric acids (see Scheme 1.6).[58]

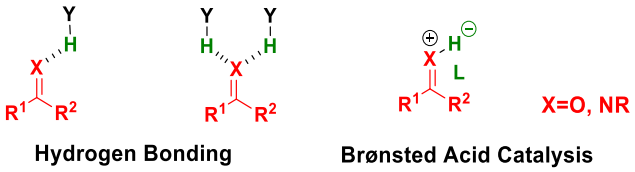
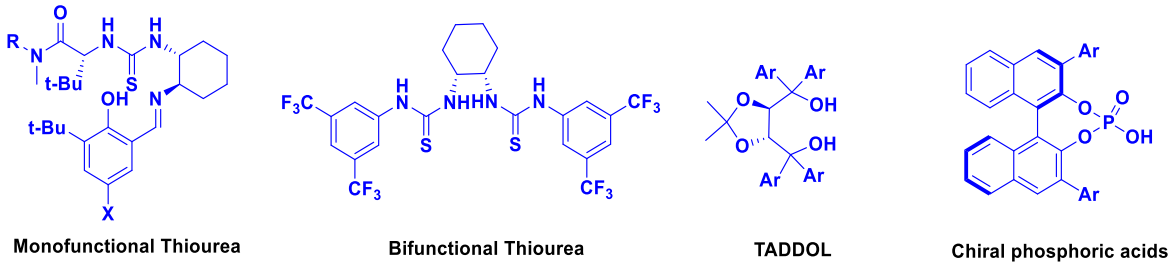



*Figure 1.5. Formation of active species.*



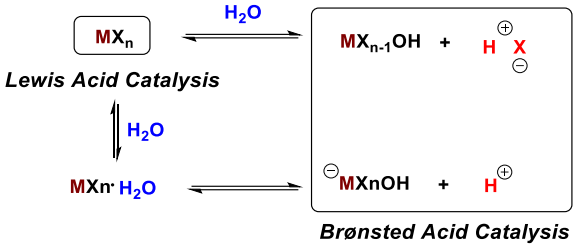

*Scheme 1.6. Chiral Brønsted acid catalysts.*

### 1.2.3. Hidden Brønsted Acids

With the broad range of applications of Lewis and Brønsted acids as catalysts in synthesis, chemists have now a good understanding of the mechanisms behind the various catalytic processes, especially in the field of Lewis acid catalysis. Nonetheless, there are many reactions for which the quest for insight into the true active species is still actively pursued. For instance, super-electrophilic species,[59] which are formed from the catalyst or from other electrophilic species,[60] can insidiously act as the real catalysts in some reactions. As an example, Lewis acids can be hydrolyzed or form Lewis acid hydrates, thereby generating strong Brønsted acids via the assistance of adventitious water or other protic species (Scheme 1.7), coming from either the solvent or from the substrate itself. In that

[57] (a) V. B. Gondi, M. Gravel, V. H. Rawal, *Org. Lett*. **2005**, *7*, 5657; (b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc*. **2005**, *127*, 1080; (c) A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc*. **2005**, *127*, 1336.
[58] (a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc*. **2004**, *126*, 5356; (b) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc*. **2005**, *127*, 9360; (c) R. Maji, S. C. Mallojjala, S. E. Wheeler, *Chem. Soc. Rev.* **2018**, *47*, 1142.
[59] (a) G. A. Olah, *Angew. Chem. Int. Ed*. **1993**, *32*, 767; (b) G. A. Olah, D. A. Klumpp, Wiley-VCH Verlag GmbH & Co. KGaA 2007.
[60] E. Negishi, *Chem. Eur. J*. **1999**, *5*, 411.

sense, these proton donors might act as the true active species in a phenomenon called "hidden Brønsted catalysis".[61]




*Scheme 1.7. Lewis vs. Brønsted acid equilibrium in the presence of water.*

In 2004, the first investigation on the mechanism on Lewis *vs.* Brønsted acid catalysis in Lewis acid "mediated" hetero-Michael reactions was reported by Spencer and co-workers.[62] The study showed that a simple proton acts as the active catalyst which comes from the hydrolysis of the metal salt, rather than the metal ion itself being a Lewis acid catalyst. In order to clearly illustrate the mechanism, a stoichiometric amount of a weak base, 2,6-di-*tert*-butylpyridine (DTBP), was introduced. DTBP is known to behave as a proton scavenger yet is unable to coordinate with most metals due to its steric hindrance.

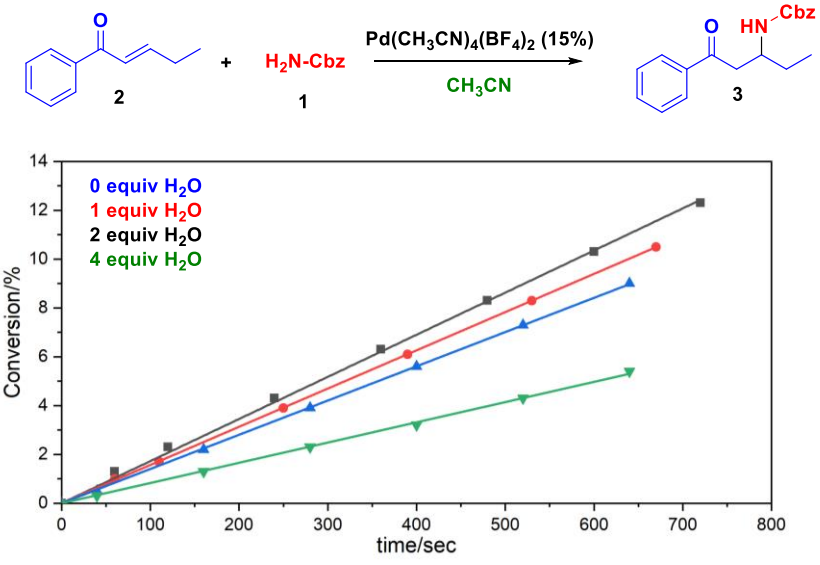
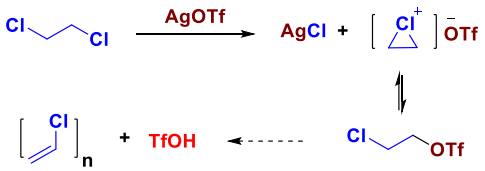



*Figure 1.6. Kinetic experiments regarding $[Pd(CH_3CN)_4](BF_4)_2$-catalyzed aza-Michael addition in the presence of varying amounts of water in $CD_3CN$.*

[61] (a) T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem*. **2011**, *76*, 9353; (b) R. K. Schmidt, K. Müther, C. Mück-Lichtenfeld, S. Grimme, M. Oestreich, *J. Am. Chem. Soc*. **2012**, *134*, 4421; (c) D. Munz, M. Webster-Gardiner, R. Fu, T. Strassner, W. A. Goddard, T. B. Gunnoe, *ACS Catal*. **2015**, *5*, 769; (d) I. Šolić, H. X. Lin, R. W. Bates, *Tetrahedron Lett*. **2018**, *59*, 4434.
[62] T. C. Wabnitz, J. Q. Yu, J. B. Spencer, *Chem. Eur. J*. **2004**, *10*, 484.

In this study, it was employed during the evaluation of a series of Lewis acid-catalyzed reactions which led to a complete shutdown of the reactivity in its presence. Another powerful evidence of hidden Brønsted catalysis were the kinetic experiments performed for the $[Pd(CH_3CN)_4](BF_4)_2$-catalyzed aza-Michael addition of the carbamate **1** to the enone **2** in $CD_3CN$. The addition of water into the reaction system led to a significant increase of the reaction rale up to 2 equivalents of water (Figure 1.6), but up to 4 equivalents of water caused the reaction to slow down.

Hidden Brønsted acid catalysis is not always due to traces of water as it might result, in some cases, from the decomposition of the ligand or solvent. In this respect, in 2011 Hintermann conducted mechanistic studies on the hydroalkoxylation reaction catalyzed by AgOTf in 1,2-dichloroethane.[61a] This study showed that the truly catalytic species is the strong Brønsted acidic triflic acid generated by AgOTf with 1,2-dichloroethane (Scheme 1.8). To highlight the generation of triflic acid, a solution of AgOTf in 1,2-dichloroethane was heated at 80 °C for 3 h. A white precipitate of AgCl was generated which might be explained by the abstraction of chloride from the chlorinated solvent by silver followed by the elimination of TfOH.



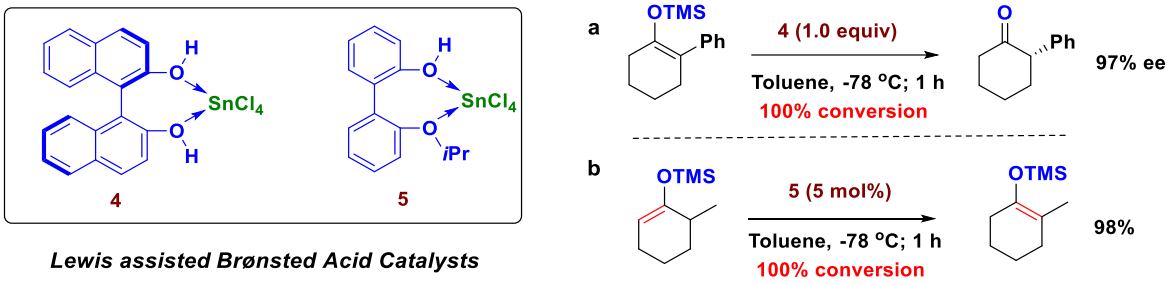

*Scheme 1.8. Generation of HOTf from AgOTf in 1,2-DCE.*

Hidden Brønsted acid catalysis is a common phenomenon which can be found in many Lewis acid catalyzed reactions such as carbonyl-olefin metathesis,[63] Friedel-Crafts alkylation,[64] Diels-Alder cycloaddition[65] or transfer hydrogenation of alkenes.[66] Thus, whether a transformation employing a Lewis acid as catalyst is truly a metal-catalyzed process or is hidden Brønsted acid catalysis, must be carefully investigated, especially when water is generated as a side-product.

[63] R. E. M. Brooner, R. A. Widenhoefer, *Chem. Eur. J.* **2011**, *17*, 6170.
[64] S. Yang, C. Bour, V. Gandon, *ACS Catal.* **2020**, *10*, 3027.
[65] D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1988**, *110*, 1238.
[66] A. Djurovic, M. Vayer, Z. Li, R. Guillot, J.-P. Baltaze, V. Gandon, C. Bour, *Org. Lett.* **2019**, *21*, 8132.

### 1.2.4. Lewis or Brønsted acid-assisted Brønsted acid catalysis

A favorable combination of Lewis and Brønsted acids through an interaction between a Lewis acid with the heteroatom of a Brønsted acid may provide higher catalytic efficiency, due to the increase of the acidity of the Brønsted acid. This phenomenon is called Lewis acid-assisted Brønsted acid catalysis.[67] The most well-known example is the one reported in 1994 by the group of Yamamoto,[68] where the Lewis acid-assisted Brønsted acid catalyst (LAB) resulted from the coordination of tin tetrachloride to binaphthol in toluene (**4**: see Scheme 1.9) which increased the acidity of the protons of the hydroxyl groups. This catalytic system induced a significant enantioselectivity for the preparation of chiral 2-phenylcyclohexanone starting from silyl enol ether derivatives (**a**: see Scheme 1.9). A few years later, a similar LAB system (**5**: see Scheme 1.9) was reported by the same group for the efficient isomerisation of the kinetic silyl enol ether product to the thermodynamic product (**b**: see Scheme 1.9).[69]



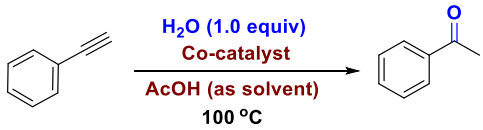

*Scheme 1.9. Lewis acid-assisted Brønsted acid catalysis; (a) Enantioselective protonation with chiral LBA; (b) Isomerization of silyl enol ethers.*

Several methods regarding the applications of Lewis acid-assisted Brønsted acid catalysis subsequently reported in the literature. In 2015, Xu and co-workers reported the preparation of carbonyl compounds by the hydration of alkynes catalyzed by a Lewis acid using acetic acid as a solvent.[70] In order to find the best combination of LBA, a series of Brønsted acids and Lewis acids were employed. The results (Table 1.1) indicated that most of the AcOH/Lewis acid combinations tested were effective. Additionally, with

[67](a) H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; (b) S. Hirashima, H. Yamamoto, *J. Synth. Org. Chem.* **2013**, *71*, 1116.
[68] K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179.
[69] K. Ishihara, H. Nakamura, S. Nakamura, H. Yamamoto, *J. Org. Chem.* **1998**, *63*, 6444.
[70] S. Liang, G. B. Hammond, B. Xu, *Chem. Commun.* **2015**, *51*, 903.

$Ga(OTf)_3$ as catalyst the catalyst loading could be reduced to 0.2 mol% delivering the ketone in nearly quantitative yield.

In a similar reaction, Bassetti and co-workers studied the reactions of iron(III)-catalyzed hydration of unactivated internal alkynes in weakly acidic media.[71] Employing $Fe_2(SO_4)_3 \cdot nH_2O$ as catalyst in glacial acetic acid as a solvent was found to enable high functional group tolerance. For example, alkynes bearing bulky substituents were compatible with the catalytic process and the transformation of aryl trimethylsilyl acetylenes into acetyl derivatives were conducted in one-pot *via* a desilylation-hydration sequence. The mechanism proposed for the catalyzed process shows that the alkyne can be protonated by the combination of the iron(III) cation with acetic acid to generate the enol or the vinylic ester intermediate which can afford the desired product by tautomeric rearrangement (Scheme 1.10).

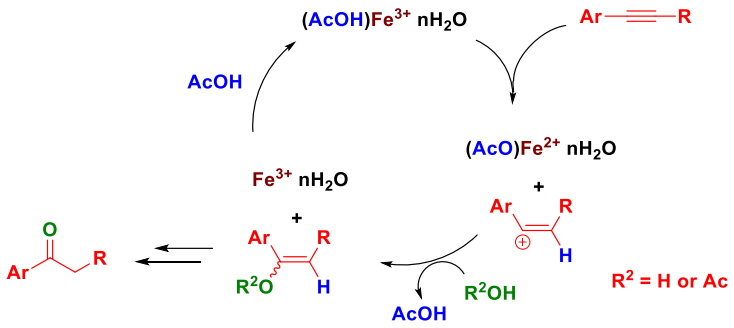



| *Entry* | *Co-catalyst (mol%)* | *Reaction time (h)* | *NMR Yield (%)* |
|---|---|---|---|
| 1 | $Yb(OTf)_3$ (0.5) | 14 | 99 |
| 2 | $Sc(OTf)_3$ (0.5) | 12 | 99 |
| 3 | $In(OTf)_3$ (0.5) | 10 | 99 |
| 4 | $Ga(OTf)_3$ (0.5) | 8 | 99 |
| 5 | $Ga(OTf)_3$ (0.2) | 6 | 99 |
| 6[a] | -- | 1.0 | trace |

*[a] at 120 °C for 1 h under microwave.*

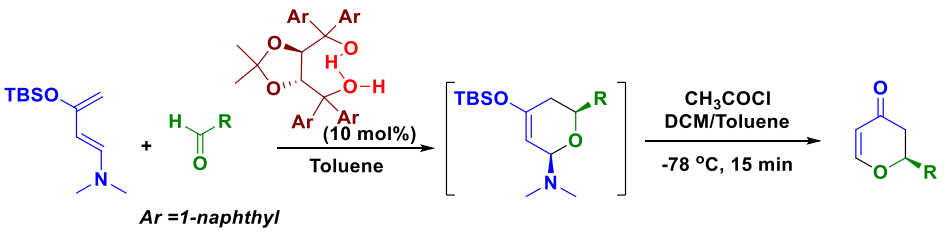
*Table 1.1. Scope of Lewis acids for alkyne hydration.*

[71] A. Antenucci, P. Flamini, M. V. Fornaiolo, S. D. Silvio, S. Mazzetti, P. Mencarelli, R. Salvio, M. Bassetti, *Adv. Synth. Catal.* **2019**, *361*, 4517.




*Scheme 1.10. Plausible catalytic cycle.*

Cooperativity between two different Brønsted acid co-catalysts in some cases can also improve the acidity and thereby, the catalytic efficiency. This phenomenon is called Brønsted acid-assisted Brønsted acid catalysis. A classic example of Brønsted acid-assisted Brønsted acid catalysis results from intramolecular hydrogen bonding between two hydroxyl groups.[72] For example, Rawal and co-workers reported a hetero-Diels–Alder reactions catalyzed by TADDOL derivative, which forms the dihydropyran product with high enantioselectivity (Scheme 1.11).[73] Intramolecular hydrogen-bonding between two hydroxyl groups increases the acidity of the catalyst. This intramolecular hydrogen-bonding was also confirmed by X-ray crystallographic analysis.[74]




*Scheme 1.11. Asymmetric Diels–Alder reactions catalyzed by a TADDOL derivative.*

## 1.3. Introduction to diarylalkane and 1,1,2-triarylethlane formation

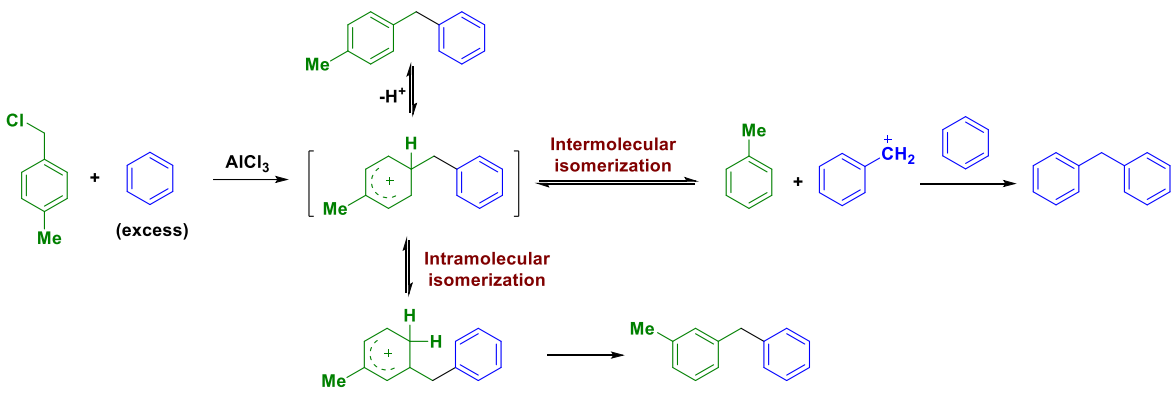
Diarylalkanes and 1,1,2-triarylethanes are important building blocks for medicinal chemistry and materials science. They are also present in many natural products. As a result, several groups became interested in the development of efficient and versatile methods for their synthesis. The most common strategies to access diaryalkanes and 1,1,2-

[72] H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed*. **2005**, *44*, 1924.
[73] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.
[74] D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **1998**, *110*, 2092.

triarylethanes involve Friedel-Crafts reactions, hydroarylations, cross-coupling reactions among other methods.

### 1.3.1. Friedel-Crafts reactions of benzylic halides and alcohols with aromatic nucleophiles

Friedel-Crafts benzylation is one of the most important approaches for the preparation of both classes of diaryl- and triarylmethane compounds. The classical Friedel-Crafts procedure for benzylation of arenes was reported in 1877 by Charles Friedel and James Mason Crafts.[75] The benzyl halide was activated by a stoichiometric amount of a strong Lewis acid such as $AlCl_3$ or $FeCl_3$ to form a reactive carbocation leading to the benzylated product after a nucleophilic addition along a hydro-halide as side-product. The mechanism of the benzylation of aromatic nucleophiles with benzyl chloride in nitromethane catalyzed by $AlCl_3{\cdot}CH_3NO_2$ was reported by Grayson and Brown in 1953.[76] Following kinetic studies, the reaction mechanism was demonstrated to be in overall third order: first order in benzyl halide, catalyst and nucleophile. Systematic mechanistic studies on the factors influencing substrate and regioselectivity in the Friedel-Crafts benzylation were reported by Olah and co-workers in 1972.[77] Different catalysts were employed for this study and showed that very active catalysts such as $AlCl_3$, $AlBr_3$, $GaCl_3$, $GaCl_2$, $ZrCl_4$ or $HfCl_4$ were forming unexpected by- products due to intra- and intermolecular isomerizations. However, softer Lewis acids such as $InCl_3$, $InBr_3$, $SbCl_5$, $WCl_6$ or $FeCl_3$ as well as weaker catalysts such as $BF_3$, $SbF_3$, $AsBr_3$, $MgBr_2$ or $ZnCl_2$ only

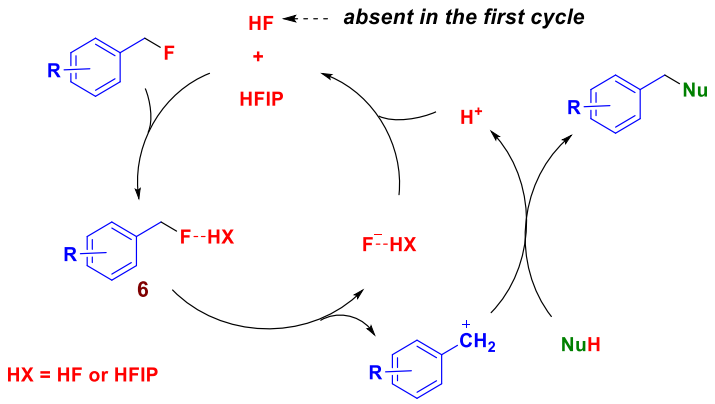



*Scheme 1.12. Mechanism of the formation of 4-methyldiphenylmethane from 4-methylbenzyl chloride with benzene.*

[75] C. Friedel, J. M. Crafts, *Compt. Rend.* **1877**, *84*, 1391.
[76] H. C. Brown, M. Grayson, *J. Am. Chem. Soc.* **1953**, *75*, 6283.
[77] G. A. Olah, S. Kobayashi, M. Tashiro, *J. Am. Chem. Soc.* **1972**, *94*, 7448.

formed the desired product, but in low yields. For example, the preparation of 4-methyldiphenylmethane from 4-methylbenzyl chloride and benzene[78] led to the formation of diphenylmethane and 3-methyldiphenylmethane with strong Lewis acid catalysts such as $AlCl_3$ or $GaCl_3$ (Scheme 1.12).

Recently, a hydrogen-bonding promoted Friedel-Crafts benzylation of arenes was reported by the group of Paquin using benzyl fluorides as electrophiles.[79] HFIP was employed as a solvent, which plays an important role in the reaction by forming an H-bond with benzyl fluorides to generate complex **6** (see Scheme 1.13). Then, during the formation of the electrophilic carbocation by ionization of the C–F bond, $F^-$ is generated and can form an H-bond with HFIP or simply with HF. Because HF is a better H-bond donor than HFIP, the true catalytic species is HF and HFIP serves as the initiator of the reaction (Scheme 1.13). However, the *in-situ* generation of HF limits the scale-up of this reaction for safety reasons.

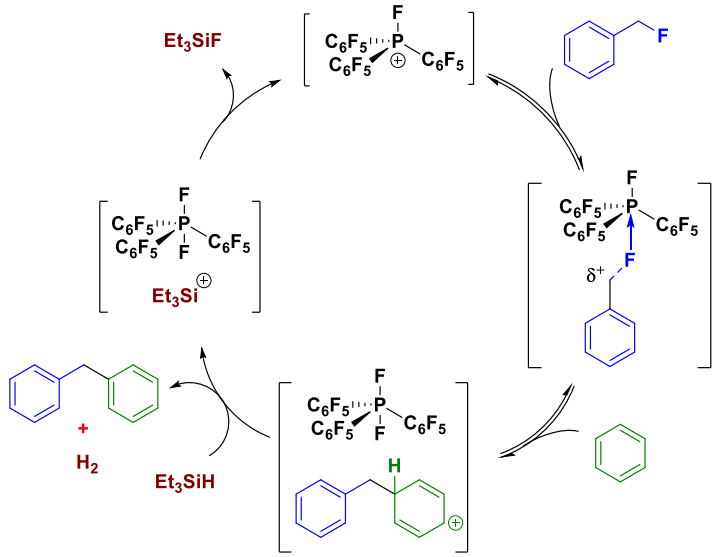



*Scheme 1.13. Mechanism of the Friedel-Crafts benzylation.*

A similar study on the Friedel-Crafts benzylation of arenes was reported by the group of Stephan.[80] Here, a silane was employed to capture fluoride during the catalytic process which makes the reaction more environmentally friendly (Scheme 1.14). The organofluorophosphonium $[(C_6F_5)_3PF][B(C_6F_5)_4]$ was employed as a catalyst and the electrophilic phosphonium cation $[(C_6F_5)_3PF]^+$ promoted the ionization of the C–F bond. This results in an acceleration of the generation of the benzylic carbocation. Then, the formed carbocation undergoes a nucleophilic addition by the arene to form the desired product after abstraction of a proton from the silane. As a result, the fluorophosphorane

[78] O. Tsuge, M. Tashiro, *Bull. Chem. Soc. Jap*. **1967**, *40*,119.
[79] P. A. Champagne, Y. Benhassine, J. Desroches, J.-F. Paquin, *Angew. Chem. Int. Ed.* **2014**, *53*, 8588.
[80] J. Zhu, M. Pérez, D. W. Stephan, *Angew. Chem. Int. Ed.* **2016**, *55*, 8448.

generated can re-enter into the catalytic cycle by silylium ion abstraction of fluoride to liberate a fluorosilane (see Scheme 1.14).



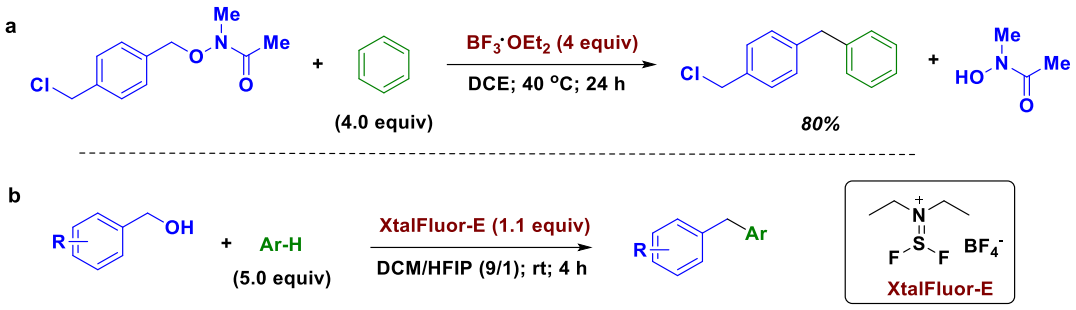

*Scheme 1.14. Mechanism of [$(C_6F_5)_3PF$][$B(C_6F_5)_4$] catalysis of the Friedel-Crafts reaction of benzyl fluorides.*

Even though benzylation of arenes is an efficient method for the formation of diarylalkanes using reaction conditions that have prevailed for more than a century, it still posed a safety hazard. Hydrohalides are common side-products for most of these reactions and they are often highly toxic and irritating. In addition, from the point of view of atom-economy and green chemistry, the classical Friedel-Crafts procedures for benzylation of arenes are far from being satisfying. In that sense, using benzylic alcohols as electrophiles seems to be an ideal alternative for the Friedel-Crafts alkylation. Alcohols are more stable, less toxic and water is the only by-product generated during the reaction, making their use more appealing and environmentally friendly.

Since benzylic alcohols were thought to be an attractive alternative for Friedel-Crafts alkylations to avoid the use of toxic halogenated substrates, several methods for the activation of benzylic alcohol derivatives were recently reported. For example, in 2011, the group of Bode described the reaction between benzylic hydroxamates and aromatic nucleophiles catalyzed by a stoichiometric amount of boron trifluoride ($BF_3{\cdot}OEt_2$) for the formation of diaryalkanes (a: see Scheme 1.15)[81]. The main advantage of this method is the activation of the hydroxamates by $BF_3{\cdot}OEt_2$ to form a better leaving group, resulting

[81] G. Schäfer, J. W. Bode, *Angew. Chem. Int. Ed.* **2011**, *50*, 10913.

in a reaction highly tolerant toward other benzylic functional groups such as halides and alcohols present on both reactants. Another interesting study about the *in-situ* activation of benzyl alcohols with XtalFluor-E for the preparation of 1,1-diarylmethanes and 1,1,1-triarylmethanes was reported by Paquin and co-workers (b: see Scheme 1.15).[82] In this case, benzyl alcohols were pre-activated by XtalFluor-E *via* the formation of a better leaving group (-$OSF_2NEt_2$) which accelerated the generation of the corresponding benzyl carbocations. In addition, this method it is also applicable to secondary benzyl alcohols.

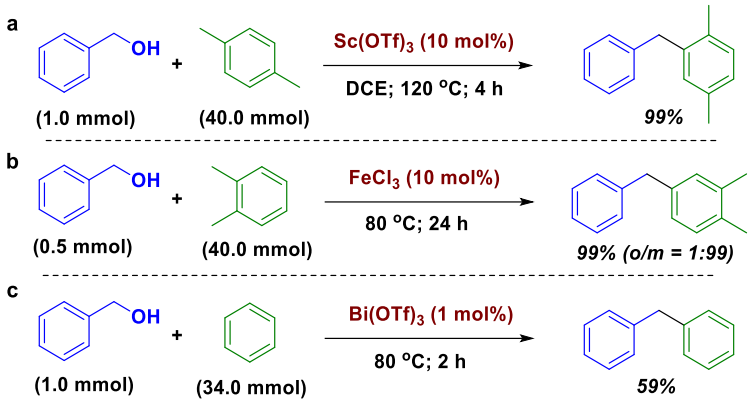



*Scheme 1.15. Friedel-Crafts benzylation reactions.*

Both methods described above prevent the use of toxic halogenated substrates to afford a wide range of 1,1-diarylmethanes in moderate to excellent yields under mild conditions, but the requirement of super-stoichiometric amounts of promoter still represents a serious limitation. The first example of catalytic dehydrative Friedel-Crafts benzylation was reported in 1997 by Fukuzawa and co-workers.[83] $Sc(OTf)_3$ (10 mol%) showed a high catalytic efficiency for the formation of diarylmethanes from benzyl alcohols with a variety of arene nucleophiles such as benzene, xylene or mesitylene. Thereafter, a series of new catalytic systems for the direct Friedel-Crafts reactions with benzylic alcohols was developed, featuring harder Lewis acids such as $FeCl_3$, $Bi(OTf)_3$ or $Ca(NTf)_2$ (Scheme 1.16).[84]. A remarkable example was described by Rueping and co-workers,[84c] where $Bi(OTf)_3$ was employed as a catalyst with a low catalyst loading (1.0 mol%), delivering the desired Friedel-Crafts benzylation products in moderate to high yields up to 95%. However, a few drawbacks remained for Lewis acid-catalyzed direct Friedel-Crafts reactions with benzylic alcohols: 1) the aromatic nucleophiles have to be used in large

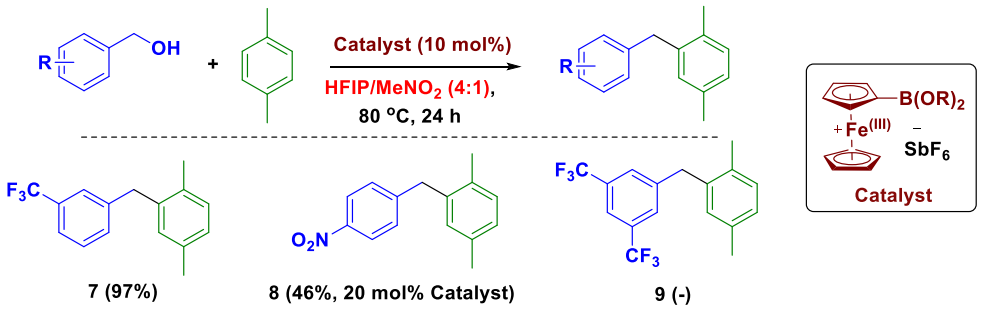
[82] J. Desroches, P. A. Champagne, Y. Benhassine, J.-F. Paquin, *Org. Biomol. Chem*. **2015**, *13*, 2243.
[83] T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *J. Org. Chem.* **1997**, *62*, 6997.
[84] (a) I. Iovel, K. Mertins, J. Kischel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed*. **2005**, *44*, 3913; (b) K. Mertins, I. Iovel, J. Kischel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed*. **2005**, *44*, 238; (c) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, *Adv. Synth. Catal.* **2006**, *348*, 1033; (d) K. Mertins, I. Lovel, J. Kischel, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 691.

excess or even as solvent, 2) high temperature are often required and 3) substrates bearing strong electron-withdrawing group are incompatibles with most of those procedures.




*Scheme 1.16. Lewis acid catalyzed Friedel-Crafts alkylations with benzylic alcohols*

Recently, Hall and co-workers examined this transformation with electron-deficient benzylic alcohols catalyzed by ferrocenium boronic acid salts.[85] Arenes bearing electron-deficient $CF_3$ or $NO_2$ groups can be activated to form the desired products in 97% (**7**) and 46% (**8**) yield with *p*-xylene respectively but the *bis*-$CF_3$ substituted benzylic alcohol is not reactive in those reaction conditions (Scheme 1.17).

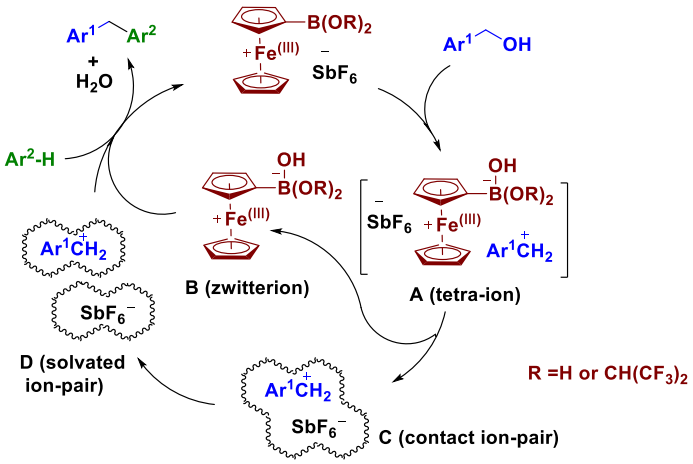



*Scheme 1.17. Direct Friedel-Crafts of benzylic alcohols by ferroceniumboronic acid catalysis.*

The mechanistic studies show that both the Fe(III) ion and the free boronic acid are critical components for the process (Scheme 1.18). A benzylic carbocation intermediate was formed by the powerful activator ferrocenium boronic acid salt with the assistance of HFIP. The authors proposed that an ion-exchange process is involved. Firstly, the formed carbocation combines with the catalyst to produce the tetra-ionic species **A**, which then decomposes to two ion pairs, **B** and **C**. Both contains the carbocation and the $SbF_6^-$ anion

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

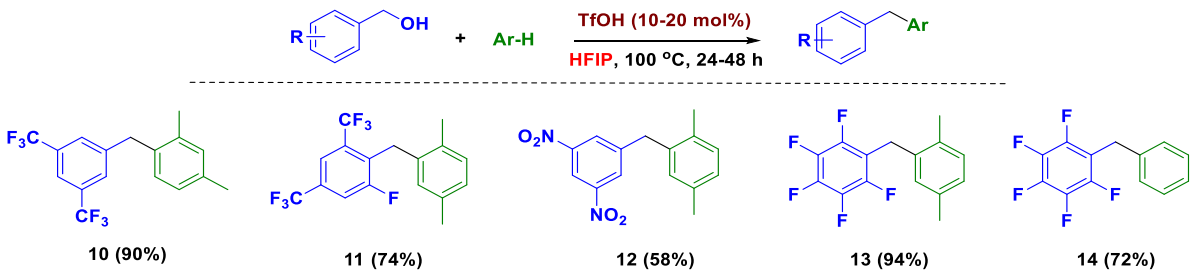
from the catalyst. The ion-pair **C** is separated and stabilized with the help from the solvent. Finally, the benzylation product is formed after a nucleophilic addition to the benzylic carbocation. Since the catalyst was a boronic acid, the authors described this reaction as a mild form of Lewis acid catalysis. However, based on our experience with HFIP, we consider this interpretation questionable and will discuss it in more detail in chapter 2.




*Scheme 1.18. Proposed catalytic cycle of activation for ferrocenium boronic acid salt.*

One large limitation in the Friedel-Crafts benzylation from benzylic alcohols was its incompatibility with highly electronically deactivated benzylic alcohols like those bearing *bis*-$CF_3$ groups. Recently, this problem was solved by our group using a catalytic amount of a strong Brønsted acid such as TfOH and $HSbF_6 \cdot 6H_2O$ in the presence of HFIP as a solvent. [86] For example, diarylmethanes were prepared from highly deactivated pentafluorobenzyl alcohols with benzene and xylene as nucleophiles in excellent yields (**10**: 94% and **11**: 72%). Benzylic alcohols bearing up to two $CF_3$ groups or two $NO_2$ groups were also well-tolerated (Scheme 1.19). Furthermore, kinetic analysis of Brønsted acid-catalyzed Friedel-Crafts alkylation of highly deactivated benzyl alcohols showed a 5$^{th}$ order dependence on the HFIP concentration. Moreover, $^1$H NMR titration of a substrate in HFIP with triflic acid (TfOH) reveals a pronounce up field shift of the HFIP signals, while those of the benzyl alcohol remain relatively intact, suggesting TfOH is involved in H-bonding with HFIP clusters rather than in the direct activation of an alcohol.

[86] V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085.

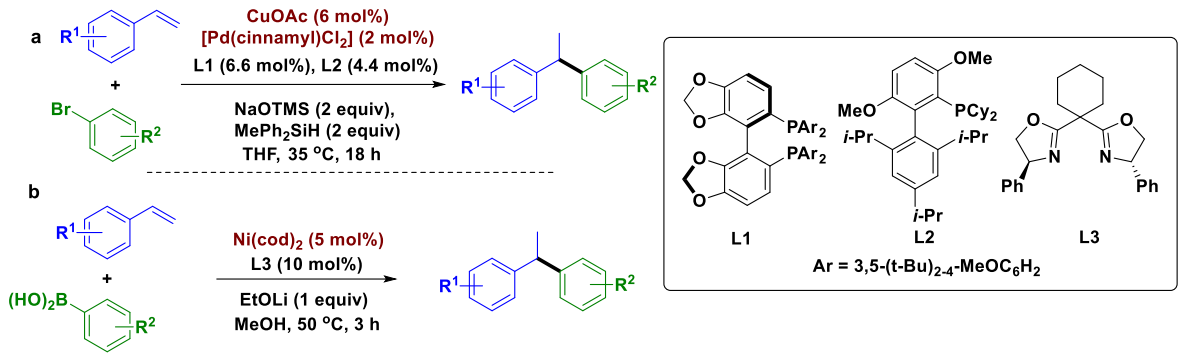



*Scheme 1.19. Triflic acid-catalyzed Friedel-Crafts alkylation of highly deactivated benzyl alcohols in HFIP.*

### 1.3.2. Hydroarylation of vinylarenes

Although chemists made significant progress on the Friedel-Crafts benzylation of arenes, providing a convenient and environmental benign approach to 1,1-diarylalkanes, the stoichiometric generation of water as by-product may result in expensive issues for scale-up. The preparation of 1,1-diarylalkanes *via* direct substitution of arenes with styrene derivatives is an excellent atom economical alternative to the classical Friedel–Crafts-type alkylation of arenes.[87] Various transition-metal catalysts were employed in the hydroarylation of alkenes such as Pd(0), Ni(0), $Mo(CO)_6$, $MoCl_5$ or $W(CO)_6$. As an example, the asymmetric hydroarylation of vinylarenes with an extensive array of aryl bromides catalyzed by CuH and Pd was reported by Buchwald and co-workers (a: see Scheme 1.20).[88] 1,1-Diarylalkanes, which can be found in several pharmaceutical drug agents and natural products such as β-substituted vinylarenes and six-membered heterocycles, were prepared from styrenes and aryl bromides under mild conditions. Another study reported by Mei and co-workers in 2019 described a Ni-catalyzed enantioselective hydroarylation of styrenes with arylboronic acids (b: see Scheme 1.20).[89] This approach also demonstrated an excellent functional group tolerance to access relevant 1,1-diarylalkane products such as (*R*)-ibuprofen while using methanol as a hydride source.

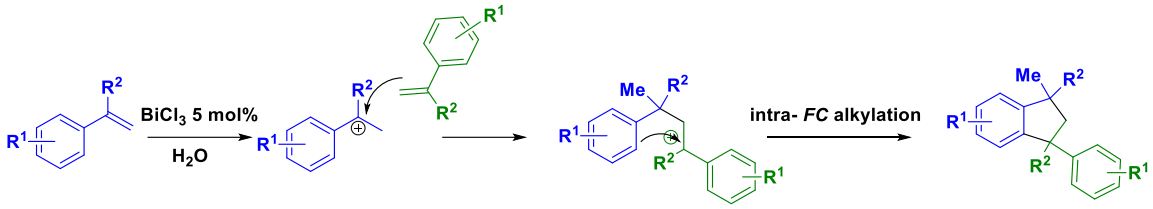
[87] M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem*. **2010**, *6*, 6.
[88] S. D. Friis, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc*. **2016**, *138*, 8372.
[89] Y. Chen, B. Shuai, X. Xu, Y. Li, Q. Yang, H. Qiu, K. Zhang, P. Fang, T. Mei, *J. Am. Chem. Soc*. **2019**, *141*, 3395.




*Scheme 1.20. Asymmetric hydroarylation of styrenes.*

Transition metal-catalyzed hydroarylation of alkenes prevailed for more than a century, but the reaction often requires expensive, toxic metals and bulky ligands that might cause those methods to not be cost-effective. Moreover, pre-functionalized arene nucleophiles such as aryl halides or aryl boronic derivatives are required which leads to the formation of stoichiometric amounts of waste. Thus, the direct hydroarylation of styrenes using non-pre-functionalized arenes as nucleophiles is a more environmentally friendly and atom-economical route for the preparation of 1,1-diarylalkanes. A number of methods were reported in the last decade which employed Lewis acids such as $TiCl_4$[90], $FeCl_3$[91], $ZnBr_2$[92], $BiCl_3$[93], $Ca(NTf_2)_2$[94], $B(C_6F_5)_3$[95] or $[Ph_3C][B(C_6F_5)_4]$[96]as catalyst. For example, Hua and co-workers[933] reported the formation of 1,1-diarylalkanes in good to excellent yields from electron-rich arenes and styrenes using $BiCl_3$ as a catalyst. Interestingly, without arene but in the presence of a catalytic amount of $BiCl_3$, dihydroindenes were formed from α-substituted styrenes. The mechanism of formation of dihydroindenes proposed is that the styrene acts as a nucleophile and reacts with the carbocation formed by activation of the catalyst. The cyclized product is formed by an intramolecular Friedel-Crafts alkylation process (Scheme 1.21).

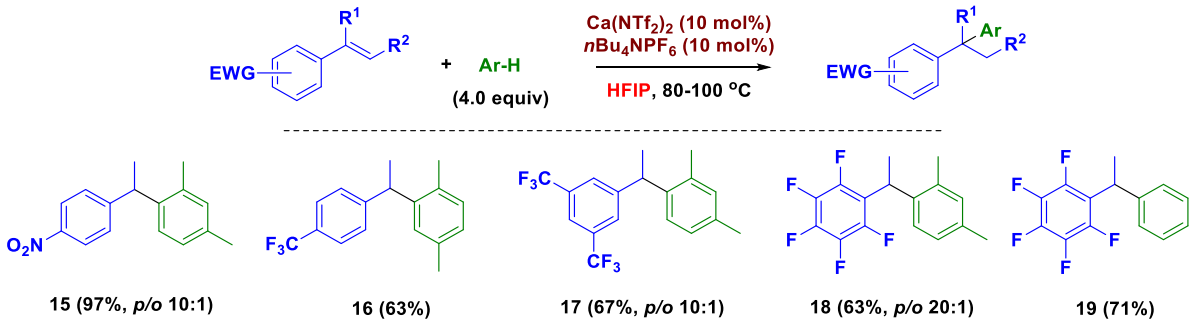
[90] S. Duan, R. Jana, J. A. Tunge, *J. Org. Chem.* **2009**, *74*, 4612.
[91] J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller, *Org. Lett.* **2006**, *8*, 19.
[92] S. Y. Lee, A. Villani-Gale, C. C. Eichman, *Org. Lett.* **2016**, *18*, 5034.
[93] H. Sun, B. Li, R. Hua, Y. Yin, *Eur. J. Org. Chem*. **2006**, *2006*, 4231.
[94] (a) N. Bisek, M. Niggemann, *Chem. Eur. J.* **2010**, *16*, 11246; (b) C. Qi, V. Gandon, D. Lebœuf, *Angew. Chem. Int. Ed.* **2018**, *57*, 14245.
[95] J. N. Bentley, C. B. Caputo, *Organometallics*, **2018**, *37*, 3654.
[96] (a) W. Zhu, Q. Sun, Y. Wang, D. Yuan, Y. Yao, *Org. Lett.* **2018**, *20*, 3101; (b) B. Tang, X. Hu, C. Liu, T. Jiang, F. Alam, Y. Chen, *ACS Catal*. **2019**, *9*, 599.




*Scheme 1.21. Dihydroindene formation from styrenes catalyzed by $BiCl_3$.*

Lewis acid-catalyzed direct hydroarylation of styrenes tend to give excellent yields for styrenes bearing electron-donating or moderate electron-withdrawing group, but not with the ones bearing strong electron-deficient groups such as $-CF_3$, $-NO_2$ or pentafluorobenzene. Niggemann and co-worker[96a] reported a highly efficient method for the hydroarylation reaction of aryl and aliphatic alkenes at room temperature in the presence of $Ca(NTf_2)_2$. This complex proved to be an efficient Lewis acid, showing a high affinity towards alcohols when combined with an ammonium salt. In this reaction, it was assumed that the ammonium salt of the weakly coordinating anion can promote an anion metathesis to generate the heteroleptic complex $Ca(NTf_2)(PF_6)$, which is more Lewis acidic than $Ca(NTf_2)_2$.

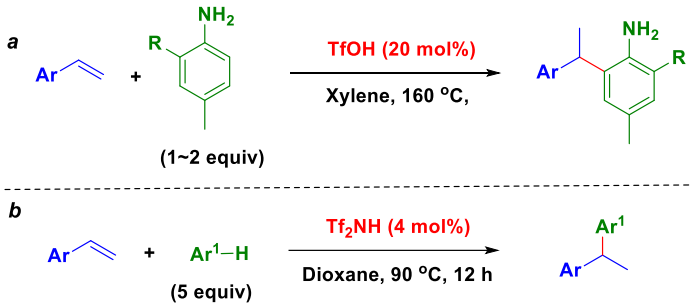
Recently, an efficient method involving the same promoter system was reported by Lebœuf and co-workers for the direct hydroarylation of deactivated styrenes with aromatic nucleophiles in HFIP. A series of deactivated styrenes bearing $-CF_3$, $-NO_2$ or pentafluorobenzene groups were employed (Scheme 1.22).[94b] The mechanism, investigated by NMR experiments and DFT calculations, shows that the true catalyst is a $[Ca(NTf_2)(HFIP)_n]^+$ complex. Here, the role of calcium is not to act as a Lewis acid activating the styrene but instead to increase the acidity of the H-bond network of HFIP,




*Scheme 1.22. Calcium(II)-catalyzed intermolecular hydroarylation of deactivated styrenes in HFIP.*

which is employed as a solvent. Protonation of the electron-poor styrene derivative to form a benzylic carbocation leads to the desired 1,1-diarylalkanes after nucleophilic addition.

Brønsted acids were also employed as catalysts for the direct hydroarylation of vinylarenes to produce 1,1-diarylalkanes. Monosubstituted styrenes can be arylated upon exposure to strong acids under prolonged heating at high temperatures. For example, in 2006, Coates and co-workers reported a TfOH-catalyzed *ortho*-alkylation of anilines with a variety of styrenes (a: see Scheme 1.23).[97] 1,1-Diarylalkanes were synthetized in good yields at high temperature (160 °C), even those bearing electron-rich substituents such as a naphthyl group. Another study reported by Jiang and co-workers shows that $Tf_2NH$ could efficiently catalyze the hydroarylation of styrenes with aromatic nucleophiles in 1,4-dioxane at 90 °C (b: see Scheme 1.23).[98] Thus, the 1,1-diarylalkanes were produced smoothly in high yields. Although methods frequently involve Brønsted acids to catalyze the direct hydroarylation of vinylarenes, low yields are ofien observed due to high temperatures as well as long reaction times that are usually required, leading to the oligomerization of the substrates.



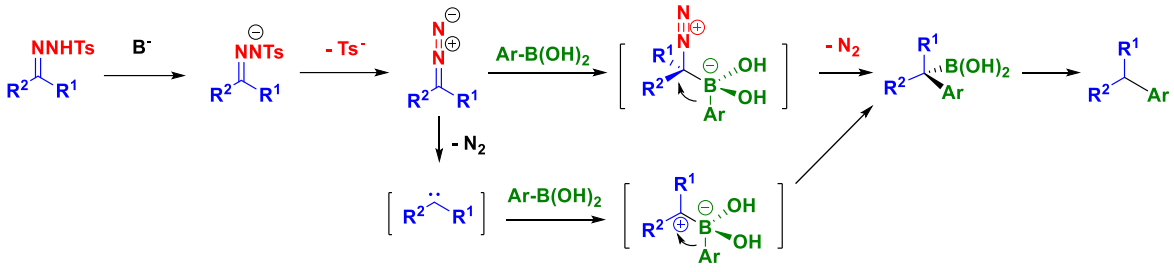

*Scheme 1.23. Brønsted acid-catalyzed direct hydroarylation of vinylarenes.*

### 1.3.3. Cross-coupling reaction of vinylarenes with electrophiles or nucleophiles

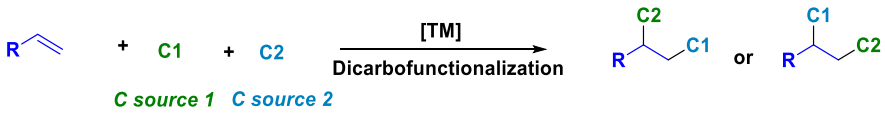
Another efficient method to access 1,1-diarylalkanes are cross-coupling reactions, such as the Suzuki-Miyaura cross-coupling of electrophilic arenes such as benzylic halides with aryl boronic acids. For example, Georgiou and co-workers reported a Pd-catalyzed Suzuki-Miyaura cross-coupling of benzylic bromides, iodides or bromo-methyl-naphthalenes with aryl boronic acids for the formation of 1,1-diarylalkanes in

[97] A. E. Cherian, G. J. Domski, J. M. Rose, E. B. Lobkovsky, G. W. Coates, *Org. Lett*. **2005**, *7*, 5135.
[98] M. Liu, J. Zhang, H. Zhou, H. Yang, C. Xia, G. Jiang, *RSC Adv*. **2016**, *6*, 76780.

synthetically useful yields.[99] With the development of the substrate scope for cross-coupling reactions, a wide range of aryl reagents was employed. For instance, Molander and co-workers successfully coupled benzylic trifluoroborate salts with aryl triflates catalyzed by $PdCl_2$(dppf) to produce 1,1-diarylalkanes.[100] Moreover, the metal-free coupling of boronic acids with tosylhydrazones was reported by Barluenga and co-workers.[101] Tosylhydrazones can be easily formed from benzylic aldehydes or ketones and then deprotonated in the presence of a base to form a diazo compound. This diazo compound can then produce a benzyl boronic acid following two possible routes (Scheme 1.24): 1) the diazo compound can react with the boronic acid and release $N_2$ to form a benzyl boronic acid through a boronate intermediate; 2) a carbene can be generated by the decomposition of the diazo and then react with the boronic acid through a zwitterionic intermediate. The final product is formed by protodeboronation of the benzyl boronic acid. The reaction also tolerates highly functionalized groups directly starting from benzylic aldehydes or ketones to do a two-step sequence in one-pot.




*Scheme 1.24. Possible mechanistic pathways for metal-free coupling of boronic acids with tosylhydrazones.*

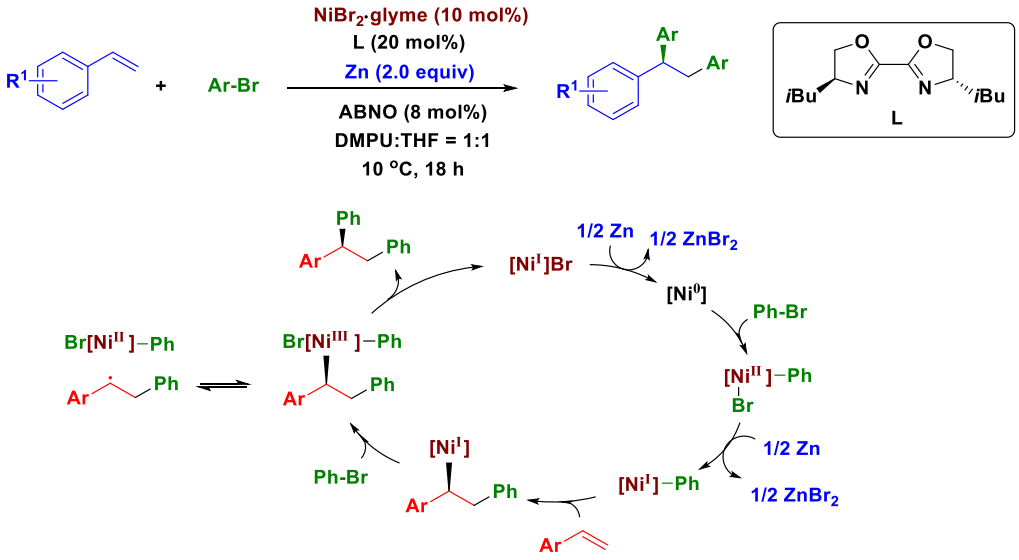



*Scheme 1.25. Cross-coupling reaction of vinylarenes with electrophiles or nucleophiles.*

The coupling of styrenes with nucleophiles or electrophiles is also an efficient strategy for preparing 1,1,2-triarylethanes which are important building-blocks for medicinal chemistry and the synthesis of natural products. 1,2-Dicarbofunctionalization of vinylarenes represents a rapid way to increase the complexity of alkanes by coupling with

[99] S. Chowdhury, P. E. Georghiou, *Tetrahedron Lett.* **1999**, *40*, 7599.
[100] G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393.
[101] J. Barluenga, M. Tomas-Gamasa, F. Aznar, C. Valdes, *Nat. Chem.* **2009**, *1*, 494.

a range of electrophiles and nucleophiles under transition metal catalysis. Several methods for the 1,2-dicarbofunctionalization of styrenes catalyzed by [Pd],[102] [Cu],[103] [Rh][104] or [Ni][105] were reported in the last decades (see Scheme 1.25). Depending on the reagents, the reaction can be divided in two categories: 1) cross-coupling with two electrophiles; 2) cross-coupling with a nucleophile and an electrophile.[106] [Ni] and [Pd] are common catalysts for the reaction of styrenes with two electrophiles, a reductant being necessary in this case. For example, a Ni-catalyzed 1,2-diarylation of styrenes with aryl-bromides to prepare 1,1,2-triarylethanes was recently reported by Diao and co-workers.[107] As a result of extensive optimizations, the enantioselective reaction was conducted under mild conditions, while being tolerant to a broad variety of functional groups. The mechanistic study (Scheme 1.26) shows that the Ni-catalyzed process follows a radical




*Scheme 1.26. Ni-catalyzed asymmetric reductive diarylation of vinylarenes.*

[102] (a) S. Yahiaoui, A. Fardost, A. Trejos, M. Larhed, *J. Org. Chem*. **2011**, *76*, 2433; (b) M. Catellani, G. P. Chiusoli, *Tetrahedron Lett.* **1982**, *23*, 4517; (c) H. Stadtmueller, R. Lentz, C. E. Tucker, T. Stuedemann, W. Doerner, P. Knochel, *J. Am. Chem. Soc*. **1993**, *115*, 7027; (d) M. P. Go´mez, J. A. Garcı´a-Lo´pez, *Angew. Chem. Int. Ed.* **2016**, *55*, 14389; (e) X.-X. Wu, W.-L. Chen, Y. Shen, S. Chen, P.-F. Xu, Y.-M. Liang, *Org. Lett*. **2016**, *18*, 1784.

[103] (a) J. Lin, T. Li, J. Liu, G. Jiao, Q. Gu, J. Cheng, Y. Guo, X. Hong, X. Liu, *J. Am. Chem. Soc*. **2019**, *141*, 1074; (b) Z. Li, G. Fang, Q. Gu, X. Liu, *Chem. Soc. Rev.*, **2020**, *49*, 32.

[104] (a) A. M. Dreis, C. J. Douglas, *J. Am. Chem. Soc.* **2009**, *131*, 412; (b) L. Souillart, E. Parker, N. Cramer, *Angew. Chem. Int. Ed*. **2014**, *53*, 3001; (c) T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2012**, *51*, 7567.

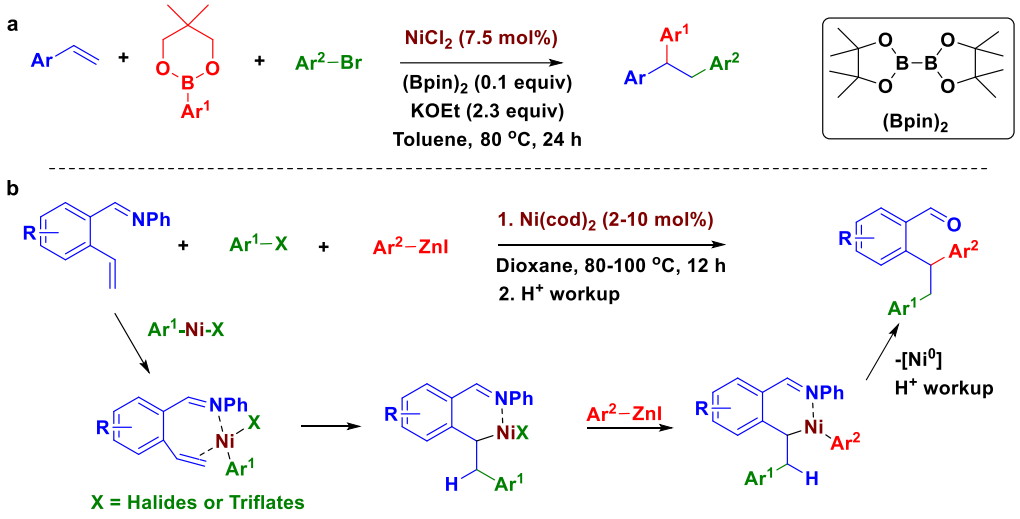
[105] (a) J.-W. Gu, Q.-Q. Min, L.-C. Yu, X. Zhang, *Angew. Chem. Int. Ed*. **2016**, *55*, 12270; (b) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; (c) W. Li, J. K. Boon, Y. Zhao, *Chem. Sci.* **2018**, *9*, 600.

[106] X. Qi, T. Diao, *ACS Catal.* **2020**, *10*, 8542.

[107] D. Anthony, Q. Lin, J. Baudet, T. Diao, *Angew. Chem.* **2019**, *131*, 3230.

addition pathway, the radical being formed at the benzylic position before binding reversibly to the Ni catalyst. The enantioselectivity was improved by using ABNO, which can stabilize the radical intermediates. Despite the efficiency of the reaction, the installation of two different aryl groups was a major drawback. However, this issue could be solved by coupling styrenes with a nucleophile and an electrophile.

1,2-Dicarbofunctionalization of vinylarenes by cross-coupling with a nucleophile and an electrophile usually offers good chemo- and regioselectivity because of the completely different reactivities of the two coupling partners. For example, Brown and co-workers reported a Ni-catalyzed stereoselective 1,2-diarylation of vinylarenes using aryl bromides as electrophiles and aryl-boron reagents as nucleophiles (**a**: see Scheme 1.27).[108] This method provides a range of 1,2-diarylation products with high stereoselectivity and is tolerant to densely functionalized vinylarenes, nucleophiles and electrophiles. The mechanistic study shows that a [$Ni^0$] complex was generated more efficiently with 0.1 equivalent of $B_2pin_2$ in the presence of KOEt than with common reductants such as Zn and Mn. Another efficient method was reported by Giri and co-workers through a Ni-catalyzed regioselective 1,2-dicarbofunctionalization of styrenes employing arylzinc reagents as nucleophiles and aryl halides or triflates as electrophiles (**b**: see Scheme 1.27).[109] The regioselectivity was improved by using a removable directing group on the

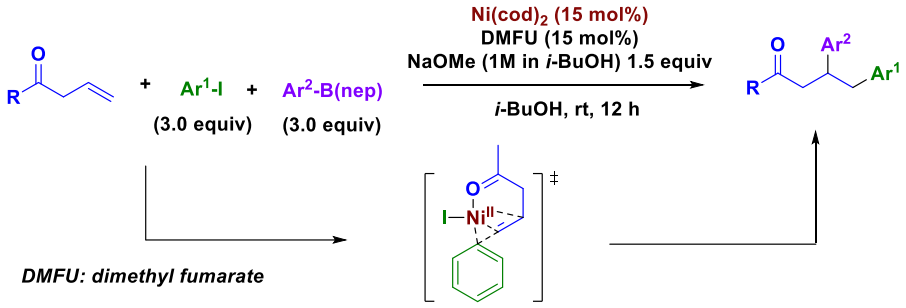



*Scheme 1.27. Ni-catalyzed coupling of vinylarenes with a nucleophile and an electrophile.*

[108] P.Gao, L. Chen, M. K. Brown, *J. Am. Chem. Soc.* **2018**, *140*, 10653.
[109] B. Shrestha, P. Basnet, R. K. Dhungana, S. KC, S. Thapa, J. M. Sears, R. Giri, *J. Am. Chem. Soc*. **2017**, *139*, 10653.

styrene, which can form a bidentate coordination complex with an Ar-Ni-X (X = halides or triflates) intermediate. A Heck C($sp^3$)-NiX intermediate was stabilized by the directing-group, which results in high regioselectivities by slowing down the $\beta$-H elimination process. Then, the desired product was obtained by a transmetalation/reductive elimination process with the arylzinc reagents in good to excellent yields along a high functional group tolerance, notably in the presence of bulky substituents.

Recently Engle and co-workers[110] reported a strategy for the 1,2-difunctionalization of alkenyl ketones with an electrophilic aryl iodide and a nucleophilic arylboronic ester to produce the 1,2-diarylated products under nickel catalysis (Scheme 1.28). Various aryl iodides, arylboronic esters and alkenyl ketones were examined and the corresponding 1,2-diarylated products were obtained with yields ranging from 32 to 83%. The reaction also shows high regiocontrol using a diverse array of ketone starting materials. The mechanistic studies based on DFT calculations support a carbonyl binding mode, which also is the key for the high regiocontrol of this reaction. Studies of electronic effect on the three coupling partners indicate that migratory insertion is the rate-limiting step.



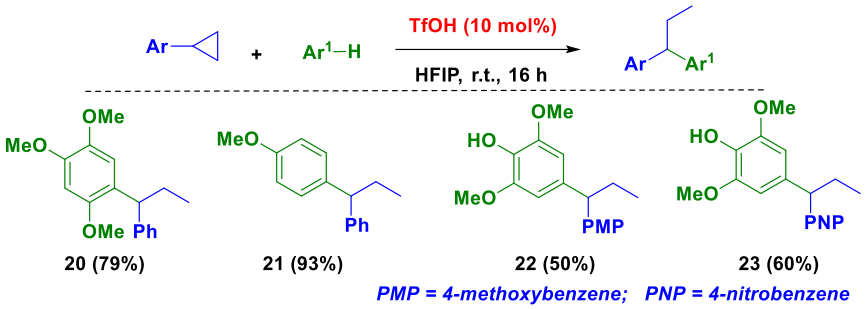

*Scheme 1.28. Ni-catalyzed 1,2-difunctionalization of alkenyl ketones with a nucleophile and an electrophile.*

### 1.3.4. Other methods for the formation of 1,2-diarylalkanes and 1,1,2-triarylethlanes

The formation of 1,2-diarylalkanes and 1,1,2-triarylethanes has been studied by several groups in recent years and a number of efficient methods were depicted, in addition to those developed above, other methods were devised. For example, our group reported the TfOH-catalyzed ring-opening hydroarylation of monosubstituted cyclopropanes in HFIP

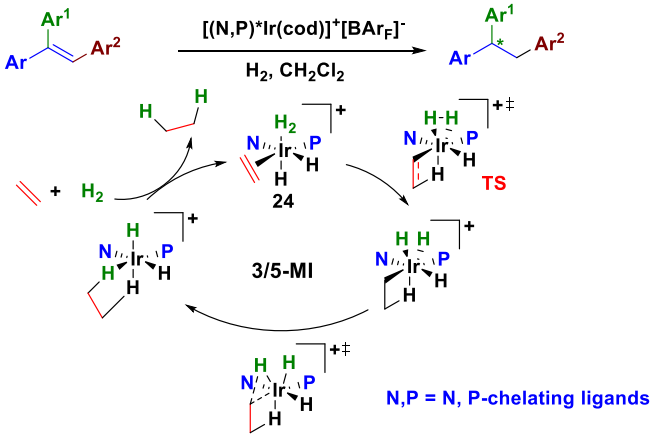
[110] R. Kleinmans, O. Apolinar, J. Derosa, M. K. Karunananda, Z Li, V. T. Tran, S. R. Wisniewski, K. M. Engle, *ChemRxiv* 2021, DOI: 10.26434/chemrxiv.14150174.

(Scheme 1.29).[111] This efficient way to prepare 1,2-diarylalkanes from a broad variety of monosubstituted cyclopropanes and aromatic nucleophiles follows a $S_N1$-type mechanism. The catalytic species is a strong Brønsted acid formed by a combination of TfOH and HFIP.




*Scheme 1.29. TfOH-catalyzed ring-opening hydroarylation of monosubstituted cyclopropanes in HFIP.*

The hydrogenation of 1,2-disubstituted vinylarenes is another strategy to prepare 1,1,2-triarylethanes. For example, Andersson and co-workers reported a method to prepare chiral 1,1,2-triarylethanes by hydrogenation of the double bond of the starting material catalyzed by an iridium catalyst bearing N,P-chelating ligands.[112] Many chira1 1,2-triarylethanes were prepared by hydrogenation of trisubstituted olefins in excellent enantioselectivities and high conversions. A similar study was reported by Diéguez and co-workers which employed $Ir(cod)_2$ and a new N,P-chelating ligand as catalyst for the

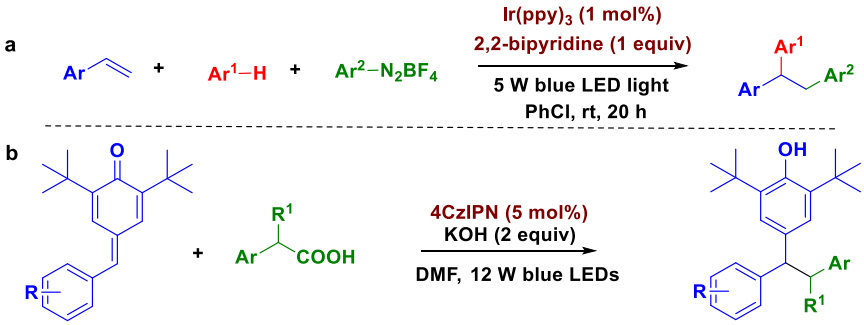



*Scheme 1.30. 3/5-MI catalytic cycles for Ir-hydrogenation.*

[111] E. Richmond, J. Yi, V. D. Vuković, F. Sajadi, C. N. Rowley, J. Moran, *Chem. Sci.* **2018,** *9*, 6411.
[112] P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W. M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855.

hydrogenation of 1,2-disubstituted vinylarenes.[113]The mechanism was ascertained based on experimental and computational studies that demonstrated that the enantiocontrol in the iridium hydrogenation is due to the π-olefin complex **24** and the transition state (TS) of the $Ir^{III}/Ir^{V}$ migratory-insertion/reductive-elimination catalytic cycles for Ir-hydrogenation (Scheme 1.30). However, one issue is the initial preparation of the tri-substituted olefin, which can be challenging.

Photo-redox catalysis is another efficient approach for the synthesis of 1,1,2-triarylethanes. Li and co-workers [114] developed a strategy where 1,1,2-triarylethane frameworks of interest were prepared by visible light photo-redox catalysis of 1,2-diarylation of vinylarenes with aryl diazonium salts and arenes (a: see Scheme 1.31). A metal-free approach to access 1,1,2-triarylethanes by photo-redox catalysis was also reported by Lu and co-workers.[115] *para*-Quinone methides were used as starting materials to react with carboxylic acids with the help of an organo-photoredox catalyst. Under these mild conditions, a variety of 1,1,2-triarylethanes were obtained in good to excellent yields (b: see Scheme 1.31).

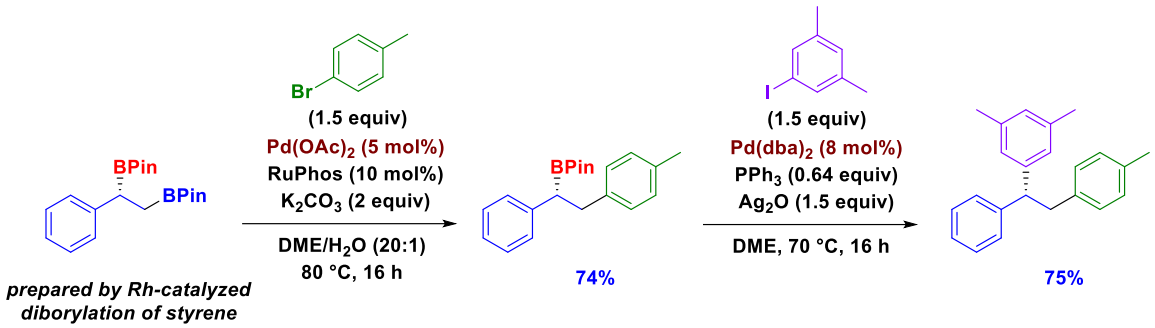



*Scheme 1.31. 1,1,2-triarylethane formation under photo-redox catalysis.*

As discussed above, various strategies for the formation of 1,1,2-triarylethane frameworks were described. In addition, many other interesting investigations were reported such as electrochemical 1,2-diarylation of alkenes[116] or a multiple arylation followed by a cross-coupling sequence.[117] For example, Crudden and co-worker[117] developed a strategy to produce chiral multi- arylated structures. 1,1,2-Triarylethane frameworks were prepared

[113] J. Mazuela, P. Norrby, P. G. Andersson, O. Pamies, M. Dieguez, *J. Am. Chem. Soc.* **2011**, *133*, 13634.
[114] X. Ouyang, J. Cheng, J. Li, *Chem. Commun.* **2018**, *54*, 8745.
[115] J. Guo, G. Huang, Q. Wu, Y. Xie, J. Weng, G. Lu, *Org. Chem. Front.* **2019**, *6*, 1955.
[116] J. Qin, M. Luo, D. An, J. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 1861.
[117] C. M. Crudden, C. Ziebenhaus, J. P. G. Rygus, K. Ghozati, P. J. Unsworth, M. Nambo, S. Voth, M. Hutchinson, V. S. Laberge, Y. Maekawa, D. Imao, *Nat. Commun.* **2016**, *7*, 11065.

from 1,2-diboronates via a first coupling with aryl bromides under Pd-catalysis. The formed product was isolated and submitted to another Pd-catalyzed cross coupling with aryl iodides to produce the desired 1,1,2-triarylethane (Scheme 1.32). However, most of these methods require complex starting materials, additional synthetic steps to prepare the substrates or harsh reaction conditions, which make these strategies not ideal.

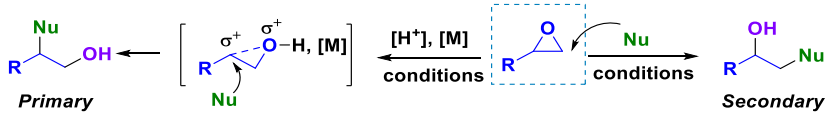



*Scheme 1.32. Diborylation of styrenes followed by a cross-coupling sequence.*

## 1.4. Epoxides in organic synthesis

### 1.4.1. Ring opening mono-functionalization of epoxides

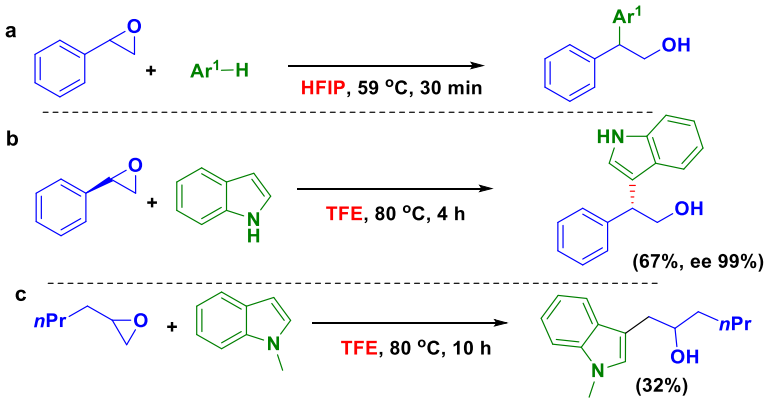
Epoxides represent important building blocks in synthetic chemistry, due to their reactivity and the generation of hydroxy groups which can be further functionalized. Based on the ring opening mechanism of terminal epoxides, two types of products can be generated: primary or secondary alcohols (see Scheme 1.33). The reactivity of epoxides is superior to olefins, alcohols and cyclopropanes due to their strained ring bearing an electronegative O atom. Furthermore, once the epoxide is opened, the primary aliphatic alcohols generated can be further transformed to other functional groups, such as esters, carboxylic acids or halides. The newly formed functional group can subsequently use for further derivatizations to build more useful and complex molecules.




*Scheme 1.33. General mechanism of ring opening arylation of epoxides*

Arylations of terminal epoxide that lead to secondary alcohols as products have been reported many times, especially for aliphatic epoxides. However, the production of primary alcohols via ring-opening arylation of terminal epoxides by Lewis or Brønsted acid catalysis is still limited to electron-rich styrene oxides. Substrates bearing strong

electron-withdrawing groups remain inaccessible. For instance, 1,1-diarylalkanes bearing a primary aliphatic alcohol were prepared from styrene oxides in HFIP (a: see Scheme 1.34). The study carried out by the group of Qu demonstrated that the ring-opening of styrene epoxides could be achieved in HFIP by heating under reflux to access 1,1-diarylalkanes in the absence of a catalyst.[118] However, the reaction was essentially limited to electron-rich arenes. In the other cases, the oligomerization of the epoxide was observed. This study also illustrated that the cycloalkylation reaction of (2*R*,3*R*)-2-((phenoxy)-methyl)-3-phenyloxirane was highly efficient to generate the core structure of many natural products, such as vitamin E, with the assistance of HFIP. Similar investigations were reported by the group of Mayr.[119] Styrene oxides were engaged with electron-rich heteroarenes, such as indoles and pyrroles to provide the corresponding products with high regio- and stereoselectivity in TFE without any catalyst (b: see Scheme 1.34). The alkylation process was completed by the assistance of TFE and the corresponding product was delivered in good yields. However, compared with HFIP, TFE is less acidic and an inferior ionizing solvent, but is still a good H-bond donor. During the alkylation process, an H-bond is formed between the epoxide and the aggregates of TFE and a partial positive charge on the benzylic position in the transition state is stabilized, providing high regio- and stereoselectivity. Mayr's strategy was also employed with epoxides bearing an aliphatic substituent, but the reaction only led to the linear product in low yields and require longer reaction time (c: see Scheme 1.34).

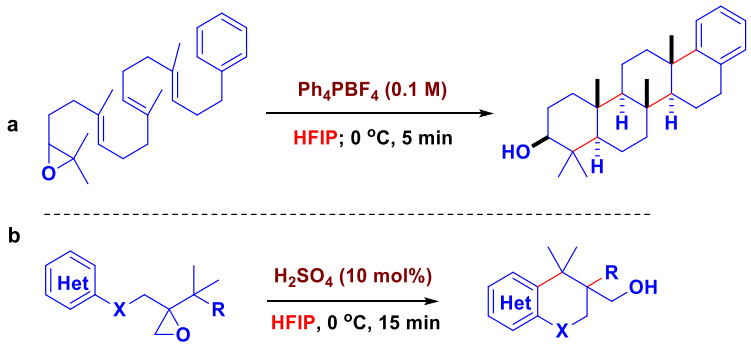



*Scheme 1.34. The ring-opening of epoxides in fluorinated solvent without catalyst.*

Intramolecular C–C bond-formation of epoxides is another important application of the ring-opening of epoxide reaction. In 2015, epoxide-initiated cation-olefin

[118] G. Li, J. Qu, *Chem. Commun*. **2010**, *46*, 2653.
[119] M. Westermaier, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 1638.

polycyclizations catalyzed by $Ph_4PBF_4$ in HFIP were reported by the group of Qu (a: see Scheme 1.35).[120] This study showed that di-, tri- and even tetracyclization of epoxy olefins could be achieved in the presence of an excess amount of $Ph_4PBF_4$ in HFIP in good to excellent yields. The mechanistic study indicates that the true catalyst for this reaction are traces of HF generated by the solvolysis of $BF_4^-$ in HFIP. Under these conditions, the oxygen of the epoxide is protonated and stabilized by HFIP, and the desired product is formed after an intermolecular nucleophile addition. A recent example of a cyclization with epoxides was also reported by Magauer and co-workers.[121] They developed a strategy to synthesize vicinal quaternary all-carbon centers *via* the cycloisomerization of neopentylic epoxides tethered to electron-rich aromatic rings catalyzed by sulfuric acid (b: see Scheme 1.35). A wide range of substrates were examined under mild condition in HFIP, and the corresponding products were prepared in high yields within 15 min. The reaction proved to be compatible with a large variety of functionalities such as thiophene and furan.

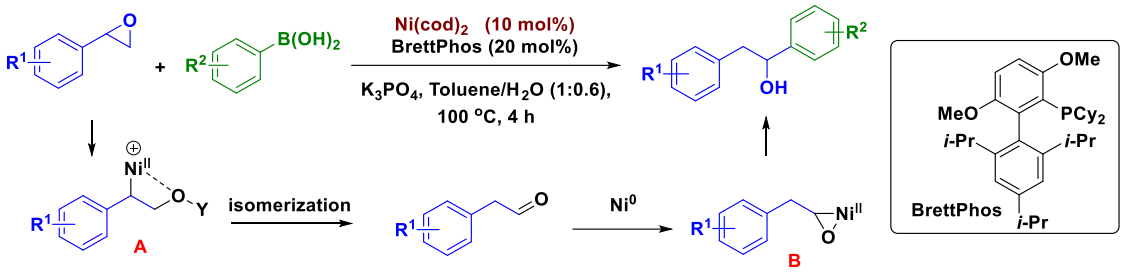



*Scheme 1.35. Cyclization of epoxides.*

Epoxides can also be employed as starting materials for cross-coupling reactions catalyzed by transition metals but give poor access to branched products. Usually, only the linear product was formed for the classical transition metal catalyzed cross-coupling arylation of epoxides. For example, the group of Doyle developed a method to produce α-substituted alcohols with excellent yields though the cross-coupling of styrenyl epoxides with boronic acids under nickel catalysis (Scheme 1.36).[122] Their mechanistic investigations emphasized that the regioselectivity was determined by the initial oxidative addition to access either a metalaoxetane **A** or the formation of $\eta^2$-

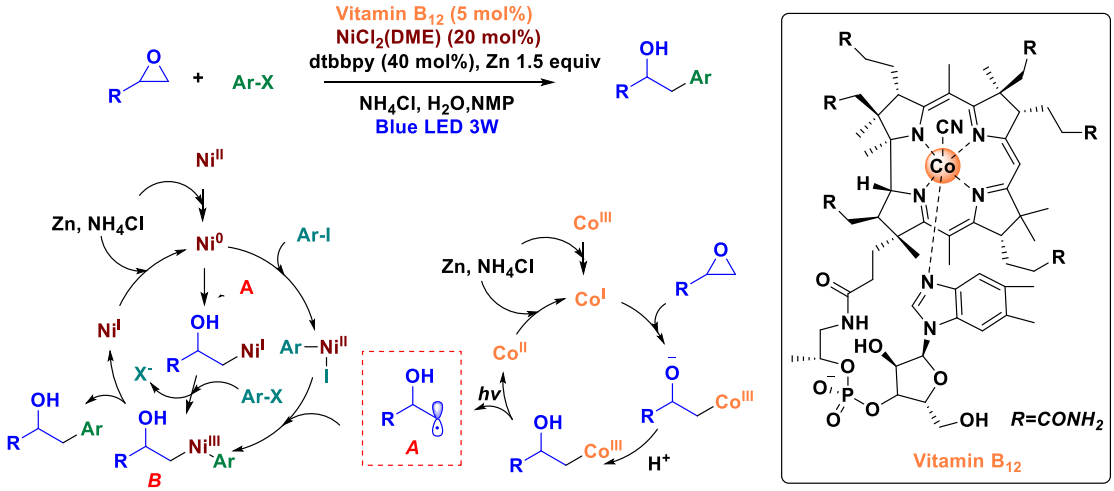
[120] Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2016**, *18*, 268.
[121] M. Schmid, K. R. Sokol, L. A. Wein, S. T. Venegas, C. Meisenbichler, K. Wurst, M. Podewitz, T. Magauer, *Org. Lett.* **2020**, *22*, 6526.
[122] D. K. Nielsen, A. G. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 6056.

oxanickellacycle **B**, following a β-hydride elimination and reinsertion of the aldehyde intermediate which is formed by isomerization of the metalaoxetane.




*Scheme 1.36. Ni-catalyzed cross-coupling of styryl epoxides with boronic acids.*

A recent study by Gryko and co-workers focused on the production of secondary alcohols via the ring-opening of epoxide with aryl halides by Co/Ni dual catalysis (Scheme 1.37).[123] A wide range of epoxides (aliphatic and aryl epoxides) and aryl halides were examined, and the corresponding linear products were obtained smoothly in 30 to 77% yields with high regioselectivity. The mechanism proposed was based on experimental studies and DFT calculations. A natural cobalt complex vitamin $B_{12}$ was employed as catalyst and generated a nucleophilic $Co^{I}$ complex in the presence of a reducing agent such as Zn. The epoxide was opened by the bulky vitamin $B_{12}$ catalyst from the less substituted position, which is the key for the regioselectivity. Due to the light-sensitive cobalt–carbon bond, a primary radical was generated under blue light by the homolytic



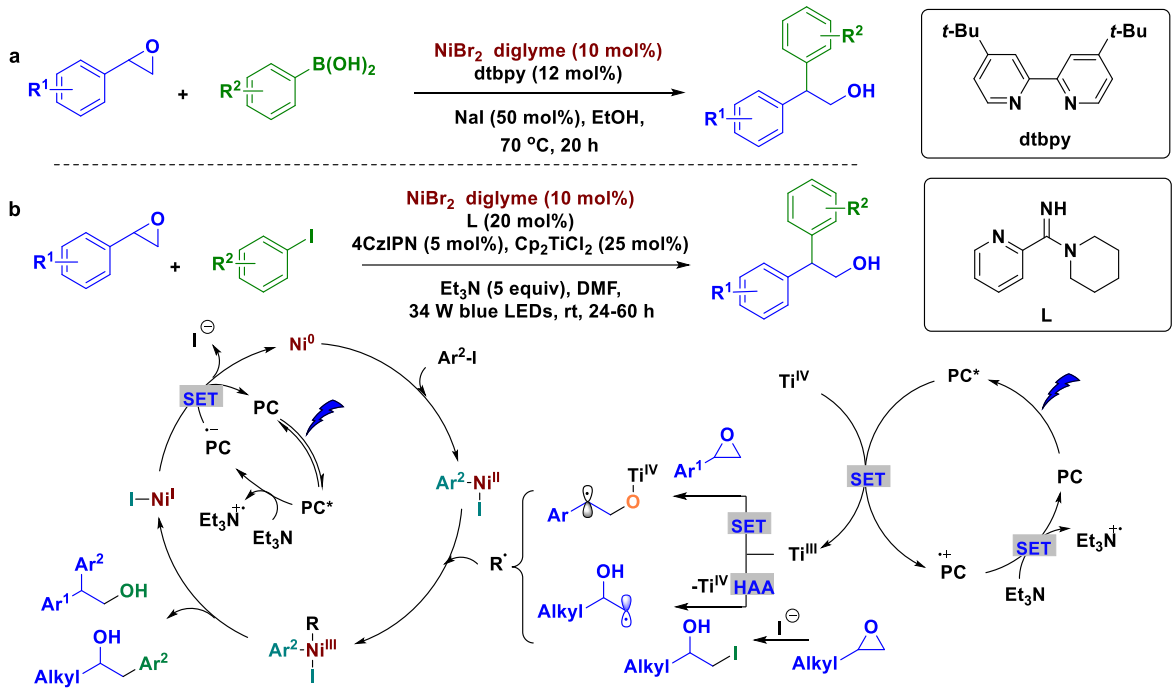

*Scheme 1.37. Regioselectivity in ring opening of epoxides with aryl halides by Co/Ni catalysis.*

[123] A. Potrząsaj, M. Musiejuk, W. Chaładaj, M. Giedyk, D. Gryko, *J. Am. Chem. Soc*. **2021**, *143*, 9368.

cleavage of the Co−C bond in alkyl cobalamin. The newly formed primary radical **A** then participates in the Ni-catalyzed cycle: oxidative addition of an aryl halide with $Ni^0$ gives an aryl $Ni^{II}$ species, which reacts with the primary radical from the Co-catalyzed cycle to form intermediate **B**. Alternatively, intermediate **B** can be generated from the interception of primary radical by $Ni^0$ before undergoing an oxidative addition. The desired linear selective product was produced following the reductive elimination of **B**.

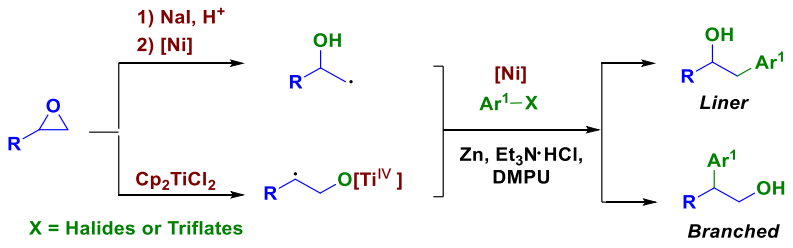
Although there are not many reports about transition metal catalyzed cross-coupling arylation of epoxide to access branched products, a few strategies were recently described. For example, Hu and co-workers reported a Ni-catalyzed Suzuki-type cross-coupling of boronic acids with epoxides (a: see Scheme 1.38).[124] A range of substituted alcohol products was produced under mild reaction condition in yields up to 80%. Notably, the reaction was conducted without needing any exogenous base. The regioselectivity of the cross-coupling of styryl epoxides is different with that of aliphatic epoxides. The former selectively generates the branched product, while the latter leads to the formation of the linear product. A cross-electrophilic coupling of epoxides and (hetero)aryl iodides was also reported by Doyle and co-workers,[125] which employed [Ni], [Ti] and an organic photo-redox catalyst to access the desired alcohols (b: see Scheme 1.38). Three different types of epoxides, such as styrene oxides, cyclic epoxides and terminal aliphatic epoxides, were tested to furnish the corresponding cross-coupling products in 23% to 94% yields. The regioselectivity differs between aliphatic and styrene oxides. Only linear products were observed with aliphatic epoxides, but branched products were obtained with styrene oxides. Three different catalytic cycles were involved during the catalytic process (b: see Scheme 1.38). Firstly, the photocatalyst is excited and then reduces Ti(IV) to Ti(III) *via* a SET process. Then, the corresponding radical is generated *via* a SET process by Ti(III) with styrenyl epoxide. Finally, the radical formed participates in the Ni-catalyzed cross-coupling catalytic cycle to provide the branched product. The radical generation of terminal alkyl epoxides involves a halogen atom abstraction, resulting in the formation of the linear product.

[124] X. Lu, L. Yan, J. Li, J. Li, H. Zhou, R. Jiang, C. Liu, R. Lu, R. Hu, *Chem. Commun*. **2020**, *56*, 109.
[125] M. Parasram, B. J. Shields, O. Ahmad, T. Knauber, A. G. Doyle, *ACS Catal*. **2020**, *10*, 5821.




*Scheme 1.38. Cross-coupling reactions employing epoxides as starting materials.*

A remarkable strategy for controlling the regioselectivity of Ni-catalyzed cross-coupling arylation of styryl epoxide with aryl halides was reported by the group of Weix.[126] Epoxides were opened to produce substituted alcohols with aryl bromides, vinyl bromides, and vinyl triflates in high yields. Based on the mechanism that they proposed, the regioselectivity is determined via the formation of terminal or internal radicals (see Scheme 1.39). The use of NaI was critical as it gives the secondary alcohol from epoxide under acidic conditions with a terminal iodide, which can then generate a terminal radical in the presence of the Ni catalyst. The linear arylation product is thus obtained following the participation of the terminal radical in the catalytic cycle. On the other hand, the



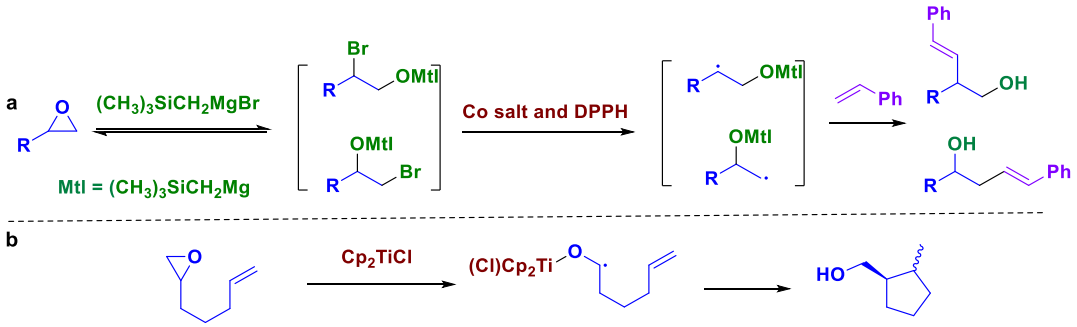

*Scheme 1.39. The mechanism of co-catalyst control in regioselective ring-opening of epoxides with aryl halides under Ni-catalysis.*

[126] Y. Zhao, D. J. Weix, *J. Am. Chem. Soc.* **2014**, *136*, 48.

epoxide can be opened by the other co-catalyst [$Ti^{III}$] to generate an internal radical by the combination of [$Ti^{III}$] with the epoxide oxygen, which results in the formation of the branched arylation product.

### 1.4.2. Reductive ring opening of epoxides for the synthesis of alcohols

Oshima and co-workers developed a cobalt-mediated Mizoroki–Heck-type reaction to produce homocinnamyl alcohols from epoxides and styrenes.[127] The mechanistic investigations showed that the epoxide ring can be opened via the addition of (*E*)-2-phenylethenyl Grignard reagents. Subsequently, a radical is generated by an SET process with an electron-rich Co-complex. Finally, the desired product was formed after it reacted with styrenes (**a**: see Scheme 1.40). This mechanism is completely different from the one involving the reductive addition of alkenes to epoxides. Similar radicals can be generated by reductive additions of epoxides with alkenes, although the radical is normally generated due to the combination of an epoxide with a paramagnetic transition metal. For example, in the Ti(III)-induced cyclization of epoxy-olefins developed by Nugent and Rajanbabu,[128] the radical is generated by a combination of a Ti-complex with the oxygen of the epoxide. The cyclization product is formed after the reductive addition of the alkene (**b**: see Scheme 1.40).

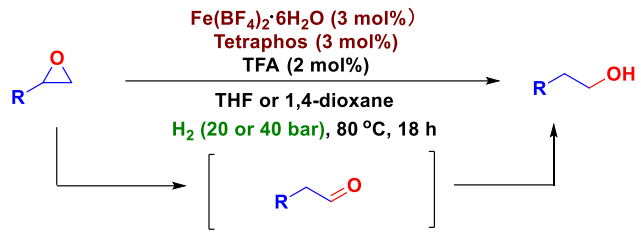



*Scheme 1.40. Mechanism of the generation of a radical for the addition of epoxides with olefins.*

The ring-opening of epoxides in the presence of a hydrogen donor is a valuable approach for the formation of primary aliphatic alcohols. Although epoxide ring-opening reactions offer versatile access to a variety of functional group patterns, the conversion of epoxides to primary aliphatic alcohols though reductive ring-opening of epoxides is still

[127] Y. Ikeda, H. Yorimitsu, H. Shinokubo, K. Oshima, *Adv. Synth. Catal.* **2004**, *346*, 1631.
[128] T. V. Rajanbabu, W. A. Nugent, *J. Am. Chem. Soc.* **1988**, *110*, 8561.

underdeveloped. The direct hydration of the corresponding alkene is the common pathway to access alcohols, but it typically leads to the Markovnikov-selective alcohols. On the other hand, direct hydration of alkenes to produce the anti-Markovnikov alcohols is more difficult. Recently, some strategies leading to the formation of the anti-Markovnikov alcohols by the reductive ring-opening of epoxides were described. Beller and co-workers developed a strategy using Fe as a catalyst, which is naturally abundant and has a low toxicity, for the regioselective hydrogenation of epoxides into primary alcohols in the presence of $H_2$ (Scheme 1.41).[129] A series of anti-Markovnikov alcohols including various natural products were prepared in 56 to 98% yield with high functional group tolerance, permitting functional groups such as double bonds, ester, halides, etc. The mechanistic study showed that an aldehyde intermediate is generated through a Meinwald rearrangement in the presence of the iron/tetraphos complex. Then, the desired anti-Markovnikov alcohols are formed after hydrogenation of the aldehyde intermediate. During the whole catalytic process, the iron/tetraphos complex acts as an active catalyst for both the Meinwald rearrangement and the hydrogenation. However, the reaction is limited to terminal epoxides, since non-terminal epoxides generate the corresponding ketone intermediate instead of the aldehyde, which is significantly harder to reduce.

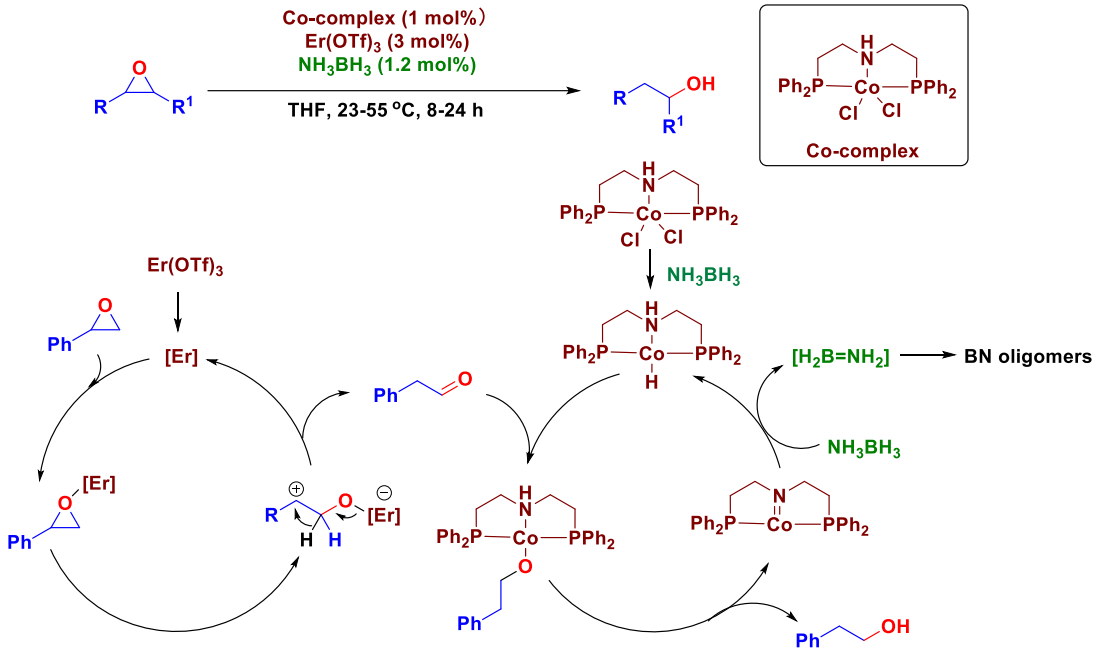



*Scheme 1.41. Iron-catalyzed regioselective hydrogenation of terminal epoxides to alcohols.*

Another interesting strategy to produce anti-Markovnikov alcohols though the reductive ring-opening of terminal and internal epoxides was reported by Werner and co-workers (see Scheme 1.42).[130] A cobalt pincer catalyst was employed in a low catalyst loading (1 mol%) and allows the reaction to be conducted at lower temperature (⩽55 °C). The mechanistic studies indicated that the regioselectivity was controlled by using a highly efficient isomerization catalyst, $Er(OTf)_3$. The epoxide can be activated by the erbium-salt to form a ring opened intermediate containing a carbocation at the benzylic position

[129] W. Liu, W. Li, A. Spannenberg, K. Junge, M. Beller, *Nat. Catal.* **2019**, *2*, 523.
[130] X. Liu, L. Longwitz, B. Spiegelberg, J. Tönjes, T. Beweries, T. Werner, *ACS Catal.* **2020**, *10*, 13659.

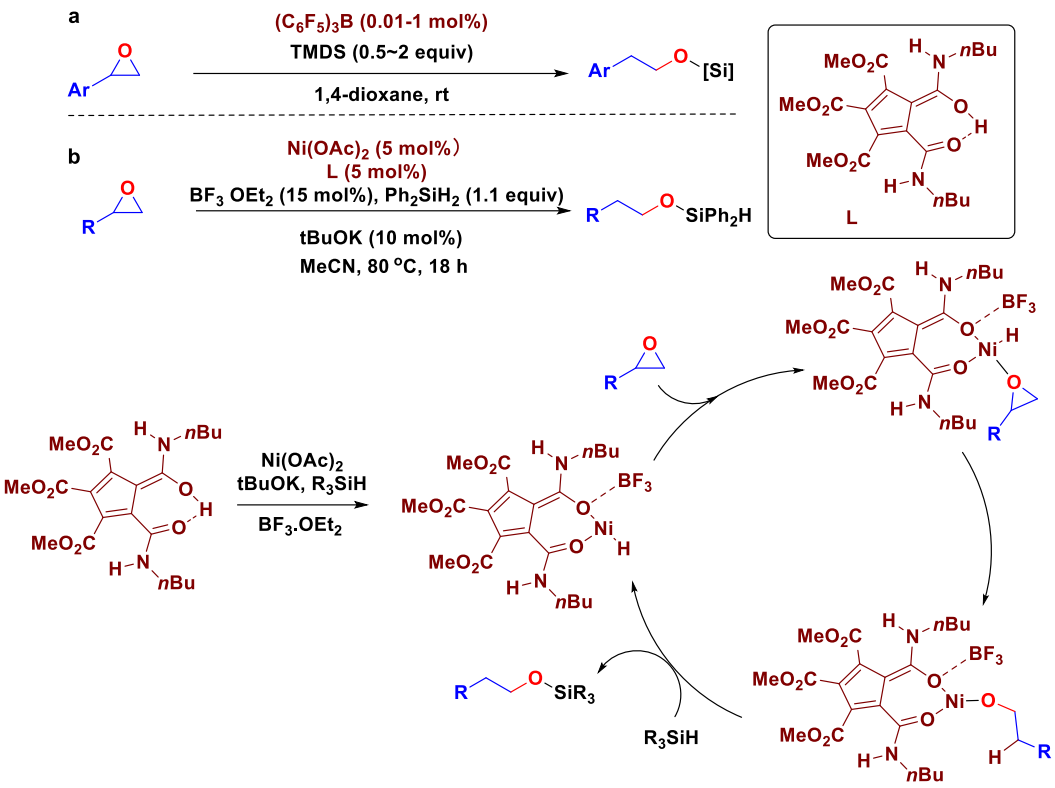
– the key step for the regioselectivity. The newly formed carbocation intermediate undergoes a [1,2]-hydride shift to generate the aldehyde or ketone intermediate. On the other hand, the Co-complex is reduced by ammonia borane which can then reduce the aldehyde or ketone to yield the desired anti-Markovnikov alcohols. The Co-complex can be reduced and re-enter to the catalytic cycle in the presence of ammonia borane which was used as H-bond donor.




*Scheme 1.42. Co-catalyzed regioselective hydrogenation of terminal and internal epoxides to alcohols.*

The hydride source is also an important factor for the hydration of epoxides. Besides hydrogen gas and borane, silanes can also be employed as hydride source for the reductive ring-opening of epoxides. The latter produce a range of silyl ethers which can be easily hydrolyzed to produce primary alcohols in the presence of a base. For example, Chang and co-workers employed the highly electron-deficient aryl borane $B(C_6F_5)_3$ as catalyst for the hydrosilylation of epoxides (**a**: see Scheme 1.43).[131] Silanes are used as a hydrogen source to generate the Piers' borane $(C_6F_5)_2BH$. Mechanistic studies indicate that in the presence of epoxides, the true catalytic species alkyloxy(diaryl)borane is generated with $(C_6F_5)_2BH$. Although the silyl ethers can be prepared in high yields, the control of the regioselectivity is difficult. Another strategy using silanes as a hydride source was

[131] J. Zhang, S. Park, S. Chang, *Chem. Commun*. **2018**, *54*, 7243.




*Scheme 1.43. The ring-opening hydrosilylation of epoxides employed hydrosilanes as hydride source.*

reported by Lambert and co-workers. [132] The reaction was co-catalyzed by pentacarboxycyclopentadienyl (PCCP) diamide Ni-complex and a Lewis acid (**b**: see Scheme 1.43). A range of terminal and internal epoxides were examined and showed high regioselectivities and high yields. The mechanistic studies show that the [Ni] catalyst can be activated by the PCCP ligand, *t*BuOK and silane. The activated [Ni] intermediate combines with the epoxide oxygen which is followed by a hydride insertion to access the Ni-alkoxide intermediate. This intermediate then reacts with the silane to produce the desired product and regenerate the activated [Ni] intermediate.

## 1.5. Conclusion of Chapter 1 and the aim of this thesis

Lewis and Brønsted acid-catalyzed reactions are common in homogeneous catalysis. Yet, in recent years the association of those catalysts with HFIP as a solvent allows to push the boundaries of several transformations to access new families of compounds. However, the mechanisms of acid catalysis using HFIP as solvent are more complicated due to HFIP's ability to stabilize cationic intermediates, its H-bond donating ability or its

[132] K. A. Steiniger, T. H. Lambert, *ChemRxiv*, **2019**, https://doi.org/10.26434/chemrxiv.9936389.v1

cooperative interactions with acids. Recent findings indicate that in many Lewis and Brønsted acid-catalyzed transformations conducted in HFIP, the solvent plays an important and, sometimes, intimate role. The catalytic process involves cooperation between catalyst, substrates and HFIP hydrogen-bond clusters, which may provide Lewis- or Brønsted acid-assisted-Brønsted acid catalysis or hidden Brønsted acid catalysis. Boronic acids are catalysts of recent interest for organic synthesis, such as for the Friedel-Crafts alkylation, Beckmann rearrangement or transposition reactions. They are often thought to act as a mild organic Lewis acid catalyst or through the reversible formation of a covalent bond with hydroxyl groups. However, it might also generate a strong Brønsted acid, which could be the true catalytic species. Based on the properties of boronic acids and of HFIP described above, the use of boronic acid catalysts in HFIP potentially different reaction mechanism compared to other solvents can be expected. Thus, the aim of the second chapter is identifying the true catalytic mechanism of boronic acid catalyzed Friedel-Crafts alkylation and Beckmann rearrangement in HFIP.

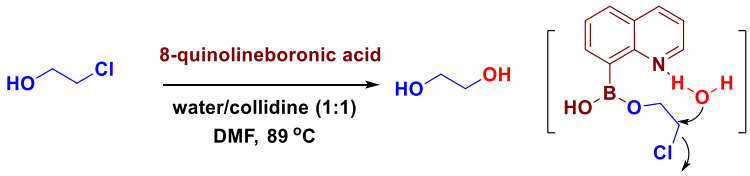
Based on previous reports, the common methods to prepare 1,1-diarylalkanes remain limited with the substrates scope, especially with substrates bearing strong electron withdrawing groups. Some methods have been designed by our group in Friedel-Crafts alkylation and hydroarylation, but most of them require harsh reaction conditions. In addition, the products arising from mono-functionalizations are difficult to use directly for further derivatizations. To go beyond, the idea for this thesis was to use epoxide derivatives to generate primary aliphatic alcohols that could be engaged in further transformations. Furthermore, common methods of preparing 1,1,2-triarylethanes typically require pre-functionalized nucleophiles or electrophiles. Finding simpler approaches for the direct formation of 1,1,2-triarylethanes is clearly underexplored. New methodologies concerning the ring-opening of epoxides with arene nucleophiles have been recently reported, as epoxides could serve as a gateway to densely functionalized molecules in medicinal chemistry, crop science, and material science. However, those reactions remain limited in various ways. Lewis or Brønsted acid catalyzed ring-opening of epoxide are mainly limited to electron-rich styrene oxides. Regardless of the mechanism involved, most epoxide-opening reactions do not take advantage of the alcohol generated, such that the direct 1,2-dicarbofunctionalization of epoxide has not been reported. The aims of chapter 3 and 4 are to employ epoxides in arylation reactions

to prepare 1,1-diarylalkanes, 1,1,2-triarylethanes and 1,2-diarylethanes via primary alcohols by Lewis or Brønsted acid catalysis in HFIP.

# 2. Boronic Acids as Lewis Acid Catalysts for the Activation of Hydroxyl Groups: Myth or Reality?

## 2.1. Scientific background and context

Boronic acid catalysis has emerged as a mild method for promoting a wide variety of reactions. It has been proposed that the mode of catalysis involves Lewis acid or covalent activation of hydroxyl groups by boron, which promotes excellent chemoselectivity. The first example of boronic acid catalysis was reported by Letsinger and coworkers.[133] 8-Quinolineboronic acid was employed as a catalyst for the hydrolysis of chloroethanol to produce diols in DMF/water in the presence of collidine as a base. Mechanistic studies indicated that the boronic acid acted as a binding site, forming a covalent B–O bond. The authors concluded that the quinoline enables the activation of water to serve as a nucleophile, facilitating the substitution reaction in an intramolecular fashion (Scheme 2.1).

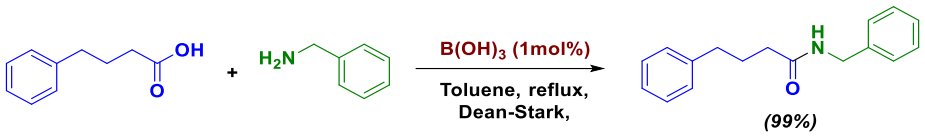



*Scheme 2.1. Boronic acid-catalyzed hydrolysis of chloroethanol.*

After this report, there was little immediate follow-up work. However, interest in boronic acid catalysis has revived in the past two decades, and several boronic acid-catalyzed methods have been developed. The most popular example is the direct amidation of carboxylic acids with amines catalyzed by boronic acids or boric acid, which allows amides and even some peptides to be produced smoothly. For example, Fürstner and co-workers developed a strategy for the direct amination of carboxylic acids with amines by boric acid catalysis (Scheme 2.2).[134] Various carboxylic acids in combination with primary or secondary amines and even anilines were employed to produce the corresponding amides with excellent yields (up to 99%), the reaction being compatible

[133] (a) R. L. Letsinger, D. B. MacLean, *J. Am. Chem. Soc.* **1963**, *85*, 2230; (b) R. L. Letsinger, S. Dandegaonker, W. J. Vullo, J. D. Morrison, *J. Am. Chem. Soc.* **1963**, *85*, 2223; (c) R. L. Letsinger, J. D. Morrison, *J. Am. Chem. Soc.* **1963**, *85*, 2227.
[134] (a) P. Tang, H. Krause, A. Fürstner, *Org. Synth*. **2005**, *81*, 262; (b) P. Tang, H. Krause, A. Fürstner, *Org. Synth*. **2012**, *89*, 432.

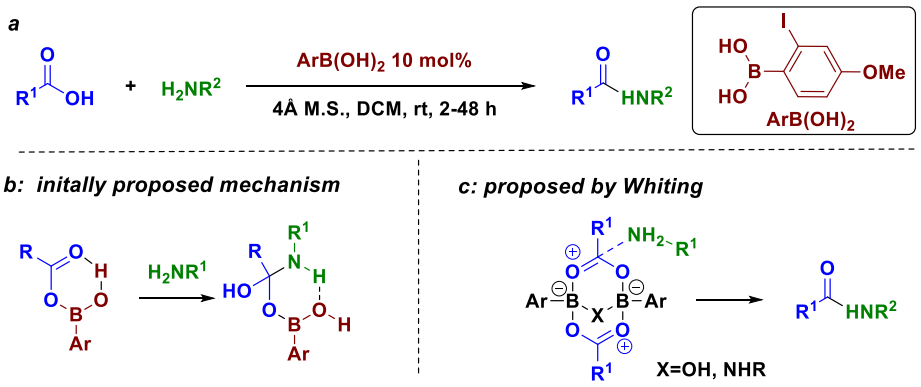
with alkenes, heteroarenes and cyclopropanes. However, the reaction required high temperature along with the use of a Dean-Stark apparatus to remove the by-product water from the reaction system.




*Scheme 2.2. Boric acid-catalyzed direct amination of carboxylic acid.*

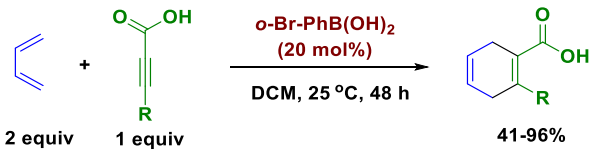
A few years later, Hall and co-workers developed a method employing *ortho*-iodo or bromoarylboronic acid as catalyst for the direct amidation of carboxylic acids under mild conditions (room temperature).[135] A wide range of primary and secondary amines was employed to produce the corresponding amides in excellent yields (up to 99%) (a: see Scheme 2.3). The authors concluded from mechanistic studies that the *ortho*-iodide can form a strong H-bond with amines, lowering the activation energy and accelerating the generation of the desired product. The general mechanism of boronic acid-catalyzed direct amidation of carboxylic acids was studied on many occasions. The initially proposed mechanism suggested that the key step was the formation of a B–O covalent bond, which would generate an acyloxy-boron electrophile.[136] After addition of the amine to the carbonyl, the resulting hemiaminal intermediate would be stabilized by an intramolecular H-bond (b: see Scheme 2.3). Collapse of the tetrahedral intermediate would produce the corresponding amide and allow the turn-over of the catalyst. Recently, Whiting and co-workers [137] proposed a different mechanism for boron-catalyzed direct amidation reactions on the basis of extensive experimental and theoretical studies (c: see Scheme 2.3). The proposed key intermediate is a dehydrated bicyclic dimeric intermediate containing a B-X-B bridge (X=OH or NHR). The electrophilic intermediate would be formed by the dimerization of acyloxy-boron species and reacts with an amine or with a boronic acid/amine complex to generate the amide.

[135] (a) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed*. **2008**, *47*, 2876; (b) N. Gernigon, R. M. Al-Zoubi, D. G. Hall, *J. Org. Chem*. **2012**, *77*, 8386.
[136] N. Gernigon, R. M. Al-Zoubi, D. G. Hall, *J. Org. Chem*. **2012**, *77*, 8386.
[137] S. Arkhipenko, M. T. Sabatini, A. S. Batsanov, V. Karaluka, T. D. Sheppard, H. S. Rzepa, A. Whiting, *Chem. Sci.*, **2018**, *9*, 1058.




*Scheme 2.3. Boronic acid-catalyzed direct amidation reaction.*

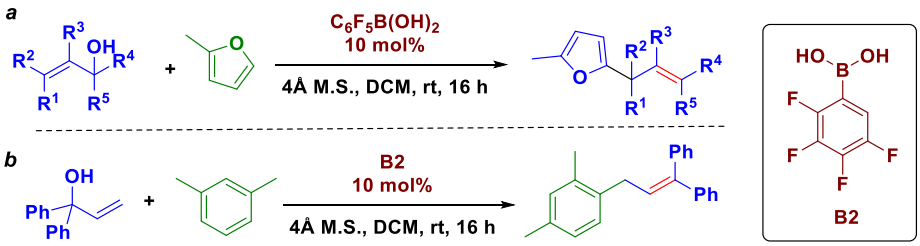
The same activation mode can also be applied to other reactions that benefit from the electrophilic activation of carboxylic acids, such as the esterification of carboxylic acids with alcohols [138] and anhydride formation from vicinal dicarboxylic acids. [139] The mechanism, which involves reversible B–O bond formation between boronic acid and carboxylic acid, allows the reactions to be conducted under mild conditions and avoids the use of coupling reagents. In addition, the use of boronic acid catalysis in the process of direct activation of carboxylic acids prevents the incompatibility of carboxylic acid groups with other functional groups or bases. In a representative example, Hall and co-workers reported the Diels–Alder cycloaddition of dienes with unsaturated carboxylic acids under boronic acid catalysis (Scheme 2.4).[140] A wide range of cycloadducts were produced in excellent yields from 2-alkynoic acids with various dienes. Mechanistic studies indicated that the reversible formation of a B–O bond between the boronic and carboxylic acids lowers the LUMO energy of the unsaturated carboxylic acid, speeding up the reaction under mild conditions.




*Scheme 2.4. Boronic acid-catalyzed Diels–Alder cycloadditions of unsaturated carboxylic acids.*

[138] T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5047.
[139] A. Sakakura, T. Ohkubo, R. Yamashita, M. Akakura, K. Ishihara, *Org. Lett.* **2011**, *13*, 892.
[140] H. Zheng, D. G. Hall, *Tetrahedron Lett.* **2010**, *51*, 3561.

The other important application of boronic acid catalysis is the electrophilic activation of alcohols. Boronic acid-catalyzed reactions of alcohols include Friedel-Crafts alkylation, cycloadditions, 1,3-allylic transposition and the dehydrative cyclization of alcohols bearing pendant nucleophiles. It has been proposed that the formation of a covalent B–O bond between the alcohol and the boronic acid promotes the complete or partial ionization of the C–O bond of the alcohol, allowing the desired product to be formed following a nucleophilic addition or rearrangement. For example, the Friedel-Crafts allylation reaction of allylic alcohols with arenes under boronic acid catalysis was reported by McCubbin and co-workers (a: see Scheme 2.5).[141] The pentafluorophenylboronic acid catalyst promotes the formation of a carbocation from the corresponding alcohol, and a subsequent trapping by electron-rich arenes or heteroarenes gives the Friedel-Crafts products with excellent yields. The drawback of this reaction is that the nucleophile scope was limited to electron-rich arenes; even anisole was not sufficiently nucleophilic for this reaction. A similar strategy for boronic acid-catalyzed Friedel-Crafts alkylation starting from allylic and benzylic alcohols was reported by Hall and co-workers (b: see Scheme 2.5). [142] 2,3,4,5-Tetrafluorophenylboronic acid was employed as a catalyst, which significantly improved the scope of the arene nucleophiles to include slightly activated or unactivated arenes, such as indole, furan, xylenes and etc. The same catalyst was also employed for the 1,3-transposition of allylic alcohols[143] and cyclization[144] of alcohols bearing a pendant nucleophile to produce various classes of useful compounds in high yields. The mechanism of 1,3-transposition of allylic alcohols was proposed to occur through two possible pathways. The first involves the formation of a B–O bond where the

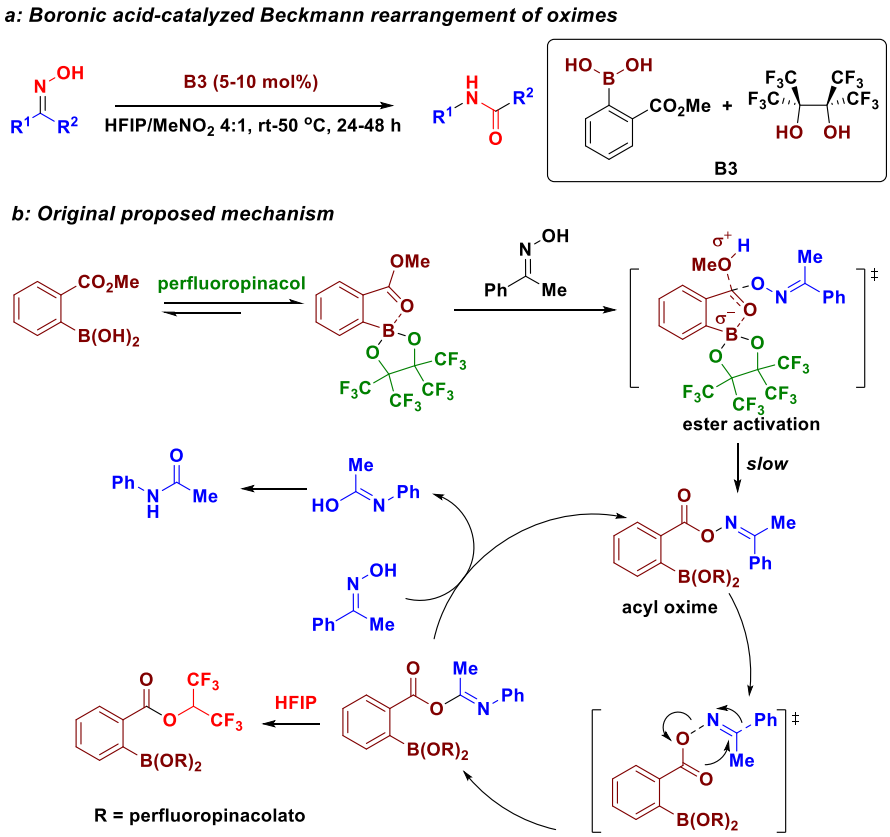



*Scheme 2.5. Boronic acid-catalyzed Friedel-Crafts allylation reactions of allylic alcohols.*

[141] J. A. McCubbin, H. Hosseini, O. V. Krokhin, *J. Org. Chem.* **2010**, *75*, 959.
[142] C. L. Ricardo, X. Mo, J. A. McCubbin, D. G. Hall, *Chem. Eur. J.* **2015**, *21*, 4218.
[143] H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci.*, **2011**, *2*, 1305.
[144] H. Zheng, S. Ghanbari, S. Nakamura, D. G. Hall, *Angew. Chem. Int. Ed*. **2012**, *51*, 6187.

boronic acid acts as a directing group. The second pathway involves the formation of an allylic carbocation, and the resulting tetrahedral boronate counterion recombines with the carbocation to form the target product.

Recently, the boronic acid-catalyzed Beckmann rearrangement of oximes in the presence of perfluoropinacol was disclosed by Hall and co-workers (Scheme 2.6).[145] A wide variety of diaryl, aryl-alkyl, heteroaryl-alkyl, and dialkyl oximes were employed, reacting at room-temperature to deliver amides in high yields (up to 99%). Mechanistic studies indicated that a boronic ester was formed by the diol and boronic acid. The rate-limiting step was found to be the formation of an acyl oxime boronic ester. The acyl oxime then undergoes a rearrangement to generate the acyl imidate. The amide product is generated following a transesterification of the acyl imidate with a free oxime. The mechanism was evaluated through control experiments, NMR and kinetic studies in order to explain the active role of the boryl unit of the catalyst in both steps of this unique and selective mode of N−OH bond activation.




*Scheme 2.6. Boronic acid-catalyzed Beckmann rearrangement of oximes.*

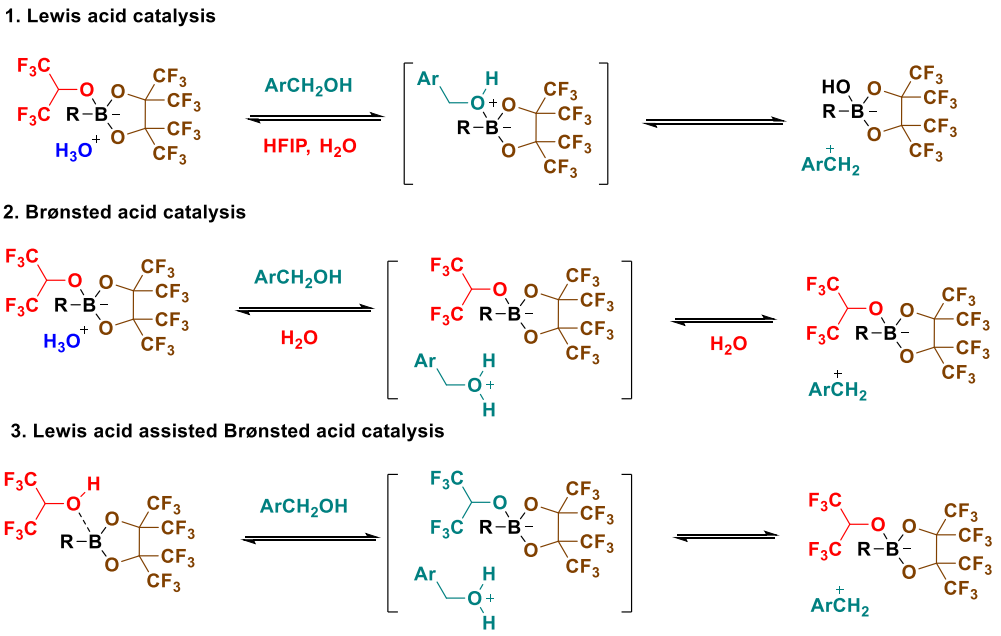
[145] X. Mo, T. D. R. Morgan, H. T. Ang, D. G. Hall, *J. Am. Chem. Soc*. **2018**, *140*, 5264.

As described above, boronic acid-catalyzed reactions involving hydroxyl groups have been proposed to involve Lewis acid or covalent activation, achieving excellent chemoselectivity due to the mild nature of the catalyst, but limited evidence exists to support these claims. In-depth studies into the catalytic mechanism have been performed in the case of carboxylic acids, whereas only preliminary mechanistic evidence exists for the reactions of alcohols and oximes. If we consider the Friedel-Crafts reaction of benzylic alcohols catalyzed by ferrocenium boronic acid salt (**B1**) in HFIP/$MeNO_2$ (4:1) reported by Hall and co-workers,[146] different potential ferrocenium salt catalysts were examined as control experiments. Interestingly, those lacking a boron-based group still gave the product in 15% yield in the presence of 4 Å M.S. Nevertheless, the authors ruled out the possibility that Brønsted acid catalysis might have been responsible for the reactivity based on the observation that TFA did not catalyze the reaction. However, this result remains insufficient to rule out Brønsted acid catalysis for a number of reasons. First, the arylboronic acid catalyst systems required for reactions involving alcohols and oximes (**B1**-**B3**, Scheme 2.8) are substantially more electrophilic than those used for the activation of carboxylic acids. More specifically, the boronic acid catalysts used for the activation of alcohols and oximes require either multiple electron-withdrawing groups, cationic boronic acids or complexation with highly electronically deactivated diols. Second, it must be stressed that another critical parameter in these reactions is the solvent. Our group as well as many others have pointed out the enabling effect of solvents, such as (HFIP) and nitromethane ($MeNO_2$) on Brønsted and Lewis acid-catalyzed reactions through the formation of an H-bond network.[147] In the case of HFIP, we emphasized that the role of the catalysts was to significantly increase the acidity of an H-bond cluster of HFIP, which was the true catalytically active species. Furthermore, boronic acids could, in principle, form covalent bonds with a protic solvent such as HFIP to produce species that could have a drastically different p$K_a$ than the parent boronic acid. However, this possibility was never taken into consideration in the initial studies by the group of Hall.

Following discussions between our group and the Hall group regarding those issues, an in-depth mechanistic investigation to determine the active species for **B3** catalyzed-Friedel-Crafts arylation of benzylic alcohols with arenes was reported by Hall and co-

[146] X. Mo, J. Yakiwchuk, J. Dansereau, J. A. McCubbin, D. G. Hall, *J. Am. Chem. Soc.* **2015**, *137*, 9694.
[147] V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun.* **2020**, *56*, 11548

workers in 2019. [148] The role of **B3** catalyst was re-evaluated by employing perfluoropinacol as a co-catalyst for the Friedel-Crafts arylation of benzylic alcohols with arenes. A tetra-coordinated species was detected by $^{13}B$ NMR and ESI-MS experiments, and the reaction can be inhibited by the employment of the hindered based 2,6-di-*tert*-butylpyridine (2,6-DTBP). Thus, they proposed that perfluoropinacol could react with boron to form a boronic ester, thereby becoming sufficiently Lewis acidic to activate either HFIP or adventitious water. Consequently, several modes of activation for the benzylic alcohols were proposed (Scheme 2.7): 1) the formed boronic ester acts as a strong Lewis acid to directly activate alcohols with the assistance of HFIP; (2) an acidic proton was generating by the combination of a boronic ester with HFIP, and this proton is then captured by residual water, which delivers it to the alcohol, and (3) the combination of a boronic ester with HFIP increases the acidity of the proton of HFIP and provides a Lewis acid-assisted Brønsted acid catalysis mode. They also pointed out that except for the above-mentioned catalysis modes, there may exist other activation modes and further mechanistic investigations are needed.

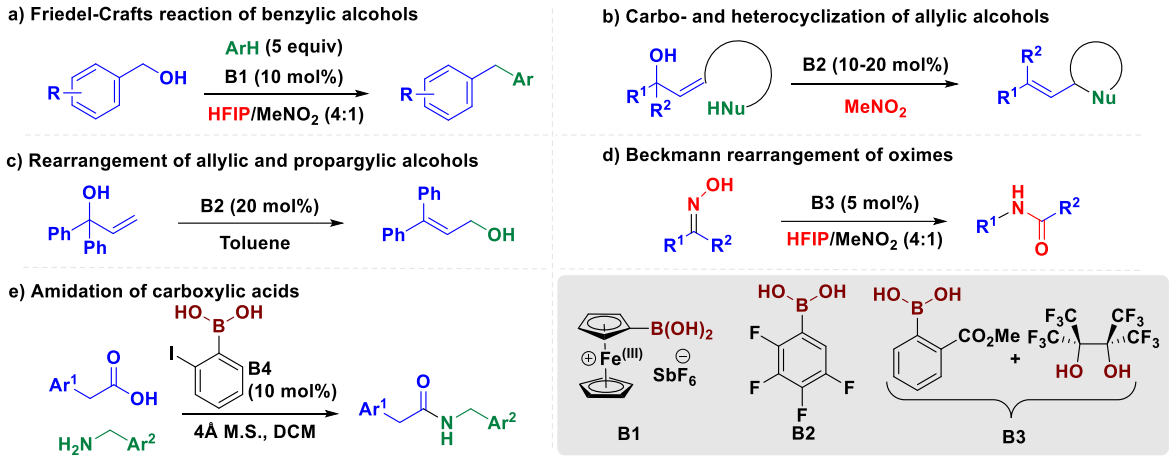



*Scheme 2.7. Mechanistic proposal for the activation of the benzyl alcohols.*

In parallel, to get a deeper insight into the catalytic mechanisms enabled by boronic acids for reactions of alcohols and oximes, we reinvestigated four representative examples

[148] H. T. Ang, J. P. G. Rygus, D. G. Hall, *Org. Biomol. Chem.* **2019**, *17*, 6007.

(Scheme 2.8),[149] 1) using control experiments with Brønsted acids; 2) observing the influence of hindered Brønsted bases on the catalytic reactions; and 3) determining experimental Gutmann-Beckett values for a range of boronic and Brønsted acids in the reaction solvents of interest.

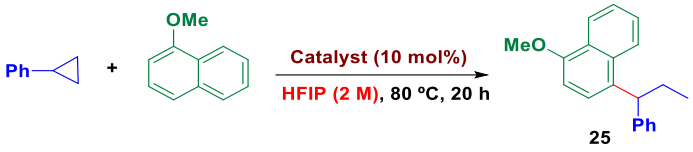



*Scheme 2.8. Representative boronic acid-catalyzed transformations of alcohols, oximes and carboxylic acids.*

[149] (a) H. C. Zheng, S. Ghanbari, S. Nakamura, D. G. Hall, *Angew. Chem. Int. Ed.* **2012**, *51*, 6187; (b) X. B. Mo, T. D. R. Morgan, H. T. Ang, D. G. Hall, *J. Am. Chem. Soc.* **2018**, *140*, 5264; (c) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876; (d) H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci*. **2011**, *2*, 1305.

## 2.2. Discussion

### 2.2.1. Fortuitous discovery




| Entry | Catalyst | Additive | Yield [%][a] |
|---|---|---|---|
| 1.1 | TfOH | | 97 |
| 1.2 | **B1** | | 68 |
| 1.3 | **B1** | 2,6-DTBP (15 mol%) | <1 |
| 1.4 | **B2** | | <1 |
| 1.5 | **B3** | | 96 |
| 1.6 | **B3** | 2,6-DTBP (15 mol%) | <1 |
| 1.7 | **B4** | | <1 |
| 1.8 | HCl | | 94 |
| 1.9 | $H_2SO_4$ | | 92 |
| 1.10 | CSA | | 95 |
| 1.11 | TFA | | 36 |
| 1.12 | $(COOH)_2$ | | 12 |
| 1.13 | $CH_3CO_2H$ | | <5 |
| 1.14 | B(OH)3 | | <5 |

*[a] Yields were determined by $^1H$ NMR using hexamethyldisiloxane as an external standard; CSA = camphorsulfonic acid.*

*Table 2.1. Comparison between boronic and Brønsted acids for the catalytic ring-opening hydroarylation of phenylcyclopropane.*

Recent research in our laboratory and others has shown the enabling effect of solvents such as HFIP[150] and nitromethane[151] on Brønsted acid catalyzed reactions, including some of the same types of reactions reported to be catalyzed by boronic acids. During the course of our investigations on the TfOH-catalyzed ring-opening hydroarylation of unactivated cyclopropanes in HFIP (Table 2.1, entry 1.1), we were surprised to observe

[150] (a) V. D. Vuković, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085; (b) E. Richmond, J. Yi, V. D. Vuković, F. Sajadi, C. N. Rowley J. Moran, *Chem. Sci.* **2018**, *9*, 6411; (c) E. Richmond, V. D. Vuković, J. Moran, *Org. Lett* **2018**, *20*, 574; (d) L. Lu, H. Liu, R. Hua, *Org. Lett*. **2018**, *20*, 3197.

[151] (a) M. Dryzhakov, M. Hellal, E. Wolf, F. C. Falk, J. Moran, *J. Am. Chem. Soc.* **2015**, *137*, 9555; (b) M. Dryzhakov, J. Moran, *ACS Catal.* **2016**, *6*, 3670; (c) M. Dryzhakov, E. Richmond, G. Li, J. Moran, *J. Fluor. Chem*. **2017**, *193*, 45

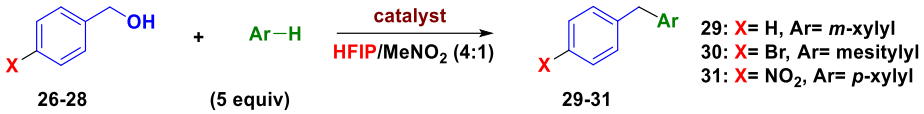
that two prototypical boronic acid catalyst systems used for the activation of alcohols and oximes (**B1** and **B3**), which normally are considered as mild organic Lewis acids, mediated the ring-opening of phenylcyclopropane to generate product **25** with excellent yields (entries 1.2 and 1.5). Given the absence of an OH functional group in the substrate and the absence of Frustrated Lewis Pair catalysts, this reaction cannot involve covalent exchange or direct Lewis acid catalysis. The only plausible mechanism appears to be hidden Brønsted acid catalysis generated though the interaction of the boronic acid with water, HFIP (in the case of **B1**) or diol (in the case of **B3**). In agreement with this suggestion, the presence of 15 mol% of 2,6-di-*tert*-butylpyridine, a bulky Brønsted base commonly used to distinguish between boron-based Lewis and Brønsted acid catalysis,[152] completely inhibited the reaction, consistent with Brønsted acid catalysis (entries 1.3 and 1.6). Additionally, Brønsted acids weaker than TfOH were not effective catalysts (entries 1.10-1.13), leading us to suspect that very strong Brønsted acids might have been produced from the boronic acids under the reaction conditions. These observations led us to wonder whether certain previously reported boronic acid-catalyzed reactions might also simply be the result of hidden Brønsted acid catalysis.

Herein, we test this hypothesis by comparing boronic and Brønsted acid catalysts against seven reported boronic acid-catalyzed reactions spanning the five representative reports depicted in Scheme 2.8. Although the boronic acid-catalyzed direct amidation of carboxylic acids with amines was studied many times, the catalytic mechanism was confirmed as a truly boronic acid catalysis, but we still examined it due to the difficult to repeat those reactions. We put these results into perspective by correlating the observed reactivity promoted by the various boronic and Brønsted acids with their inductive influence on triethylphosphine oxide (Gutmann-Beckett method). We find that in nearly all the tested reactions involving activation of alcohols and oximes, hidden Brønsted acid catalysis, rather than true boronic acid catalysis, is likely the dominant mechanism behind the reported reactivity.

[152] (a) H. C. Brown, B. Kanner, *J. Am. Chem. Soc.* **1966**, *88*, 986; (b) P. G. Gassman, D. A. Singleton, *J. Am. Chem. Soc.* **1984**, *106*, 7993; (c) C. Bergquist, B. M. Bridgewater, C. J. Harlan, J. R. Norton, R. A. Friesner, G. Parkin, *J. Am. Chem. Soc.* **2000**, *122*, 10581; (d) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem. Int. Ed*. **2006**, *45*, 793; (e) M. Vayer, R. Guillot, C. Bour, V. Gandon, *Chem Eur. J.* **2017**, *23*, 13901.

### 2.2.2. Friedel-Crafts reaction of benzylic alcohols

The first set of reactions examined was the Friedel-Crafts reaction of primary benzylic alcohols **26-28** catalyzed by hexafluoroantimonate salt **B1** in HFIP/$MeNO_2$ (4:1) (Table 2.2). The three reported substrates examined reacted as described (entry 2.1) but did not react in the presence of 2,6-DTBP (entry 2.2). The use of the weak base 2,6-di-*tert*-butylpyridine may be questioned, because HFIP can be deprotonated to form the alkoxide, which then combines with the boron center of the catalyst to form a boronate, which



26-28 29-31

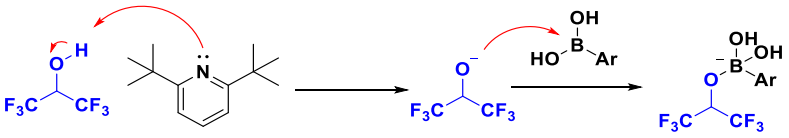
| Entry | Catalyst | Additive | Yield 29 [%] [b] | Yield 30 [%] [b] | Yield 31 [%] [c] |
|---|---|---|---|---|---|
| 2.1 | **B1** | | 95 | 94 | 40 |
| 2.2 | **B1** | 2,6-DTBP[d] | <1 | <1 | <1[e] |
| 2.3 | **B2** | | <1 | <1 | <1 |
| 2.4 | **B3** | | 62 | 19 | 5 |
| 2.5 | $HSbF_6 \cdot 6H_2O$ | | 79 | 40 | 45 |
| 2.6 | TfOH | | 98 | 98 | 95 |
| 2.7 | HCl | | 90 | 92 | <1 |
| 2.8 | $H_2SO_4$ | | 95 | 94 | 90 |
| 2.9 | CSA | | 95 | 96 | <1 |
| 2.10 | TFA | | 92 | <1 | <1 |
| 2.11 | $(COOH)_2$ | | 92 | 47 | <1 |
| 2.12 | $CH_3CO_2H$ | | 85 | <1 | <1 |
| 2.13 | $B(OH)_3$ | | 15 | <1 | <1 |
| 2.14[f] | **B1** | | 58 | 57 | |
| 2.15[f] | **B1** | 2,6-DTBP[d] | <1 | <1 | |

*[a] Yields were determined by $^1H$ NMR using hexamethyldisiloxane as an external standard. [b] 10 mol% catalyst, 50 °C, 24 h. [c] 20 mol% catalyst, 80 °C, 48 h. [d] With 15 mol% 2,6-di-tert-butylpyridine. [e] With 30 mol% 2,6-di-tertbutylpyridine; [f] in DCE at 100 °C, 24 h.*

*Table 2.2. Comparison between boronic and Brønsted acids for the catalytic dehydrative Friedel-Crafts reactions of benzylic alcohols.*

would result in the failure of the reaction due to quenching of the catalyst (Scheme 2.9). Thus, the reaction was examined in 1,2-DCE, which cannot be deprotonated by 2,6-DTBP to poison the catalyst. Still, 58% yield of **29** and 57% yield of **30** were produced at 100 °C

but not in the presence of 15 mol% of 2,6-di-*tert*-butylpyridine (entry 2.14 and 2.15). Replacing the cationic boronic acid by Brønsted acids spanning a wide p$K_a$ range revealed that, in all cases, the boronic acid could be replaced by a Brønsted acid with similar results, although the strength of the required acid varies with the electronic nature of the substrate. The conjugate acid of the boronic acid catalyst, $HSbF_6$, catalyzed the reaction of all three substrates (entry 2.3). In the case of benzylic alcohols **26** and **27**, acids as weak as acetic acid, boric acid and oxalic acid catalyzed the reaction under otherwise identical conditions (entries 2.9-2.11). Electronically deactivated alcohol **28** required a stronger Brønsted acid but could still react in the presence of $H_2SO_4$ in high yield (entry 2.6). The authors of the original study ruled out the possibility of Brønsted acid catalysis on the basis of 1) the lack of reactivity of **27** with $CF_3CO_2H$ and 2) the fact that a different boronic acid (**B2**), which has a comparable p$K_a$ in $H_2O$ and DMSO to the catalyst used (**B1**), did not catalyze the reaction in HFIP/$MeNO_2$. However, Table 2.2 shows that $CF_3CO_2H$ is one of the only acids assayed that does not promote the reaction of **27** and is therefore not representative of the real situation. As we will see later, in HFIP/$MeNO_2$, **B1** produces a Brønsted acid that is significantly stronger than $CF_3CO_2H$. For benzylic alcohol **28**, the reduced reactivity with **B1** and **B3** compared to TfOH and $H_2SO_4$ might be explained by the ability of the boronic acids to form dual H-bond complexes with the nitro functionality of the substrate, making them unavailable to activate HFIP and the alcohol moiety.



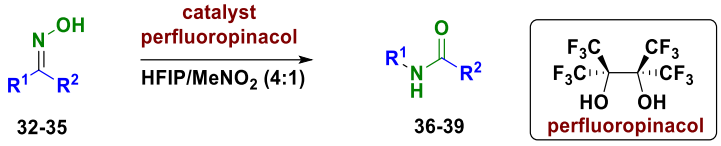

*Scheme 2.9. A possible way by which 2,6-DTBP could quench the reaction.*

### 2.2.3. Beckmann rearrangement

The second transformation that we examined was the Beckmann rearrangement of oximes into amides catalyzed by **B3**. Previous studies on acetophenone oxime (**32**) supported a mechanism involving the slow formation of a catalytically competent *O*-boronyl oxime ester (b: see Scheme 2.6). We tested three representative aryl-alkyl (**33**), aryl-aryl (**34**) and alkyl-alkyl oximes (**35**) from the original publication, as well as **32**, all under the reported conditions.

The transformations catalyzed by **B3** were efficient in each case (Table 2.3, entry 3.3) but not in the presence of 2,6-di-*tert*-butylpyridine (entry 3.4). The reaction conducted in 1,2-

DCE was quenched by 2,6-di-*tert*-butylpyridine (entry 3.13 and 3.14). In the case of **32**, none of the Brønsted acids tested promoted the rearrangement under the given reaction




**36**: $R^1 = C_6H_5$, $R^2$ = Me **37**: $R^1$ = 4-OH-($C_6H_4$), $R^2$ = Me **38**: $R^1$ = Ph, $R^2$ = Ph **39**: $R^1 = R^2 = -(CH_2)_5-$

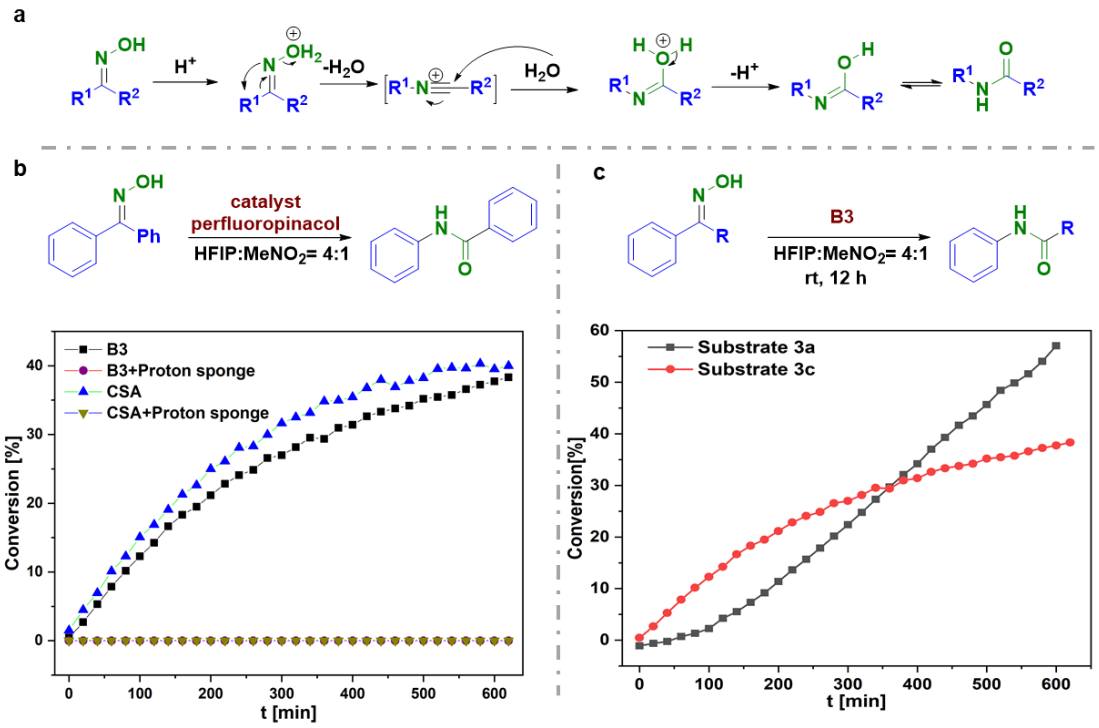
| Entry | Catalyst | Additive | Yield 36 [%] [c] | Yield 37 [%] [c] | Yield 38 [%] [c] | Yield 39 [%] [b] |
|---|---|---|---|---|---|---|
| 3.1 | **B1** | | <1 | 20 | <10 | <1 |
| 3.2 | **B2** | | <1 | <1 | <1 | <1 |
| 3.3 | **B3** | | 98 | 94 | 85 | 45 |
| 3.4 | **B3** | 2,6-DTBP | <1[e] | <1[e] | <1[e] | <1[d] |
| 3.5 | TfOH | | <1, [40][g] | 40 | 45 | <1 |
| 3.6 | HCl | | <1, [16] [g] | 16 | 95 | <1 |
| 3.7 | $H_2SO_4$ | | <1 | <1 | <1 | <1 |
| 3.8 | CSA | | <1, [94] [g] | 90 | 86 | 20 |
| 3.9 | TFA | | <1, [36] [g] | 36 | 21 | 78 |
| 3.10 | $(COOH)_2$ | | <1 | <1 | <1 | <1 |
| 3.11 | $CH_3CO_2H$ | | <1 | <1 | <1 | <1 |
| 3.12 | $B(OH)_3$ | | <1 | <1 | <1 | <1 |
| 3.13[f] | **B1** | | | 57 | | |
| 3.14[f] | **B1** | 2,6-DTBP[e] | | <1 | | |

*[a] Yields were determined by $^1H$ NMR using hexamethyldisiloxane as an external standard. [b] 30 mol% catalyst and perfluoropinacol, 80 ºC, 24 h. [c] 5 mol% catalyst and perfluoropinacol, 25 ºC, 24 h. [d] With 45 mol% 2,6-di-tert-butylpyridine. [e] With 7.5 mol% 2,6-di-tertbutylpyridine; [f] in DCE at 50 ºC, 24 h; [g] 10 mol% catalyst and perfluoropinacol, 50 ºC, 24 h.*

*Table 2.3. Comparison between boronic acids and Brønsted acids for the catalytic Beckmann rearrangement.*

conditions (room temperature). However, when the temperature was raised to 50 °C, most of the strong Brønsted acids tested triggered the reaction, including CSA. In the catalytic experiments with **B3**, the reaction kinetics for **32** did display an induction period consistent with a slow catalyst formation as previously proposed in the covalent mechanism. However, since all prior optimizations and mechanistic studies were carried out with **32**, it might have led the authors to conclusions about the mechanism which do not hold for most other substrates. For substrates **33**-**35**, a screening of Brønsted acids revealed that several of them were capable of promoting the reaction with either a similar

efficiency or even more effectively than the **B3** catalyst system (entries 3.5-3.9). CSA proved to be particularly effective in the case of substrates **33** and **34**, while $CF_3CO_2H$ was able to promote the reaction with **35** (entries 3.8-3.9).




*Using deuterated toluene-$d_8$ as an external standard; Calculated by $^1$H NMR spectrum with hexamethyldisiloxane as an internal standard.*

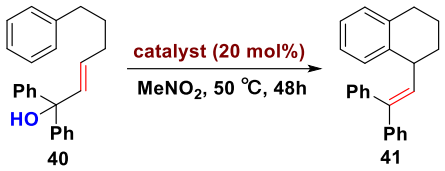
*Figure 2.1. Kinetic study and proposed mechanism of Brønsted acid catalysis.*

Indeed, the kinetic profile of the reaction of oxime **34** catalyzed by **B3** proved to be nearly identical to that of the one catalyzed by CSA, with no observation of an induction period expected for a mechanism involving slow formation of a catalytically active acyl oxime species (b: see Figure 2.1). Comparing the reactivity of **32** with **34** reveals that the mechanism is likely substrate dependent. The kinetic profile for **32** is consistent with the mechanism proposed in the original report, but this is not the case for **34** (c: see Figure 2.1). In the latter case, the experiments support Brønsted acid catalysis (a: see Figure 2.1), rather than covalent catalysis being the dominant mechanism for substrates **33-35**. The other evidence shows its truly Brønsted acid catalysis is the reaction will not happen in the presence of proton sponge for both CSA and B3 catalysis (a: see Figure 2.1). For a Brønsted acid catalysis process, the pre-activation of the oxime is not needed, and, thus, there is no induction period at the beginning of the reaction. Covalent activation and Brønsted acid catalysis therefore appear to be competitive catalytic mechanisms in the Beckmann rearrangement. Apart from the single substrate used to study the mechanism

in the original report, the other three representative substrates studied are likewise likely to be dominated by Brønsted acid catalysis.

### 2.2.4. Carbocyclization of allylic alcohols

The third reaction that we analyzed was the carbocyclization of allylic alcohols, reported to be catalyzed by boronic acid **B2** in $MeNO_2$. The transformation occurred as described (Table 2.4, entry 4.2), but was inefficient in the presence of 2,6-di-*tert*-butylpyridine (entry 4.3). Likewise, **B1** and **B3** have a relatively similar efficacy (entries 4.1 and 4.4) and the use of TfOH resulted in an excellent yield. In contrast, a weak Brønsted acid such as oxalic acid enabled the reaction under otherwise identical conditions in similar yield (entries 4.11). Both oxalic acid and boronic acids are known to act as dual H-bond donors, and likely act as H-bond catalysts here. The possibility of H-bond activation may have been previously overlooked, since in the original disclosure, control experiments designed to compare **B2** to Brønsted acids were performed with *p*-TsOH only (entry 4.8).



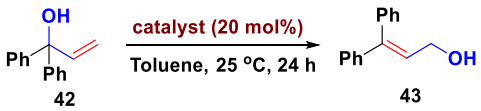

| Entry | Catalyst | additive | Yield 41 [%][a] |
|---|---|---|---|
| 4.1 | **B1** | | 72 |
| 4.2 | **B2** | | 52 |
| 4.3 | **B2** | 2,6-DTBP | <1[b] |
| 4.4 | **B3** | | 67 |
| 4.5 | TfOH | | 81 |
| 4.6 | HCl | | <1 |
| 4.7 | $H_2SO_4$ | | 36 |
| 4.8 | *p*-TsOH | | 24 |
| 4.9 | CSA | | <1 |
| 4.10 | TFA | | 12 |
| 4.11 | $(COOH)_2$ | | 50 |
| 4.12 | $CH_3CO_2H$ | | 12 |
| 4.13 | $B(OH)_3$ | | <1 |

*[a] Yields were determined by $^1H$ NMR using hexamethyldisiloxane as internal standard. [b] With 15 mol% 2,6-di-tert-butylpyridine.*

*Table 2.4. Comparison of boronic acids and Brønsted acids as catalysts for the carbocyclization of allylic alcohols.*

### 2.2.5. 1, 3-Allylic transposition of allylic alcohols

The fourth process explored was the 1,3-allylic transposition of 1,1-diphenyl allyl alcohol, also reported to be catalyzed by **B2** (Table 2.5). This reaction proved to be more challenging to rationalize as we faced major difficulties to reproduce the published results. Using either commercially available or freshly prepared and recrystallized catalyst **B2**, yields never exceeded 20%. We suspect that the reported success of this transformation might result from the presence of an impurity in the way that **B2** was synthesized. For example, borinic acids, which are much stronger Lewis acids than boronic acids, are prepared from the addition of organometallic nucleophiles to boronic esters. Boronic acids are prepared in much the same way, only a different stoichiometry of nucleophile is used. It is therefore possible that some boronic acids might contain borinic acids as trace impurities, for instance. Even a trace impurity might not be negligible given the catalyst loading of 20 mol%.




| Entry | Catalyst | Additive | Yield 43 [%][a] |
|---|---|---|---|
| 5.1 | **B1** | | 46 |
| 5.2 | **B2** | | 20[80][b] |
| 5.3 | **B2** | 2,6-DTBP | <1[c] |
| 5.4 | **B3** | | <1 |
| 5.5 | TfOH | | 6 |
| 5.6 | HCl | | 16 |
| 5.7 | $H_2SO_4$ | | 44 |
| 5.8 | CSA | | 85 |
| 5.9 | TFA | | 18 |
| 5.10 | $(COOH)_2$ | | 11 |
| 5.11 | $CH_3CO_2H$ | | <1 |
| 5.12 | $B(OH)_3$ | | <1 |

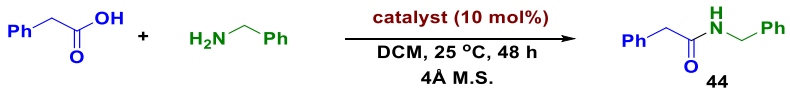
*[a] Yields were determined by $^1H$ NMR using hexamethyldisiloxane as an external standard. [b] Yield reported in reference 149d. [c] In the presence of 15 mol% 2,6-di-tert-butylpyridine.*

*Table 2.5. Comparison between boronic acids and Brønsted acids for the catalytic 1,3-allylic transposition of allylic alcohols.*

We then assessed whether Brønsted acids could enable the 1,3-transposition reaction under the conditions reported under boronic acid catalysis. Stronger Brønsted acids promoted the reaction to a limited extent (entries 5.5-5.7), but CSA was highly effective, delivering the product in 85% yield (entry 5.8). This result is similar to that reported in the literature in the presence of **B2**, which again suggests a Brønsted acid catalysis mechanism is operating in that case.

### 2.2.6. Dehydrative amidation of carboxylic acids

The fifth and final reaction that we investigated was the direct dehydrative amidation of carboxylic acids catalyzed by 2-iodophenylboronic acid **B4** (10 mol%) in $CH_2Cl_2$ (Table 2.6). Once the required 4 Å molecular sieves were well-activated, the reaction indeed proceeded as described in the literature (entry 6.1). Unlike the other reactions surveyed, the addition of 2,6-di-*tert*-butylpyridine did not affect the reaction (entry 6.2). Again, unlike the other reactions surveyed, none of the Brønsted acids were able to promote the reaction under the same set of conditions. Clearly, this reaction is not under Brønsted acid catalysis or H-bond catalysis. It is instead consistent with the previously proposed boronic acid catalyzed mechanisms involving transient B–O bond formation. Notably, we




| Entry | Catalyst | additive | Yield 44 [%][a] |
|---|---|---|---|
| 5.1 | **B4** | | 90 |
| 5.2 | **B4** | 2,6-DTBP | 93[b] |
| 5.3 | TfOH | | <1 |
| 5.4 | CSA | | <1 |
| 5.5 | TFA | | <1 |
| 5.6 | $(COOH)_2$ | | <1 |
| 5.7 | $CH_3CO_2H$ | | <1 |
| 5.8 | $B(OH)_3$ | | <1 |

*[a] Isolated yield after column chromatography over silica. [b] With 15 mol% 2,6-di-tert-butylpyridine.*

*Table 2.6. Comparison of boronic acids and Brønsted acids as catalysts for the dehydrative amidation of carboxylic acids.*

observed that the required 4 Å molecular sieves must be activated in a specific way, which was not detailed in the original publication. We compared different ways to activate the

4 Å molecular sieves, but only one was found to be effective: heating the sieves in a 550 ºC oven for 3 h, followed by a cooling down to 200 ºC prior to their removal from the oven. They were then placed at room temperature in a desiccator under argon, which was critical to the reproducibility of the reaction. Milder methods for their activation led to trace product formation, including two common ways to active 4 Å molecular sieves: heating the sieves in an oven at 150 ºC for 5 h under vacuum or heating the sieves in an oven at 350 ºC for 8 h, then cooling to room temperature in a desiccator.

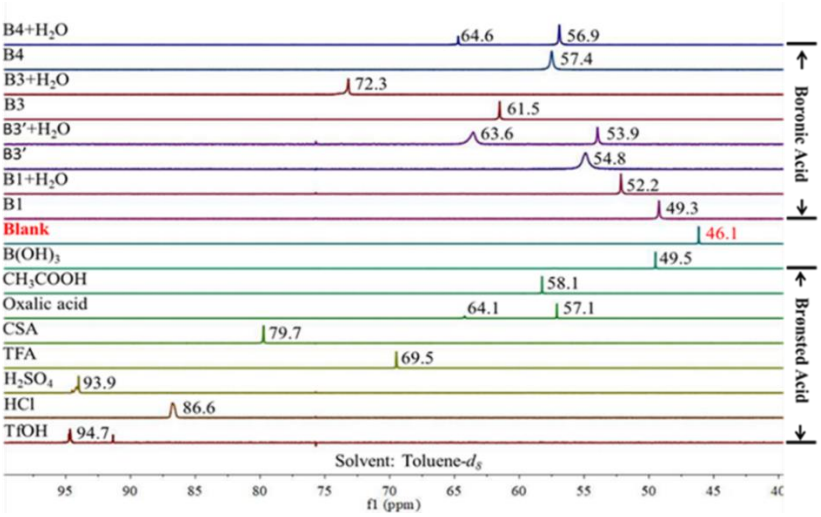
## 2.3. Gutmann-Beckett method

The Gutmann-Beckett method is a popular and reliable way to qualitatively assess the acidity of a compound. It was devised by Gutmann in 1975 for measuring the electrophilic nature (Lewis acidity) of a solvent using $^{31}$P NMR.[153] During the last few decades, a large number of reports employed the Gutmann-Beckett method to evaluate the acidity of various compound such as boranes,[154] transition complexes,[155] etc. Triethylphosphine oxide (TEPO) is a common probe molecule for the Gutmann-Beckett method due to its sensitivity to the chemical environment.[156] The strength of the interaction between an additive of interest and TEPO can be inferred from the change in chemical shift in the corresponding $^{31}$P NMR spectrum, compared to that obtained from a control experiment performed in the absence of the additive. According to the Lewis acid-base theory, $H^+$ is the smallest Lewis acid. Thus, the Gutmann-Beckett method can also theoretically be used for evaluating the acidity of protonic acids. The oxygen atom of TEPO is a very strong Lewis base and a strong H-bond acceptor. It can likewise interact with acidic hydrogen atoms, resulting in a change in the $^{31}$P chemical shift of $Et_3PO$. The more acidic the H-bond donor or the more electrophilic the solvent, the larger the downfield shift in the $^{31}$P signal of $Et_3PO$. Thus, the Brønsted acidity of an acid or the electrophilicity of the solvent can be evaluated by comparing the $^{31}$P chemical shift of the $Et_3PO$.

The p$K_a$ of an acidic molecule highly depends on the solvent. Deuterated toluene-$d_8$ was chosen as a reference solvent since it is among the most used with the Gutmann-Beckett method. The boronic acids **B1**-**B4** and a representative range of Brønsted acids were evaluated for their influence on the $^{31}$P shift of TEPO (Figure 2.2). For Brønsted acids,

[153] U. Mayer, V. Gutmann, W. Gerger, *Monat. Chem.* **1975**, *106*, 1235.
[154] M. A. Beckett, D. S. Brassington, S. J. Coles, M. B. Hursthouse, *Inorg. Chem. Commun*. **2000**, *3*, 530.
[155] C. -Y. Wu, T. Horibe, C. B. Jacobsen, D. Toste, *Nature*, **2015**, *517*, 449.
[156] V. Gutmann, *Coord. Chem. Rev.* **1976**, *18*, 225.

the $^{31}$P shifts correlated closely with their p$K_a$ in water. In toluene-$d_8$, the shifts of the various boronic acids were found to be smaller than those arising from oxalic acid and were comparable with those arising from $CH_3COOH$. Interestingly, in the presence of 3 equiv. of water, the signals for the boronic acids shifted or formed a new second signal. For **B1**, the signal shifted from 49.3 to 54.8 ppm. For **B3**, it shifted from 61.5 to 72.3 ppm, which is comparable with the shift observed for CSA (79.7 ppm, p$K_a$ 1.2). For **B4**, the addition of water caused the old signal at 57.4 ppm to be replaced by two new signals: one at 64.6 ppm and another at 56.9 ppm. The shift of the $^{31}$P signal implies that the effective acidity was increased or that a new acidic species was formed in the presence of water.



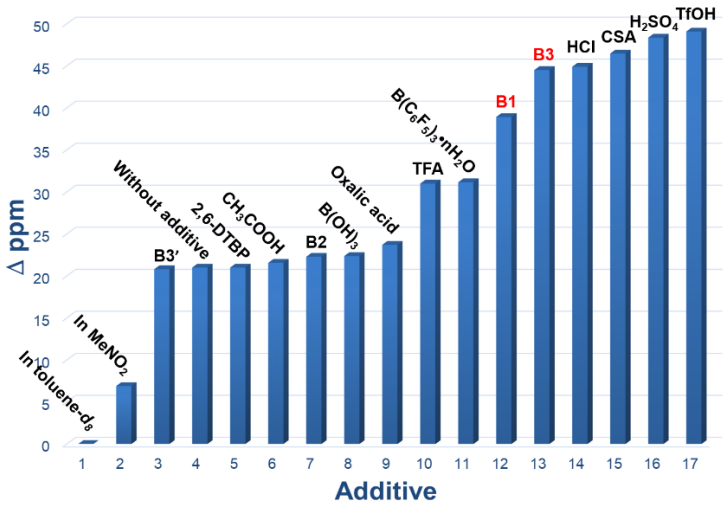

| Acid | p$K_a$ ($H_2O$) |
|---|---|
| $B(OH)_3$ | 9.23 |
| $CH_3COOH$ | 4.76 |
| Oxalic acid | 1.25, 4.17 |
| CSA | 1.2 |
| TFA | -0.25 |
| $H_2SO_4$ | -3.0, 1.99 |
| HCl | -8.0 |
| TfOH | -14 |

*Acid/TEPO = 3:1; Blank = 0.075 mmol triethylphosphine oxide dissolved in 500 µL deuterated toluene;* ***B3'*** *= (2-(methoxycarbonyl)phenyl)boronic acid.*

*Figure 2.2. Gutmann-Beckett method in deuterated toluene-$d_8$ and the p$K_a$ of Brønsted acids.*

At the outset, to correlate the catalytic effects observed for boronic and Brønsted acids with their physicochemical properties, we elected to compare their interaction with TEPO in toluene and in HFIP, in the presence and absence of boronic and Brønsted acid additives (Figure 2.3). The strength of the interaction between the additive and TEPO can be inferred from the change in the chemical shift in the corresponding $^{31}$P NMR spectrum, compared to that obtained from a control experiment performed in the absence of additive and HFIP (i.e., 46.1 ppm in toluene-$d_8$). The control experiments confirmed our hypothesis regarding the pivotal role of the solvent. Indeed, in the presence of $MeNO_2$ or HFIP/$MeNO_2$ (4:1), we observed substantial shifts in the $^{31}$P NMR signal (53.0 and 67.1

ppm, respectively), indicating that the solvents are non-innocent in the activation of alcohols, even in the absence of Lewis or Brønsted acids. This does not come as a surprise since we and others have noticed similar reactivity trends in the past for HFIP and $MeNO_2$. The former solvent forms aggregates that are excellent H-bond donors,[150,151] while the latter templates the formation of similar aggregates through interactions with molecules such as water.[157] In the case of the HFIP/$MeNO_2$ mixture, adding 2,6-di-*tert*-butylpyridine did not affect the $^{31}P$ NMR shift, confirming that, without catalyst, no Brønsted acid is generated.



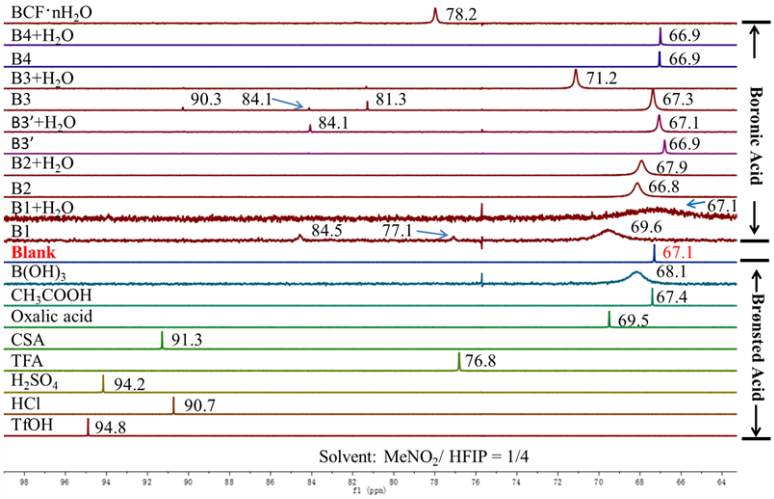

*Gutmann–Beckett plot showing the influence of an additive (3 equiv) on TEPO (1 equiv) in HFIP/$MeNO_2$ (4:1) as expressed by the variations in chemical shift of the highest frequency signal observed in the $^{31}P$ NMR spectrum when compared to the reference TEPO in toluene-$d_8$.* ***B3'*=*B3*** *in the absence of diol.*

*Figure 2.3. Gutmann–Beckett in HFIP/$MeNO_2$ (4:1).*

Mixing catalyst system **B3** with TEPO gave rise to a few new resonances (see Figure 2.4), the highest frequency of which (90.3 ppm) is 12.1 ppm further downfield than the signal generated due to the same experiment carried out with $B(C_6F_5)_3 \cdot H_2O$ (78.2 ppm). The influence of **B3** in HFIP/$MeNO_2$ (4:1) thus appears to be stronger than $B(C_6F_5)_3 \cdot H_2O$, and comparable to that of HCl (90.7 ppm, p$K_a$ -8.0) or CSA (91.3 ppm, p$K_a$ 1.2), in close agreement with the ability of **B3** to promote the opening of unactivated cyclopropanes (see Table 2.1). This is very different from the situation in toluene, where CSA shifts the signal of TEPO nearly 20 ppm further downfield than **B3** does. At least one species produced from the components of **B3**, presumably a highly electrophilic

[157] (a) M. Dryzhakov, M. Hellal, E. Wolf, F. C. Falk, J. Moran, *J. Am. Chem. Soc.* **2015**, *137*, 9555; (b) J. J. Montalvo-Acosta, M. Dryzhakov, E. Richmond, M. Cecchini, J. Moran, *Chem. Eur. J.* **2020**, *26*, 10976.

hexafluoropinacol boronate ester, can serve to generate a strong Brønsted acid in HFIP. It should be highlighted that the diol component of **B3** is essential here, as no shift was observed with the boronic acid alone (**B3'**). In line with these suggestions, it was established that a strongly Brønsted acidic species is formed from the covalent assembly of pentafluorophenylboronic acid and oxalic acid, another electron-poor bidentate species.[158] Likewise, the shift produced by the addition of **B1** (84.5 ppm) is significantly higher than that produced by $B(C_6F_5)_3 \cdot H_2O$, congruent with its demonstrated reactivity (see Table 2.1). Although this experiment does not distinguish whether Brønsted or Lewis acids are causing the observed shifts, strong boron Lewis acids such as $B(C_6F_5)_3$ are well known to rapidly react with adventitious water to form hydrates that are strong Brønsted



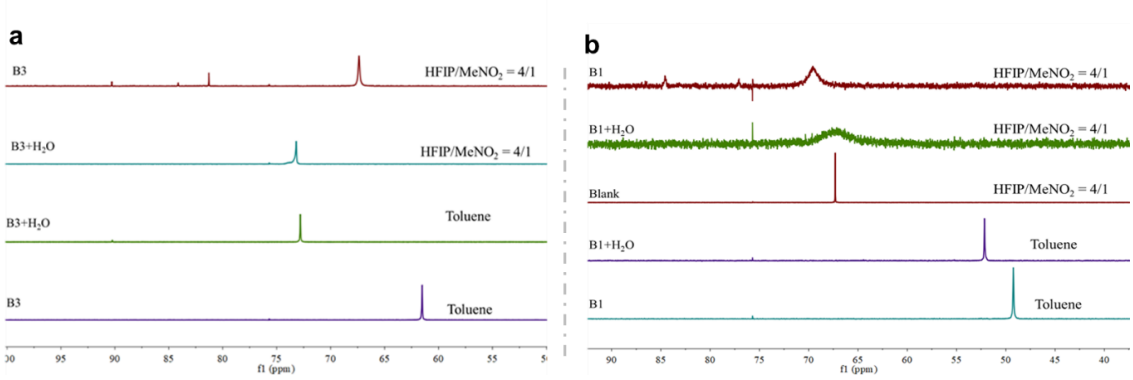

*Blank = 0.075 mmol triethylphosphine oxide dissolved in a mixture of hexafluoroisopropanol and nitromethane (4:1); $^{31}P$ NMR of **B3** + $H_2O$ and **B1** + $H_2O$ were done after added water (3.0 equiv) about 4 h.*

*Figure 2.4. The $^{31}P$ NMR spectrum of Gutmann–Beckett in HFIP/$MeNO_2$ (4:1).*

acids. In a similar way, the large magnitude of the observed shift in the $^{31}P$ NMR means that strong Brønsted acids are almost certainly produced by **B1** and **B3** in HFIP. For these reasons, the mild p$K_a$ values established for these boronic acids in DMSO or water cannot be transposed to reactions carried out in HFIP and HFIP/$MeNO_2$ to predict their reactivity. Indeed, none of the shifts corresponding to the boronic acids in the absence of HFIP exceeded 61.5 ppm (see Figure 2.2). Lastly, we found that boronic acid **B2** (66.8 ppm in HFIP/$MeNO_2$ 4:1) induces a shift in the $^{31}P$ NMR comparable to oxalic acid (69.5 ppm, pKa 1.38), in agreement with the lack of reactivity observed in the ring-opening

[158] S. Estopina-Duran, L. J. Donnelly, E. B. Lclean, B. M. Hockin, A. M. Z. Slawin, J. E. Taylor, *Chem. Eur. J.* **2019**, *25*, 3950.

transformation. Of note, in the absence of the diol component of **B3**, the shift is similar to that of **B2** (66.9 ppm). HFIP can generate more acidic complexes with boronic acids than can water; the $^{31}P$ signal of the complex of **B3** with water appears at the same position (71.2 ppm) in toluene or HFIP/$MeNO_2$ 4:1. However, for **B3** employed in HFIP/$MeNO_2$ (4:1), several additional signals appeared. The highest one at 90.3 ppm (a: see Figure 2.5) is 19.1 ppm higher than the complex of **B3** with water. A similar phenomenon was noticed with **B1**(b: see Figure 2.5). **B3** in HFIP/$MeNO_2$ (4:1) produces a Brønsted acid of similar strength to HCl in that solvent.




*Blank = 0.075 mmol triethylphosphine oxide dissolved in a mixture of hexafluoroisopropanol and nitromethane (4:1); The $^{31}P$ NMR of (**B** + $H_2O$) was done after added water (3.0 equiv) about 4 h.*

*Figure 2.5. Comparison of the acidity of **B1** and **B3** in toluene vs HFIP/$MeNO_2$, in the presence and absence of water.*

## 2.4. Conclusion of Chapter 2

This study sheds light on the activation mode of boronic acid catalysis of alcohols and oximes, showing that Brønsted acid and H-bond catalysis, rather than Lewis acid or covalent activation, are likely responsible for the observed reactivity in nearly all the representative examples studied. Specifically, catalysts **B1** and **B3** produce strong Brønsted acids in the presence of HFIP, and catalyst **B2** likely acts as a H-bond catalyst in $MeNO_2$. Our conclusions were based on the following key findings: 1) Boronic acids **B1** and **B3** are able to open unactivated cyclopropanes in HFIP; 2) the hindered Brønsted base 2,6-di-*tert*-butylpyridine, which does not form a Lewis pair with boron Lewis acids, entirely inhibits reactivity of the boronic acids in the reactions investigated; 3) boronic acid-catalyzed reactions of alcohols and oximes could be promoted by Brønsted acids or H-bond catalysts under otherwise identical conditions; 4) the Brønsted acids that facilitate those transformations exert a deshielding influence on TEPO comparable to the boronic

acids that promote the same transformations; 5) for three of the four representative oximes studied, the kinetic profile and their response to Brønsted acid catalysis are inconsistent with a covalent mechanism. Moving forward, these insights should be useful for the rational design of second-generation catalysts for dehydrative nucleophilic substitution of alcohols or for oxime rearrangements, whether or not they are based on boron. Finally, this work cautions that a wide range of control experiments are necessary to rule out a catalytic role for H-bond donors or for *in situ* generated Brønsted acids, taking into consideration the important numerous roles played by the solvent. Understanding these results can allow researchers to avoid designing catalysts that ultimately perform a function that could be carried out by much simpler compounds.

# 3. Unlocking the Friedel-Crafts Arylation of Epoxides Driven by Hexafluoroisopropanol

## 3.1. Scientific background and context

### 3.1.1. Introduction

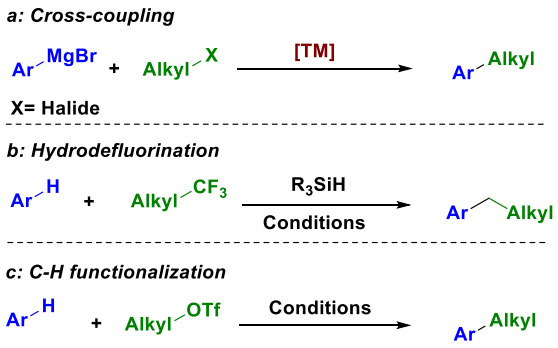
Epoxides and aliphatic alcohols represent important building blocks in synthetic chemistry, the former especially serving as a springboard to densely functionalized molecules in medicinal chemistry, crop science, and material science due to their unique reactivity.[159] In principle, the intermolecular Friedel-Crafts reaction would represent an ideal way to form C-C bonds from arenes and epoxides, since it would prevent the need for pre-activation steps with respect to the substrates and produce no stoichiometric waste beyond water, but this type of reactivity remains challenging:

Ring-opening Friedel-Crafts reactions of terminal epoxides, which give branched products, are mainly limited to electron-rich styrene oxides and arenes when Lewis or Brønsted acid catalysts are employed.[160] As a result, epoxide arylation strategies based on transition metal catalysis or photocatalysis have been developed but suffer from poor access to branched products,[161] notably for alkyl epoxides,[161e] without forgetting the pre-functionalized nucleophiles required. For styrene oxides, more branch-selective arylation examples are known, but those bearing strong electron-withdrawing groups remain inaccessible.

1,2-Difunctionalization of epoxides represents another important challenge. Although the generated alcohol can be derivatized into other functional groups, it rarely occurs in a one-pot fashion. In particular, dehydrative Friedel-Crafts reactions of the primary aliphatic alcohols generated after the ring-opening of epoxide remain undeveloped, owing to the stability of the C–O bond. Currently, the alternative strategies to construct such

[159] (a) A. K. Yudin, Aziridines and Epoxides in Organic Synthesis (Wiley-VCH, Weinheim, 2006); (b) K. Weissermel, H.-J. Arpe, Industrial Organic Chemistry 4th edn (Wiley-VCH, Hoboken, 2008).
[160] R. Talukdar, *RSC Adv.* **2020**, *10*, 31363.
[161] (a) D. K. Nielsen, A. G. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 6056; (b) Y. Zhao, D. J. Weix, *J. Am. Chem. Soc.* **2014**, *136*, 48; (c) Z. Wang, Y. Kuninobu, M. Kanai, *J. Am. Chem. Soc*. **2015**, *137*, 6140; (d) X.-Y. Lu, C.-T. Yang, J.-H. Liu, Z.-Q. Zhang, X. Lu, X. Lou, B. Xiao, Y. Fu, *Chem. Commun*. **2015**, *51*, 2388. (e) M. Parasram, B. J. Shields, O. Ahmad, T. Knauber, A. G. Doyle, *ACS Catal*. **2020**, *10*, 5821.

compounds involve cross-coupling,[162] hydrodefluorination[163] or C-H functionalization (Scheme 3.1).[164] All of them require additional synthetic steps to pre-activate the alcohol and, in most cases, the arene coupling partner as well.



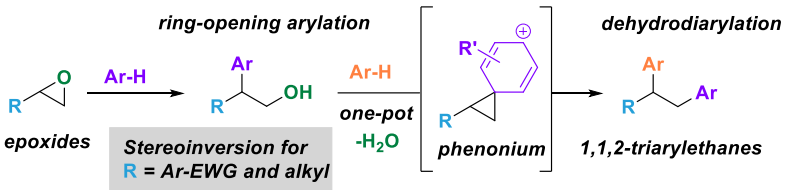

*Scheme 3.1. Strategies for producing alkylation products from linear alkyl derivatives.*

The development of a Friedel-Crafts reaction broadly applicable to both terminal epoxides and primary aliphatic alcohols would have an additional benefit: since the products of Friedel-Crafts ring-opening of epoxides are themselves primary aliphatic alcohols, sequential Friedel-Crafts reactions could then be envisaged where two distinct arenes can be installed in one pot to provide a straightforward access to 1,1,2-triarylethane frameworks of interest. Those compounds have indeed many applications ranging from the life sciences to feedstock precursors, but current methods to synthesize those scaffolds either require multi-step preparation of different cross-coupling partners or substrates, the use of directing groups, or complex reaction conditions under inert atmosphere (cf. Chapter 1).[165]

Herein, we describe our efforts to expand the Friedel-Crafts reaction to include most classes of terminal epoxides (ring-opening arylation), primary aliphatic alcohols (dehydroarylation) and a sequential dehydrodiarylation process stemming from their combination. The key to the reactivity is the use of the solvent HFIP with a Bronsted acid

[162] (a) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; (b) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; (c) S. Kim, M. J. Goldfogel, M. M. Gilbert, D. J. Weix, *J. Am. Chem. Soc.* **2020**, *142*, 9902.
[163] J. Zhu, M. Perez, C. B. Caputo, D. W. Stephan, *Angew. Chem.* **2016**, *128*, 1439.
[164] (a) Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 13596; (b) A. S. S. Wilson, M. S. Hill, M. F. Mahon, C. Dinoi, L. Maron, *Science* **2017**, *358*, 1168.
[165] (a) P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855; (b) K. B. Urkalan, M. S. Sigman, *Angew. Chem. Int. Ed.* **2009**, *48*, 3146; (c) B. Shrestha, P. Basnet, R. K. Dhungana, S. KC, S. Thapa, J. M. Sears, R. Giri, *J. Am. Chem. Soc.* **2017**, *139*, 10653; (d) B. Chen, P. Cao, X. Yin, Y. Liao, L. Jiang, J. Ye, M. Wang, J. Liao, *ACS Catal.* **2017**, *7*, 2425.

as catalyst. Indeed, the association of Lewis or Brønsted acid catalysts with HFIP is known to trigger transformations with rather unreactive alcohols, alkenes, and cyclopropanes through the formation of highly reactive hydrogen-bond networks as mentioned in Chapter 1. We hypothesized that the resulting alcohols could react in a second Friedel-Crafts reaction through the intermediacy of a well-established[166] but underexploited[167] phenonium ion without pre-activation of the alcohol thanks to the strong acidity of our system (Scheme 3.2). A wide range of epoxides and nucleophiles were examined (>100 examples), most of the ring opening arylation of epoxide are found to be stereospecific and 1,2-difunctionalization of epoxides can be conducted smoothly under our standard conditions. The success of the ring opening arylation and 1,2-difunctionalization of epoxide with our strategy allows to re-evaluate the reactivity of primary aliphatic alcohols, epoxides, and related compounds towards new synthetic applications.



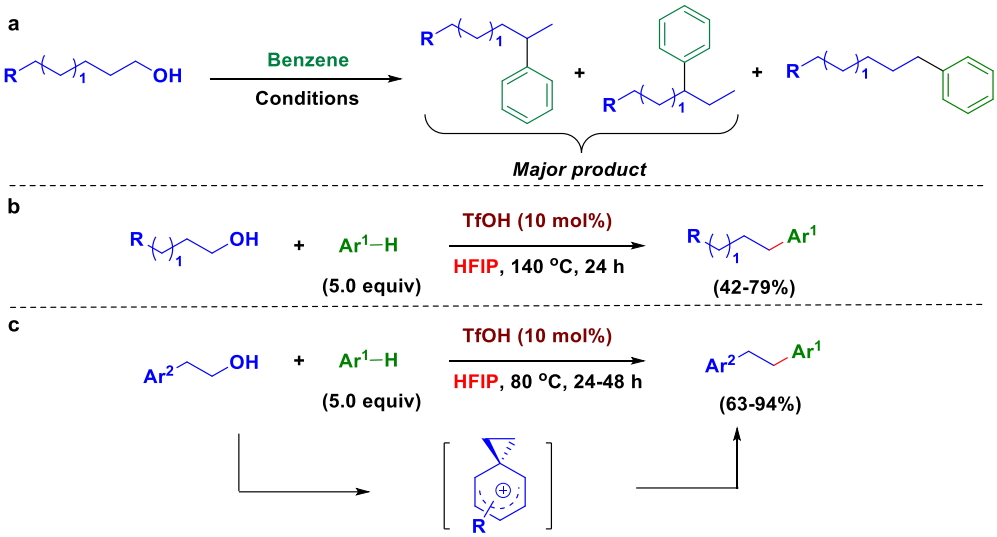

*Scheme 3.2. Strategy toward the monoarylation and dehydrodiarylation of terminal epoxides.*

### 3.1.2. Friedel-Crafts reactions on primary aliphatic alcohols

Primary aliphatic alcohols generally do not undergo Friedel-Crafts reactions, except for some examples with methanol and ethanol under extreme conditions, e.g., using high temperatures (300-400 °C) with zeolites as promoters. Only two low-yielding (<10%) examples of Friedel-Crafts reactions of primary aliphatic alcohols longer than two carbons are known, both of which give complex mixtures of linear and branched products due to rearrangements (a: see Scheme 3.3).[168] During the investigation of activation of primary aliphatic alcohols in our laboratory, my colleagues Vuk Vukovic and Florent Noel found that Friedel-Crafts reactions of the primary aliphatic alcohols could be

[166] (a) E. del Río, M. I. Menéndez, R. López, T. L. Sordo, *J. Am. Chem. Soc.* **2001**, *123*, 5064; (b) Y. Tsuji, J. P. Richard, *J. Phys. Org. Chem.* **2016**, *29*, 557.
[167] D. Lebœuf, V. Gandon, J. Ciesielski, A. J. Frontier, *J. Am. Chem. Soc.* **2012**, *134*, 6296.
[168] (a) O. Sieskind, P. Albrecht, *Tetrahedron Lett.* **1993**, *34*, 1197; (b) A. R. A. S. Deshmukh, V. K. Gumaste, B. M. Bhawal, *Catal. Lett.* **2000**, *64*, 247.

achieved at 140 °C by using the TfOH/HFIP reaction system and selectively produced a linear product for most of the substrate scope (b: see Scheme 3.3). In general, higher yields were achieved with alcohols bearing longer aliphatic chains, which might be explained by stronger intermolecular dispersion interactions between longer alkyl groups, hindering elimination processes and the eventual subsequent formation of branched products and oligomers. Interestingly, if the primary aliphatic alcohols have an aromatic substituent at the β position, the dehydrative Friedel-Crafts reaction can be conducted at much lower temperature (80 °C) in higher yield as demonstrated by my collaborator Dr. Marie Vayer (c: see Scheme 3.3). The underlying reason is the probable formation of a phenonium ion intermediate which makes the nucleophile addition easier.




*Scheme 3.3. Friedel-Crafts reactions on primary aliphatic alcohols.*

### 3.1.3. Phenonium ion

The structure of the phenonium ion was first proposed by Cram in 1949 to explain the unexpected stereochemical outcomes of acetolysis of the enantioenriched β-phenethyl tosylate derivatives. The structure was confirmed as a spirocyclopropyl benzenium ion containing a 4π cyclohexadienyl system by Olah based on NMR studies and DFT calculations under superacid conditions. Since the structure was proposed, several theoretical studies about phenonium ions were reported in the literature, notably the role of back-bonding interactions in carbocation chemistry by Sordo and co-workers.[169] They showed a back-bonding effect from the HOMO of the phenyl cation moiety to the LUMO

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

of the ethylene fragment, which involves a gain of conjugation as both π systems are responsible for the orthogonal nature of the ipso-carbon (see Figure 3.1).

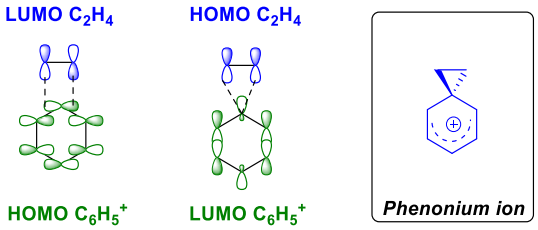
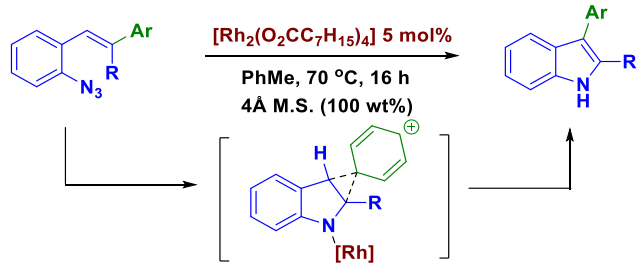



*Figure 3.1. The orthogonal ipso-carbon in the phenonium ion.*

Phenonium ions are more stable than a primary carbocation and reasonably explained by DFT calculations. The intermediacy of a phenonium ion is increasingly invoked to explain the mechanisms of rearrangement reactions, such as the well-known Wagner-Meerwein rearrangement model.[170] In another example involving a phenonium ion in a catalytic process, the synthesis of 2,3-disubstituted indoles from β, β-disubstituted styryl azides catalyzed by Rh was reported by Driver and co-workers (Scheme 3.4).[171] The method provides high selectivity and excellent yields. A mechanistic study showed that the selectivity of the migration process was controlled by the formation of a phenonium ion.

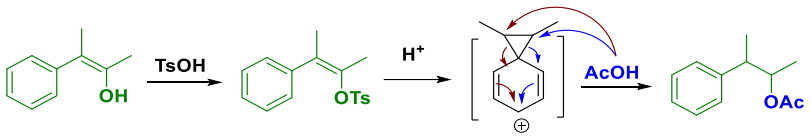



*Scheme 3.4. Rh-catalyzed synthesis of 2,3-disubstituted indoles via a phenonium intermediate.*

The formation of phenonium ions normally requires the pre-activation of the substrate, especially for the Friedel-Crafts alkylation of alcohols involving a phenonium ion intermediate. One representative way to pre-activate alcohols is to convert it to a tosyl group. The better leaving group allows easy access to the phenonium ion.[172] For example, Cram and co-workers reported a stereospecific Wagner-Meerwein rearrangement of the

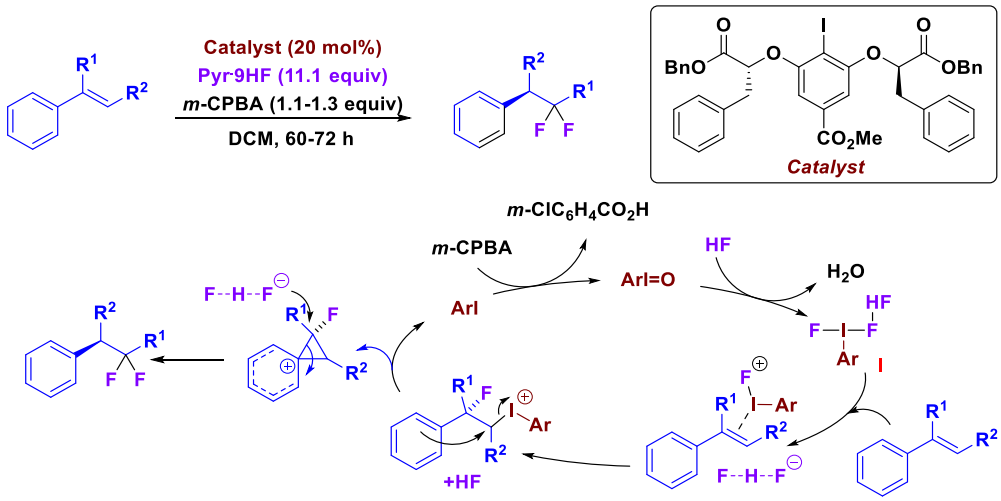
[170] L. Birladeanu, *J. Chem. Educ.* **2000**, *77*, 858.
[171] K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem. Int. Ed.* **2011**, *50*, 1702.
[172] (a) D. J. Cram, R. Davis, *J. Am. Chem. Soc.* **1949**, *71*, 3871; (b) D. J. Cram, *J. Am. Chem. Soc*. **1949**, *71*, 3863; (d) D. J. Cram, *J. Am. Chem. Soc*. **1949**, *71*, 3875.

isomers of 3-phenyl-2-butanol (Scheme 3.5).[173] The 3-phenyl-2-butanol was activated as a *p*-toluenesulfonate to access the corresponding product, which can be easily transformed into the phenonium ion intermediate in the presence of acid. The newly formed phenonium ion intermediate undergoes the acetolysis process to generate the corresponding product.




*Scheme 3.5. Acetolysis of 3-phenyl-2-butanol via a phenonium ion intermediate.*

A strategy for the migratory geminal difluorination of β-substituted styrenes to access a variety of products bearing difluoromethylated tertiary or quaternary stereocenters was also developed by Jacobsen and co-workers (Scheme 3.6).[174] Various 1,1-difluorinated products were prepared with high regio- and enantioselectivity with a range of 49 to 93% yield. Hydrogen fluoride pyridine complex was employed as a fluoride source along with a simple chiral aryl iodide as a catalyst, which can be activated in the presence of *m*-CPBA and combined with HF to generate the aryliodonium **I** species. After activation of the double bond by **I** and the nucleophilic addition of $F^-$ at the benzylic position, the



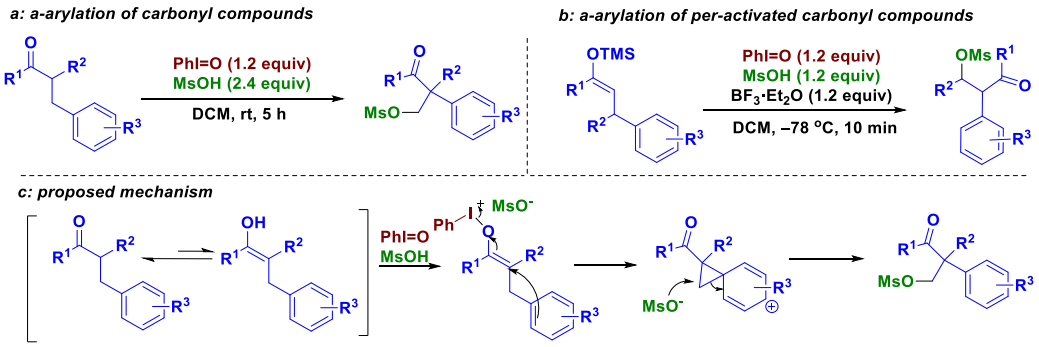

*Scheme 3.6. Difluorination of β-substituted styrenes.*

stereospecific phenonium ion intermediate was generated by elimination of the aryl iodide of the newly formed intermediate. The key step to access the 1,1-difluorinated product is

[173] D. J. Cram, *J. Am. Chem. Soc*. **1952**, *74*, 2129.
[174] S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51.

the stereospecific formation of the phenonium ion intermediate which led to the regioselective fluoride addition to give the desired product.

Another strategy involving the formation of phenonium ion intermediates is the α-arylation of carbonyl compounds through oxidative C-C bond activation that was reported by Maulide and co-workers (a: see Scheme 3.7).[175] Various carbonyl compounds were examined and showed high functional group tolerance with 50 to 95% yield. Mechanistic studies indicated that in the presence of iodosobenzene and MsOH, the fragmentation of enolonium intermediate was triggered by the nucleophilic addition of the neighboring arene to generate a phenonium ion intermediate (c: see Scheme 3.7). The desired α-arylation of carbonyl compounds was obtained following the subsequent addition of mesylate to the three-membered ring. The key to this process is the formation of the phenonium ion intermediate which led to the 1,2-aryl shift. The pre-activated carbonyl compounds (ketone-derived silyl enol ethers featuring an arene residue at the allylic position) were also evaluated and the corresponding products were obtained in 48 to 95% yield within 10 min at lower temperature (-78 °C) due to the easier formation of phenonium ion intermediate (b: see Scheme 3.7).




*Scheme 3.7. α-Arylation of carbonyl compounds through oxidative C−C bond activation.*

## 3.2. Results and Discussion

### 3.2.1. Optimization studies for the monoarylation (ring-opening arylation) of epoxides

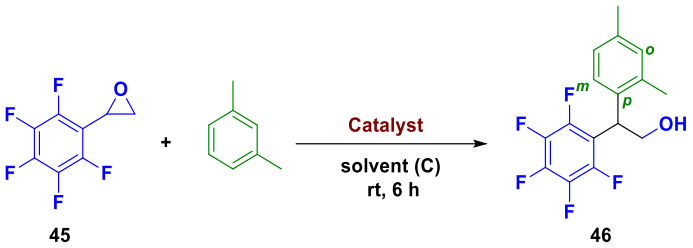
We commenced our investigations by studying the monoarylation of highly electron-deficient styrene oxides, which are notoriously challenging to functionalize. The

[175] J. Li, A. Bauer, G. D. Mauro, N. Maulide, *Angew. Chem. Int. Ed*. **2019**, *58*, 9816.

optimized conditions were determined by examining four aspects: catalyst, solvent, nucleophile loading and reaction concentration. The reaction between (pentafluorophenyl)ethylene oxide and *m*-xylene providing the target product **46** was chosen as a model reaction for the optimization.

Firstly, a range of Lewis and Brønsted acids were employed as catalysts for the ring-opening reaction and the results are shown in Table 3.1 (entry 1-18). Based on the experimental data, the yields obtained with 5 mol% of a variety of Lewis acids are relatively similar (around 70%), but their combination with an additive ($n$Bu$_4$NPF$_6$), whose use allows to increase the acidity of Lewis acids through anion metathesis by generating a heteroleptic complex M(OTf)$_2$(PF$_6$), resulted in better yields, especially for Bi(OTf)$_3$. In that case, the yield was increased from 70 to 96% (entry 8). A control experiment was also performed in the sole presence of $n$Bu$_4$NPF$_6$ and no reaction occurred (entry 9). Brønsted acids could also be employed to furnish the corresponding product in good yields. In particular, 5 mol% of TfOH produced the target product in 97% yield (entry 12). The catalyst loading could be decreased without any drop in yield (91%), but 0.5 mol% TfOH resulted in a lower yield. With the suitable promoter systems in hand (TfOH and Bi(OTf)$_3$/$n$Bu$_4$NPF$_6$ catalyst system), the loading of the nucleophile was screened (Table 3.1, entries 19-26). 5.0 equiv. of nucleophile proved the suitable amount for the reaction to obtain high yields.

Based on the properties of HFIP, such as the enhancement of the acidity, the stabilization of carbocations and low nucleophilicity, the solvent likely plays an important role during the process. In order to find out, we examined common solvents in the reaction as well as their mixture with HFIP (Table 3.1, entries 27-42). None of the conditions tested enabled improvement of the yields or selectivity. The concentration of the reaction was also studied, and lower concentration led to significant decrease of the yield (entry 12 vs. entry 13). Thus, the optimized conditions that we devised for the reaction between (pentafluorophenyl)ethylene oxide and *m*-xylene were the following ones: *m*-xylene (5 equiv) in HFIP (0.4 M) at room temperature for 6 h catalyzed by TfOH (5 mol%) or Bi(OTf)$_3$/$n$Bu$_4$NPF$_6$ (5 mol%).




| Entry | Catalyst | Cat. Loading [mol%] | Additive[b] | Solvent | [C] [M] | Nu [equiv.] | Yield 46 [%][a] *(p:o:m)* |
|---|---|---|---|---|---|---|---|
| 1 | $Sc(OTf)_3$ | 5.0 | - | HFIP | 0.4 | 5.0 | 62 (3.8:1:1) |
| 2 | $Sc(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 5.0 | 76 (5:1:1) |
| 3 | $Al(OTf)_3$ | 5.0 | - | HFIP | 0.4 | 5.0 | 72 (4.5:1:1) |
| 4 | $Al(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 5.0 | 72 (5:1:1) |
| 5 | $Y(OTf)_3$ | 5.0 | - | HFIP | 0.4 | 5.0 | 65 (5:1:1) |
| 6 | $Y(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 5.0 | 76 (5:1:1) |
| 7 | $Bi(OTf)_3$ | 5.0 | - | HFIP | 0.4 | 5.0 | 70 (5:1:1) |
| **8** | **$Bi(OTf)_3$** | **5.0** | ***n*Bu$_4$NPF$_6$** | **HFIP** | **0.4** | **5.0** | **96 (5:1:1)** |
| 9 | - | - | $nBu_4NPF_6$ | HFIP | 0.4 | 5.0 | 0 |
| 10 | TfOH | 0.5 | - | HFIP | 0.4 | 5.0 | 65 (5:1:1) |
| 11 | TfOH | 1.0 | - | HFIP | 0.4 | 5.0 | 91 (5:1:1) |
| **12** | **TfOH** | **5.0** | **-** | **HFIP** | **0.4** | **5.0** | **97 (5:1:1)** |
| 13 | TfOH | 5.0 | - | HFIP | 0.2 | 5.0 | 68 (5:1:1) |
| 14 | TfOH | 10.0 | - | HFIP | 0.4 | 5.0 | 78 (3.8:1:1) |
| 15 | $H_2SO_4$ | 10.0 | - | HFIP | 0.4 | 5.0 | 70 (4:1:1) |
| 16 | HCl | 10.0 | - | HFIP | 0.4 | 5.0 | 67(4.2:1:1) |
| 17 | TFA | 10.0 | - | HFIP | 0.4 | 5.0 | 74 (6:1:1) |
| 18 | CSA | 10.0 | - | HFIP | 0.4 | 5.0 | 70 (5.5:1:1) |
| 19 | TfOH | 5.0 | - | HFIP | 0.4 | 1.0 | 60 (3:1:1) |
| 20 | TfOH | 5.0 | - | HFIP | 0.4 | 2.0 | 78 (5:1:1) |
| 21 | TfOH | 5.0 | - | HFIP | 0.4 | 3.0 | 75 (5:1:1) |
| 22 | TfOH | 5.0 | - | HFIP | 0.4 | 4.0 | 74 (5:1:1) |
| 23 | $Bi(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 1.0 | 54 (3:1:1) |
| 24 | $Bi(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 2.0 | 74 (5:1:1) |
| 25 | $Bi(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 3.0 | 88 (5:1:1) |
| 26 | $Bi(OTf)_3$ | 5.0 | $nBu_4NPF_6$ | HFIP | 0.4 | 4.0 | 89 (5:1:1) |

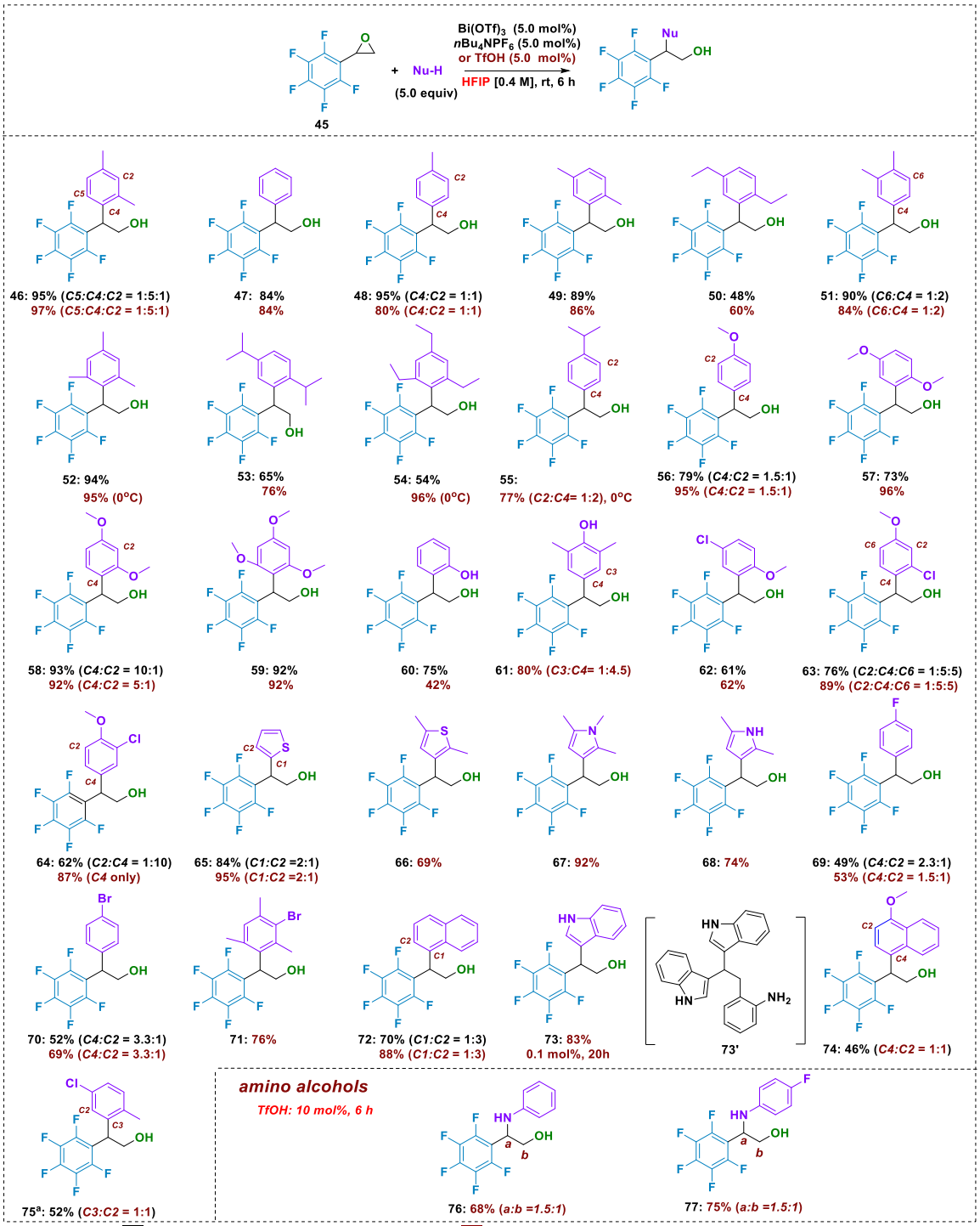
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 27 | TfOH | 5.0 | - | HFIP/$MeNO_2$ (4:1) | 0.4 | 5.0 | 60 (5:1:1) |
| 28 | TfOH | 5.0 | - | HFIP/$MeNO_2$ (1:1) | 0.4 | 5.0 | 50 (6:1:1) |
| 29 | TfOH | 5.0 | - | HFIP/$MeNO_2$ (1:4) | 0.4 | 5.0 | 40 (5:1:1) |
| 30 | TfOH | 5.0 | - | $MeNO_2$ | 0.4 | 5.0 | 43 (4:1:1) |
| 31 | TfOH | 5.0 | - | HFIP/toluene (4:1) | 0.4 | 5.0 | 42 (3:1:1) |
| 32 | TfOH | 5.0 | - | HFIP/toluene (1:1) | 0.4 | 5.0 | 41 (3:1:1) |
| 33 | TfOH | 5.0 | - | HFIP/toluene (1:4) | 0.4 | 5.0 | 33 (3:1:1) |
| 34 | TfOH | 5.0 | - | toluene | 0.4 | 5.0 | - |
| 35 | TfOH | 5.0 | - | HFIP/1,2-DCE (4:1) | 0.4 | 5.0 | 76 (5:1:1) |
| 36 | TfOH | 5.0 | - | HFIP/1,2-DCE (1:1) | 0.4 | 5.0 | 73 (5:1:1) |
| 37 | TfOH | 5.0 | - | HFIP/1,2-DCE (1:4) | 0.4 | 5.0 | 72 (5:1:1) |
| 38 | TfOH | 5.0 | - | 1,2-DCE | 0.4 | 5.0 | 46 (4.8:1:1) |
| 39 | TfOH | 5.0 | - | HFIP/DCM (4:1) | 0.4 | 5.0 | 68 (5:1:1) |
| 40 | TfOH | 5.0 | - | HFIP/DCM (1:1) | 0.4 | 5.0 | 72 (5:1:1) |
| 41 | TfOH | 5.0 | - | HFIP/DCM (1:4) | 0.4 | 5.0 | 72 (5:1:1) |
| 42 | TfOH | 5.0 | - | DCM | 0.4 | 5.0 | 55 (5:1:1) |

*[a] Isolated yields; [b] 5 mol% additive.*

*Table 3.1. Optimization of the reaction conditions.*

### 3.2.2. Scope of arene nucleophiles

With optimized conditions in hand, we first explored the scope of (pentafluorophenyl)ethanol synthesis from styrene oxide **45** using a large array of aryl and heteroaryl nucleophiles (see Table 3.2). The transformation was compatible with a wide range of mono-, to tetrasubstituted arenes, incorporating either electron-donating or electron-withdrawing substituents to afford the corresponding products **43-77** in 42-97% yields. The steric hindrance exhibited by the various functional groups on the nucleophile did not hamper the reactivity, as nearly quantitative yields were obtained in most cases (up to 97%). In the case of 1,3,5-triethylbenzene and mesitylene as nucleophiles, a mixture of monoarylated product (**52** and **54**) and 1,2-diarylated product was observed. However, conducting the reaction at 0 °C enabled the selective formation of **52** and **54** in 95% and 96% yields, respectively. The more nucleophilic 1,3,5-trimethoxylbenzene was also employed to produce the ring-opening arylated product **59** in 92% yield. Moreover, the reaction could be extended to less electron-rich nucleophiles, such as benzene (**47**), fluorobenzene (**69**) and bromobenzene (**70**), providing arylated compounds in 53-84% yields. On the other hand, nucleophiles such as 1,4-difluorobenzene and 1,4-dibromobenzene were not sufficiently reactive due to their reduced nucleophilicity. In




*Isolated yield;* ■ *catalyzed by Bi(OTf)3 and nBu4NPF6;* ■ *catalyzed by TfOH. [a] Yield determined by $^1$H NMR using hexamethyldisiloxane as an internal standard.*

*Table 3.2. Scope of arene nucleophiles.*

those cases, oligomerization and the ring-opening with the addition of HFIP occurred. Of note, lowering the reaction concentration to 0.2 M improved the yield to 90% in the case of benzene adduct **47**, in agreement with previous studies that identified the key role of H-bonded solvent clusters in Lewis and Brønsted acid-catalyzed reactions in HFIP.[176]

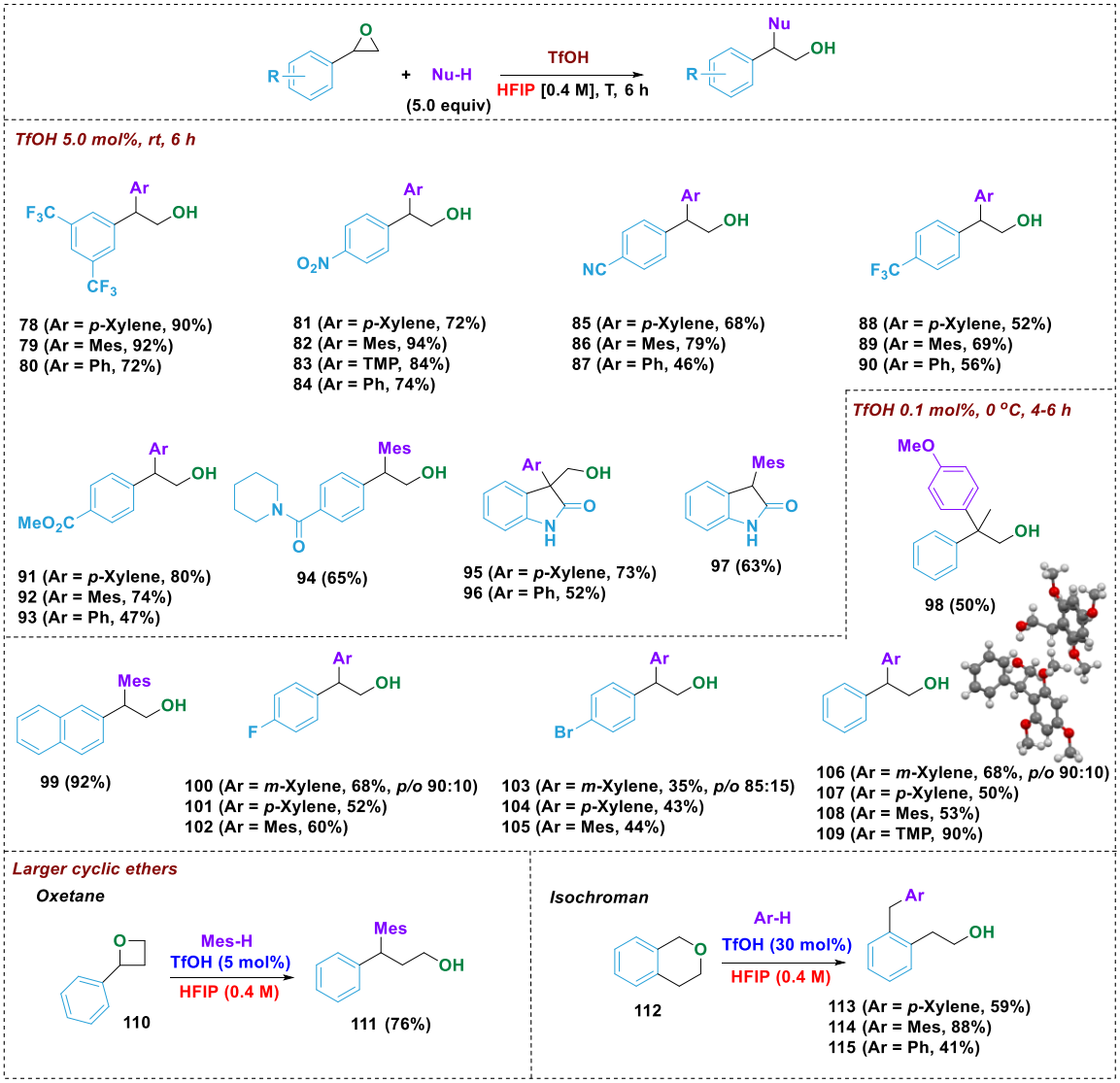
[176] V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun.*, **2020**, *56*, 11548.

Thus, the use of less nucleophilic arenes is compensated by activating the epoxide with a more acidic H-bond network. For reactions of some arenes, mixtures of regioisomers favoring the *para*-product were observed, which is typical for Friedel-Crafts alkylations. In the case of phenol, a mixture of *ortho*-C and O-alkylation products was obtained while using TfOH, but a less acidic promoter such as $Bi(OTf)_3/nBu_4NPF_6$ exclusively furnished the *ortho*-C product **60** (75%). Heteroarenes such as thiophenes, pyrroles and indoles were also tolerated, affording compounds **65**-**68** and **73** in high yields (up to 95%). In the case of indole, lower catalyst loadings (0.1 mol%) were necessary to prevent competitive hydroarylation processes, forming **73** in 83% yield. Based on the NMR analysis of the by-product, we identified the product **73'** resulting from a diarylation with another ring-opening of the indole ring. In turn, furans decomposed under the acidic reaction conditions. $Bi(OTf)_3/nBu_4NPF_6$ led to similar yields as TfOH for most arenes such as benzene, xylene and 1,3,5-trimethoxylbenzene. Useful amino alcohols were also prepared by employing as anilines as nucleophiles, yielding the corresponding amino alcohols **76** and **77** with a moderate selectivity (around 1.5:1).

### 3.2.3. Scope of styryl oxides

Pentafluorostyrene oxide is one of the most highly electron-deficient styrene oxides, and our method worked smoothly with a wide range of nucleophilic arenes to produce (pentafluorophenyl)ethanols in good to excellent yield. The efficacy of this reaction can be associated to the fact that pentafluorostyrene oxide is not prone to oligomerization so that less nucleophilic arenes such as fluorobenzene and bromobenzene were compatible with our transformation. Thus, in the next set of experiments, we examined the influence of the styryl oxide substitution pattern, using arenes with different nucleophilicity such as *p*-xylene, mesitylene and benzene (see Table 3.3). Deactivated styrene oxides incorporating synthetically relevant electron-withdrawing groups (nitro, nitrile, trifluoromethyl, ester, and amide groups) furnished products in 46-94% yields (**78**-**94**) regardless of the nucleophile employed. When less electron-deficient styrene oxides were employed, such as 4-fluorostyrene oxide and 4-bromostyrene oxide, the catalyst loading had to be decreased to 0.1 mol% to provide the target compounds in yields ranging from 35 to 68% (**100**-**105**) at 0 °C. Dimerization of the substrates was in fact observed at higher temperatures. The same reaction conditions were used to access the desired products through the ring-opening of as styrene oxide and 2-(naphthalen-2-yl)oxirane in moderate to high yields (50-92%). In the case of styrene oxide, more nucleophilic 1,3,5-

trimethoxylbenzene significantly increased the yield to 90% (**109**). On the other hand, these more reactive styrene oxides were not compatible with weak arene nucleophiles, such as benzene, due to the oligomerization of the former. The reaction was tolerant to 1,1-disubstituted epoxides (**95, 96** and **98**), including those bearing the framework of




*Mes = 1,3,5-trimethylphenyl. TMP = 1,3,5-trimethoxyphenyl.*

*Table 3.3. Scope of styryl oxides and larger cyclic ethers.*

interest indolin-2-one. 52% (**96**) and 73% (**95**) of ring-opening products were obtained following the reaction between spiro[indoline-3,2'-oxiran]-2-one and benzene and xylene. In the case of mesitylene, a product was also detected by $^{1}$H NMR in 65% yield, but, after purification, the product rearranged into **97** (63%). We believe that the more sterically hindered mesitylene led to a secondary alcohol which is not stable so that, during the purification, it decomposed to give the rearrangement product. Our method was also applied to the ring-opening of larger cyclic ethers. For instance, the reactions with 2-

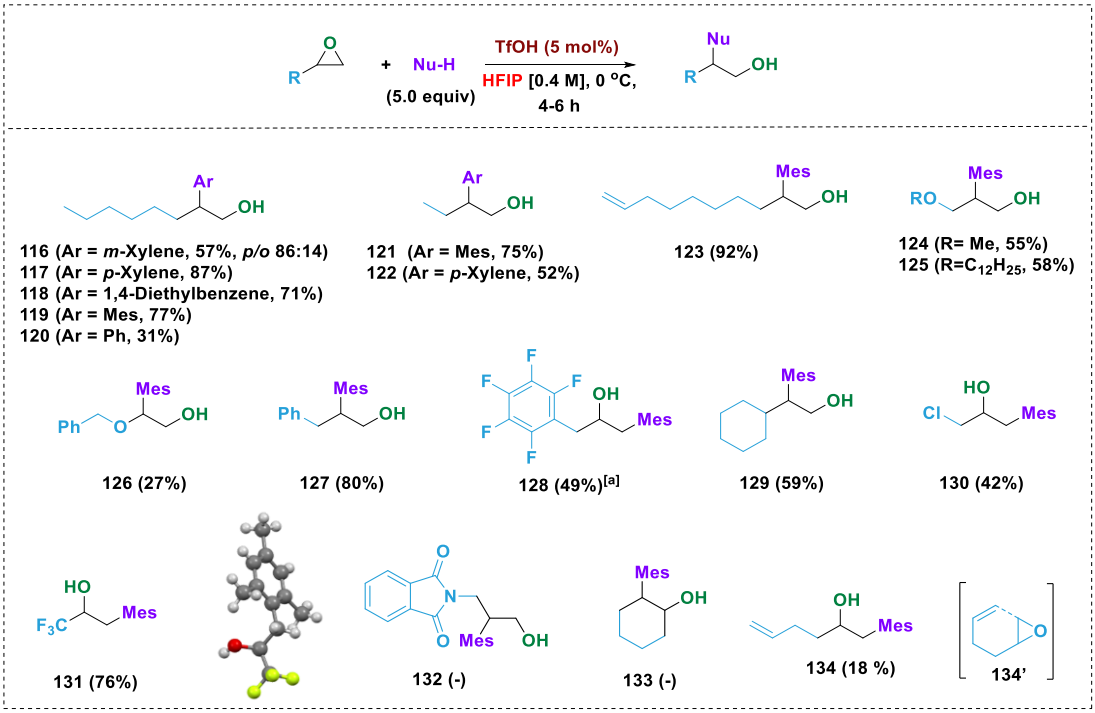
phenyloxetane **110** and isochroman **112** generated the corresponding phenyl propanol and ethanol derivatives **111**, **113**, **114** and **115** in 41-88% yields. An increased catalyst loading of 30 mol% was required to enable the complete arylation of isochroman at the benzylic position. Of note, only one example of an arylation of oxetane as well as isochroman had been reported in the literature, both of which require pre-activated arene nucleophiles.

### 3.2.4. Scope of aliphatic epoxides

Based on the scope of the different substituted arenes of epoxides, we observed that the presence of an electron-withdrawing group decreases the reactivity of the corresponding epoxide and led to high yields for the ring-opening arylation. On the other hand, the presence of an electron-rich arene resulted in lower yields due to the formation of oligomerization by-products. Thus, we next turned our attention to aliphatic epoxides in the ring-opening reaction. One of the strengths of this reaction system is its efficacy with alkyl-substituted oxiranes, selectively affording branched products in high yields (up to 92%, **116-131**) (see Table 3.4). The reaction also showed high functional group tolerance, for example, the transformation exhibits chemoselectivity in the presence of an alkene functionality, providing product **123** in 92% yield. However, in the case of a substrate with a shorter chain, the corresponding product was obtained in low yield (**134**: 18%). The reason behind is that the alkene can engage in an intramolecular interaction to form a six-membered ring (**134'**). The reaction was also tolerant of oxygen functionalities (**124-126**); the corresponding products were afforded in 27-58% yields. The lower yield with the benzyl ether can be explained by the fact that this functional group can be easily activated under our reaction conditions to lead to several by-products. In contrast with typical aliphatic epoxides, the presence of electron-withdrawing substituents near the oxirane renders the internal position less electrophilic and induces addition at the terminal position, furnishing secondary alcohols (**128**, **130**, **131**), in agreement with previous studies from Prakash and Olah.[177] This difference of regioselectivity is particularly striking in the case of **127** and **128**. Due to the deactivation of the epoxide by a pentafluorophenyl group, using 2-((perfluorophenyl)methyl)oxirane as a substrate yielded the 1,2-diarylated adduct as a minor product in 34% yield at 40 °C for 24 h. The reaction also required a higher catalyst loading of 10 mol%. Product **132** was not obtained from the corresponding epoxide because of the trapping of the catalyst by the phthalimide.

[177] G. K. S. Prakash, P. J. Linares-Palomino, K. Glinton, S. Chacko, G. Rasul, T. Mathew, G. A. Olah, *Synlett.* **2007**, 1158.

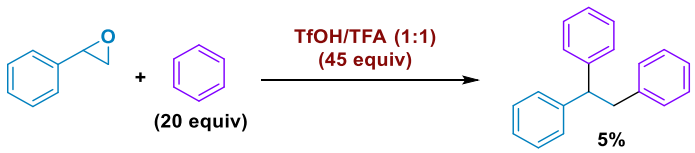
We also attempted the reaction with cyclohexene oxide, but we only observed the decomposition of the substrate.




*[a] 10 mol% TfOH, 40 °C for 24 h; Mes = 1,3,5-trimethylphenyl.*

*Table 3.4. Scope of aliphatic epoxides.*

### 3.2.5. Dehydrodiarylation of epoxides

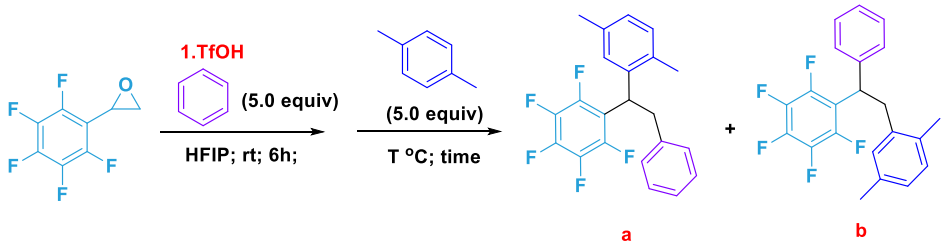



*Scheme 3.3. Dehydrodiarylation of epoxides under superacidic reaction conditions.*

Regarding the 1,2-diarylation of epoxides, only one report was described by Molnar and co-workers (Scheme 3.3). [178] The superacidic trifluoromethanesulfonic acid was employed in super-stoichiometric amounts with benzene as nucleophile, but low yields were obtained for aliphatic epoxide (15%) and styrene epoxide (5%) according to the catalyzed system (TfOH + TFA/benzene/epoxide = 45: 20: 1). Under superacidic conditions, the reaction of epoxides follows an $S_N1$ mechanism. The formed carbocation underwent various rearrangements, resulting in the formation of a series of by-products.

[178] A. Molnar, I. Ledneczki, I. Bucsi, M. Bartok, *Catal. Lett.* **2003**, *89*, 1.

Based on the previous studies from our group on the activation of primary alcohols and the results gathered from the ring-opening of epoxides under TfOH catalysis, we thought that TfOH could be also employed to activate the primary alcohols generated by the ring-opening of epoxides. We chose as a model reaction the ring-opening of pentafluorostyrene oxide using benzene (5 equiv.) as first nucleophile and *p*-xylene (5 equiv.) as second




| Entry | catalyst | Cat. loading | Time [h] | T2[°C] | [C] [M] | NMR yield [%] (*a:b*) |
|---|---|---|---|---|---|---|
| 1 | TfOH | 5.0 | 24 | 140 | 0.4 | 70 (2:1) |
| 2 | $Bi(OTf)_3$[a] | 5.0 | 24 | 140 | 0.4 | 65 (2:1) |
| 3 | TfOH | 5.0 | 24 | 100 | 0.4 | 33 (5:1) |
| 4 | TfOH | 5.0 | 24 | 80 | 0.4 | 20 (10:1) |
| 5 | TfOH | 5.0 | 48 | 60 | 0.4 | 10 (15:1) |
| 6 | TfOH | 5.0 | 48 | 80 | 0.4 | 59 (10:1) |
| 7 | TfOH | 10.0 | 24 | 80 | 0.4 | 60 (6:1) |
| 8 | TfOH | 15.0 | 24 | 80 | 0.4 | 58 (6:1) |
| 9 | TfOH | 20.0 | 24 | 80 | 0.4 | 40 (6:1) |
| **10** | **TfOH** | **5.0** | **48** | **80** | **0.2** | **82 (10:1)** |

*[a] reaction conducted with 5% $nBu_4NPF_6$.*

*Table 3.5. Optimization of the dehydrodiarylation of epoxides reaction conditions.*

nucleophile (see Table 3.5). As the first step was previously optimized, we focused on the activation of the primary alcohol formed. Conducting the reaction at high temperature (140 °C) led to the formation of the target product in high yield (65-70%) along with a moderate regioselectivity using either TfOH and $Bi(OTf)_3$/$n$Bu$_4$NPF$_6$ (entries 1 and 2). On the other hand, decreasing the temperature improved drastically the selectivity of the reaction but at the expense of the reactivity (entries 3-5). We also tried to increase the catalyst loading; however, it ended up being detrimental to the reaction as we observed the decomposition of the substrate (entries 7-9). Finally, by decreasing the concentration and increasing the reaction time, we succeeded to obtain the diarylation product in 82% yield. The optimized reaction conditions for the 1,2-diarylation of epoxides proved to be the following conditions: TfOH (5 mol%), HFIP [0.2M], rt, 6 h (step 1) and 80 °C, 48 h

(step 2). The structure of the major product was confirmed by a 2D NMR (HMBC) (see Figure 3.2), which is consistent with our mechanism proposed involving the formation of a phenonium ion.

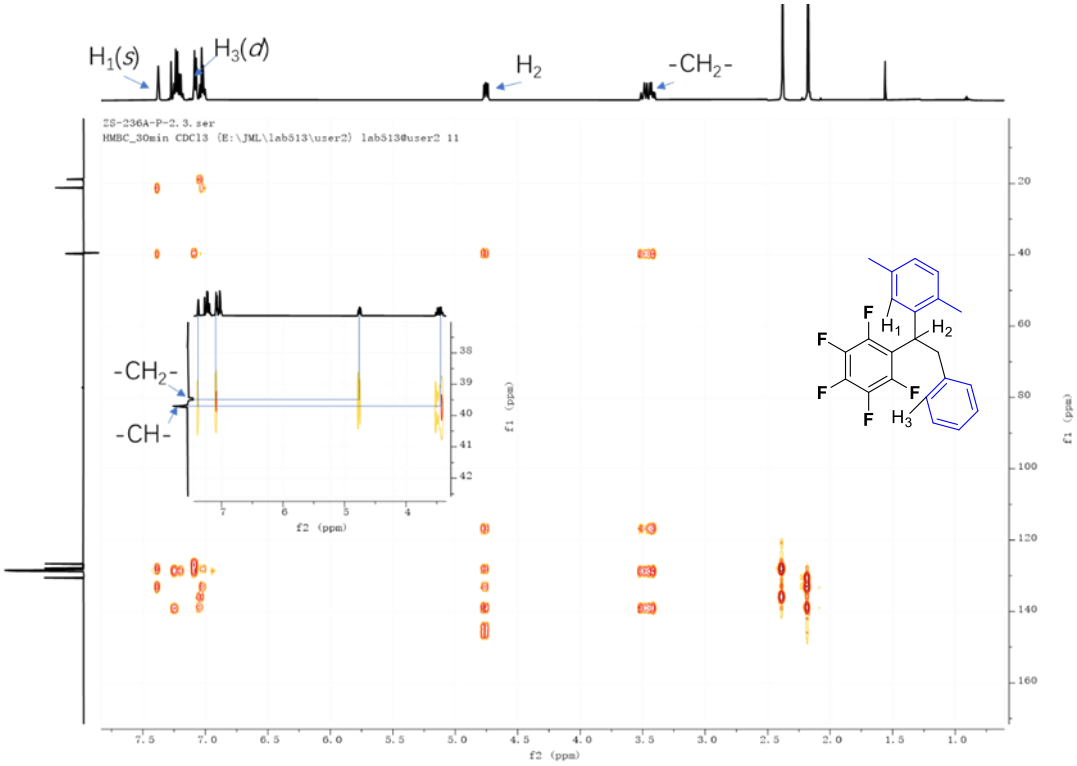
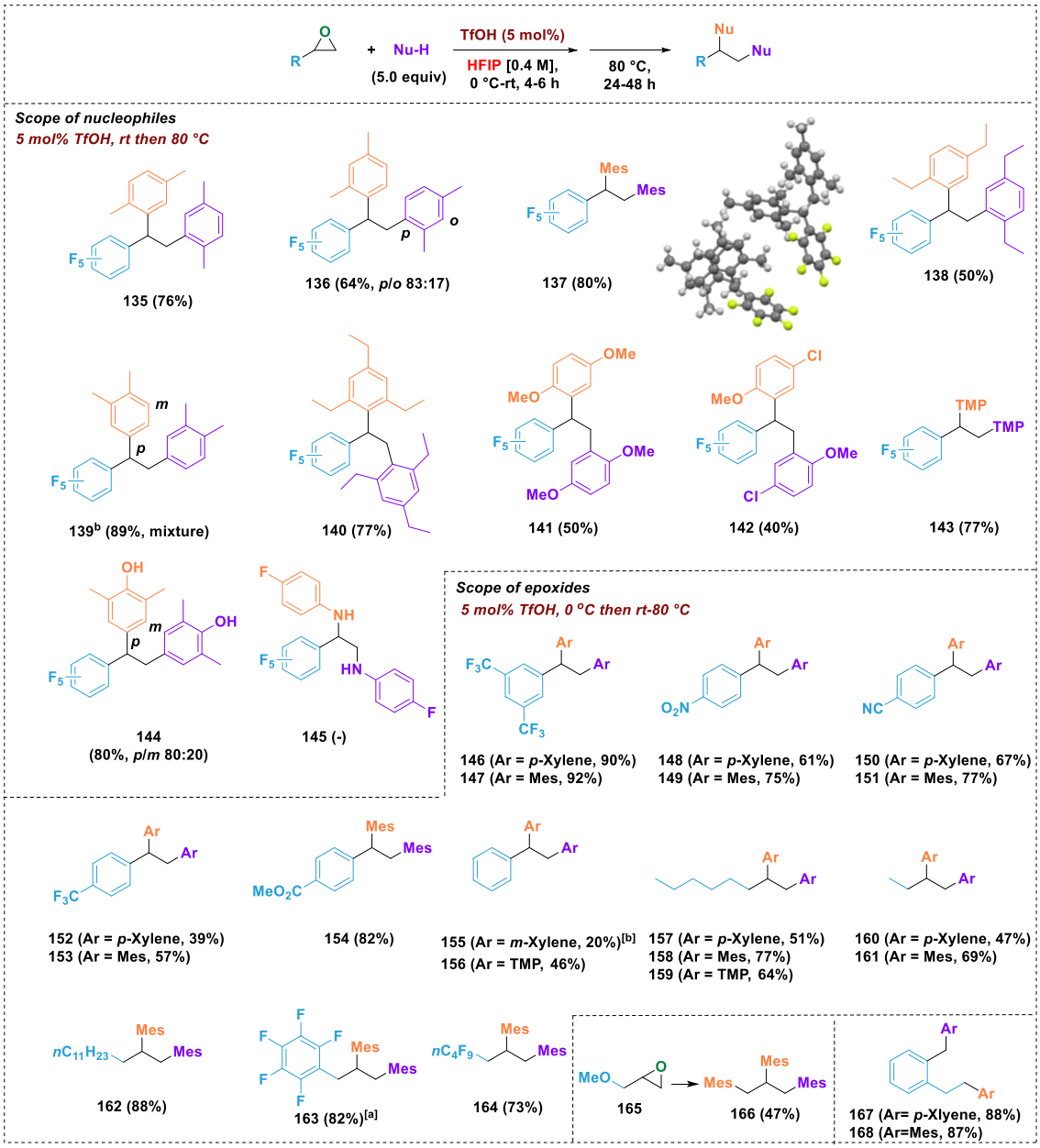



*Figure 3.2. 2D NMR (HMBC) of the1,2-diarylation of pentafluorostyrene oxide with two different nucleophiles.*

### 3.2.6. Scope of nucleophiles for dehydrodiarylation of epoxides

With the optimized conditions in hand for the activation of primary alcohols, we first studied the formation of 1,1,2-triarylethanes from pentafluorostyrene oxide using the same nucleophile for both steps. After completion of the first step at room temperature, we simply increased the temperature to 80 °C to trigger the second arylation, affording the product **135** in 76% yield. In that case, the concentration has no significant effect on the transformation as a similar yield was observed at 0.2 M or 0.4 M. A series of electron-rich arene nucleophiles bearing alkyl, methoxy, halide and hydroxy functionalities was examined in reaction with pentafluorostyrene oxide, giving the target products in 40-80% yields (**135-144**). In some cases (**136**, **139** and **144**), a mixture of regioisomers was obtained, which results from the regioselectivity of the first arylation with the styrene

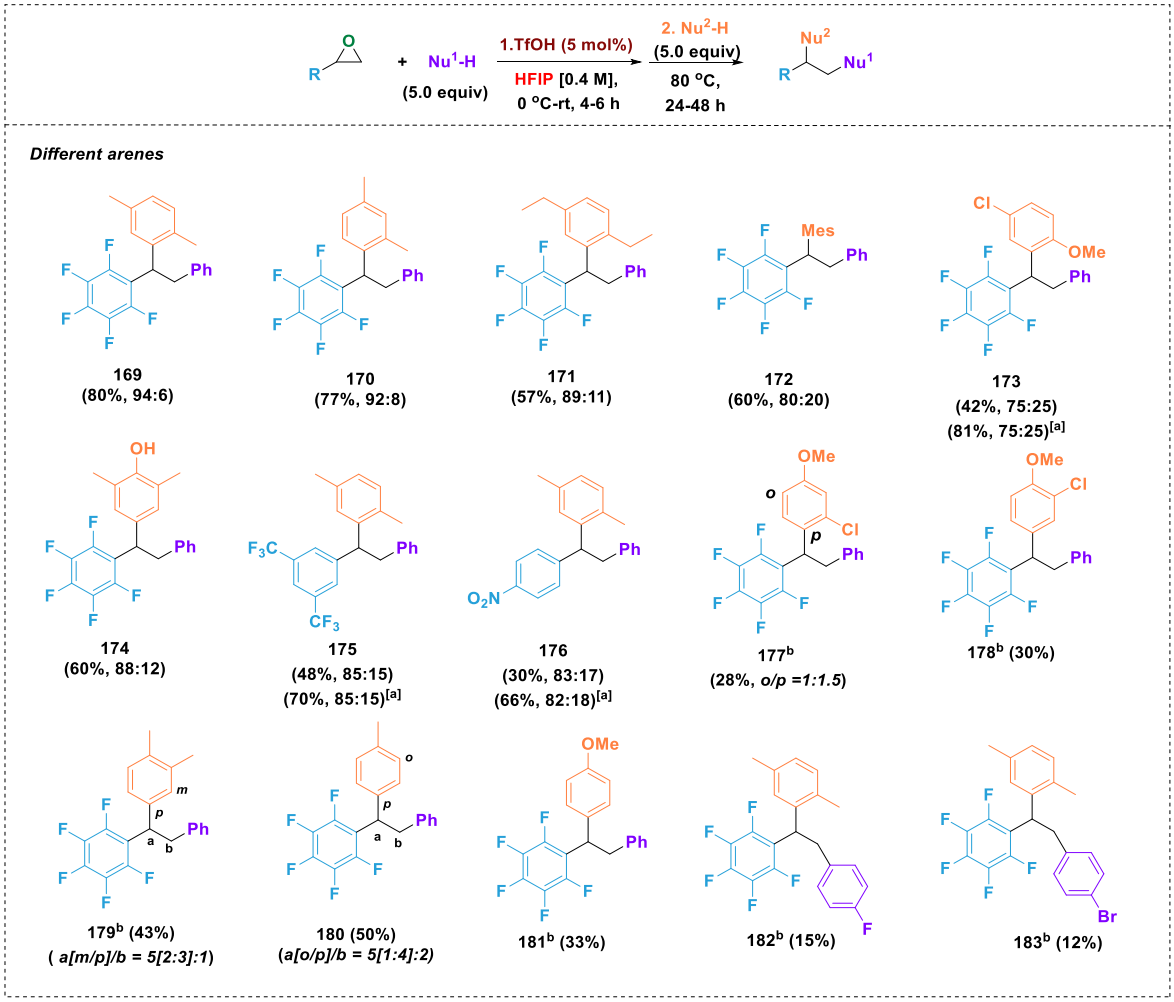



*[a] reaction conducted at 60 °C for 48 h; [b] Yield determined by $^1$H NMR using hexamethyldisiloxane as an internal standard.*

*Table 3.6. Dehydrodiarylation of epoxides.*

oxide (cf. Table 3.3). While poor nucleophilic arenes such as benzene could be employed in the first step, they are not competent nucleophiles for the second step, as the phenyl ethanol intermediate remained intact even at higher temperatures (up to 140 °C). Heteroarenes could not be employed to produce the corresponding diarylation product due to their decomposition at the higher temperature required for the second step. Although 4-fluoroaniline was employed to yield the corresponding amino alcohol in the ring-opening amination of epoxides, the diaminated product was not generated under our

conditions. Diversely substituted oxiranes (alkyl and aryl groups) also underwent the transformation to deliver the corresponding 1,1,2-triarylethanes and 1,2-diarylethanes in high yields (**146-164**, up to 92%). On the other hand, reactions with styrene oxide led to products in lower yields (**155** and **156**). In this case, the alcohol intermediate appeared to rapidly dehydrate to generate the corresponding styrene, which subsequently oligomerized. Overall, a comparison of Table 3.3, 3.4 and Table 3.6 shows that the yields obtained for the dehydrodiarylation are limited by the initial ring-opening arylation, with the subsequent dehydroarylation being highly efficient. In the case of alkyl-substituted oxiranes bearing electron-withdrawing groups, notably pentafluorobenzyl and perfluoroalkyl moieties, where the regioselectivity of the first step was inverted, the dehydrodiarylation was still accomplished in 82% and 75% yields, respectively (**163** and **164**). Going further, a triarylation was possible to attain as methyl glycidyl ether **165** gave 1,2,3-triarylpropane **166** in 47% yield. Lastly, the diarylation reaction could be also applied to isochroman to afford **167** and **168** in high yields (87-88%).



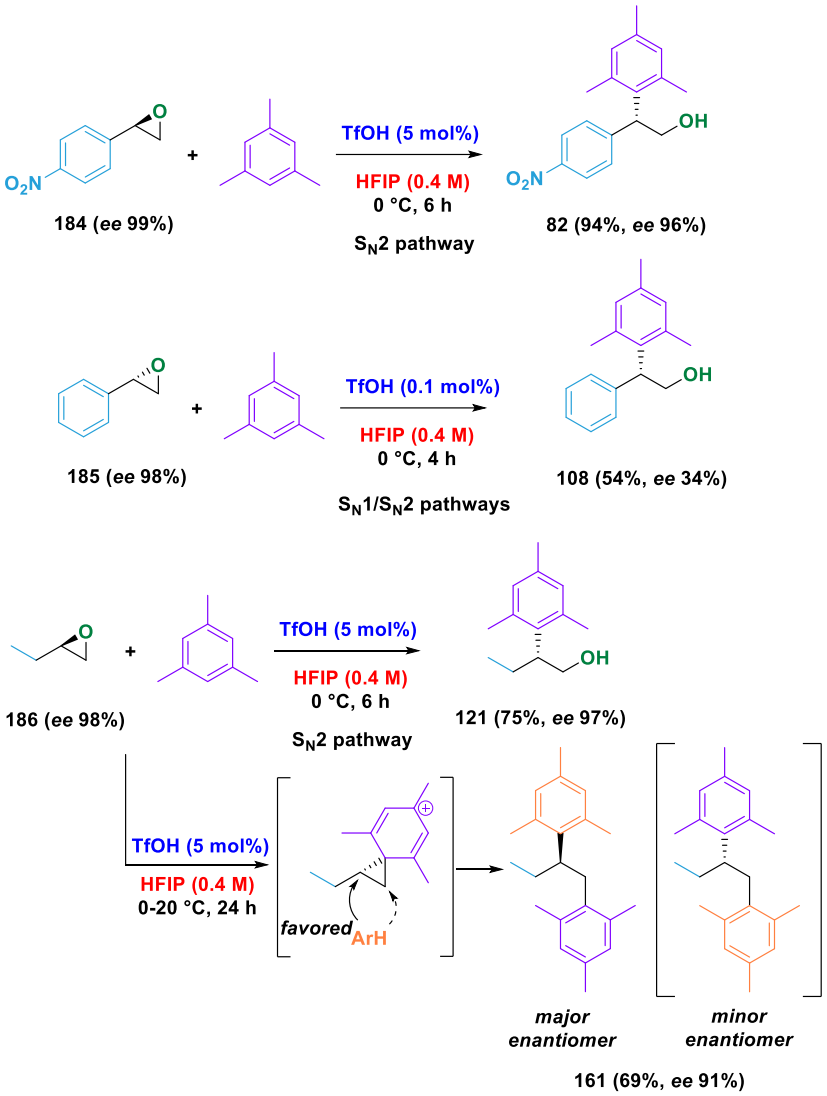

*[a] Yield over two steps. [b] Yield determined by $^1$H NMR using hexamethyldisiloxane as an internal standard.*

*Table 3.7. Dehydrodiarylation of epoxide with two different nucleophiles*.

Two different arenes could also be installed in a sequential, one-pot fashion by exploiting their difference in nucleophilicity. For instance, by using benzene as nucleophile for the epoxide ring-opening before adding a second more-nucleophilic arene, 1,1,2-triarylethanes were generated with three different aryl moieties in moderate to high yields (**169-183**). We also observed the formation of a minor regioisomer arising from nucleophilic addition at the terminal position, likely a consequence of a steric clash between the phenonium intermediate and the nucleophile (the more the nucleophile is hindered, the more the minor regioisomer is formed). In cases where the yields were moderate (**173**, **175** and **176**), we noticed that the phenyl ethanol intermediate before re-subjecting it to the reaction conditions significantly improved the yields (66-81% yield over two steps). A wide range of nucleophiles was used for the second step (see Table 3.7), such as xylene, mesitylene and anisole derivatives. Even less nucleophilic toluene was employed for the second step to access the corresponding product **180** in 50% yield, but the selectivity was moderate with a ratio *a[o/p]/b*=5[1:4]:2 (see Table 3.7). While fluorobenzene and bromobenzene could be employed in the first step, their presence only produced the diarylated compounds **182** and **183** in low yields (15 % and 12%, respectively), which might be explained by the fact that they are less prone to stabilize the phenonium intermediate.

## 3.3. Mechanistic studies

### 3.3.1. Stereochemical studies on the reactivity of epoxides




*Scheme 3.4. Stereochemical studies.*

To establish whether the ring-opening monoarylation of epoxides occurs through an $S_N1$ or an $S_N2$ process, we examined the reactivity of three representative enantioenriched chiral epoxides: 4-nitrostyrene oxide **184**, styrene oxide **185** and alkyl epoxide **186** (Scheme 3.4) which almost covered all the cases examined in our study. According to the $S_N1$ process, the formation of a carbocation intermediate led to the loss or a significant decrease of enantioselectivity for the monoarylation product. An $S_N2$ process would result in a stereoinvertive addition. Therefore, the pathway of the ring-opening of epoxide could

be confirmed by determining the enantiomeric excesses of the monoarylation products prepared from enantioenriched chiral epoxides. Firstly, in the case of **184** and **186**, the chiral information was nearly completely transferred to the product alcohols **82** (96% *ee*) and **121** (97% *ee*), respectively through a stereoinvertive arylation of the epoxide. In contrast, in the case of **185**, a significant erosion of the enantiomeric excess from 98% *ee* to 34% *ee* was observed. Thus, the results are consistent with the scenario where electron-poor styrene oxides and aliphatic epoxides undergo a highly stereospecific $S_N2$ Friedel-Crafts alkylation, whereas more electron-rich styrene oxides proceed through competitive $S_N1$ and $S_N2$ mechanisms. In the same vein, we determined the *ee* of the diarylated product **161**, which diminished from 97% to 91% in **121**, being consistent with the intermediacy of a phenonium intermediate. The slight decrease of *ee* was attributed to competing nucleophilic addition to the phenonium intermediate at either the internal (major) or terminal (minor) carbon, as mentioned previously.

### 3.3.2. DFT calculations

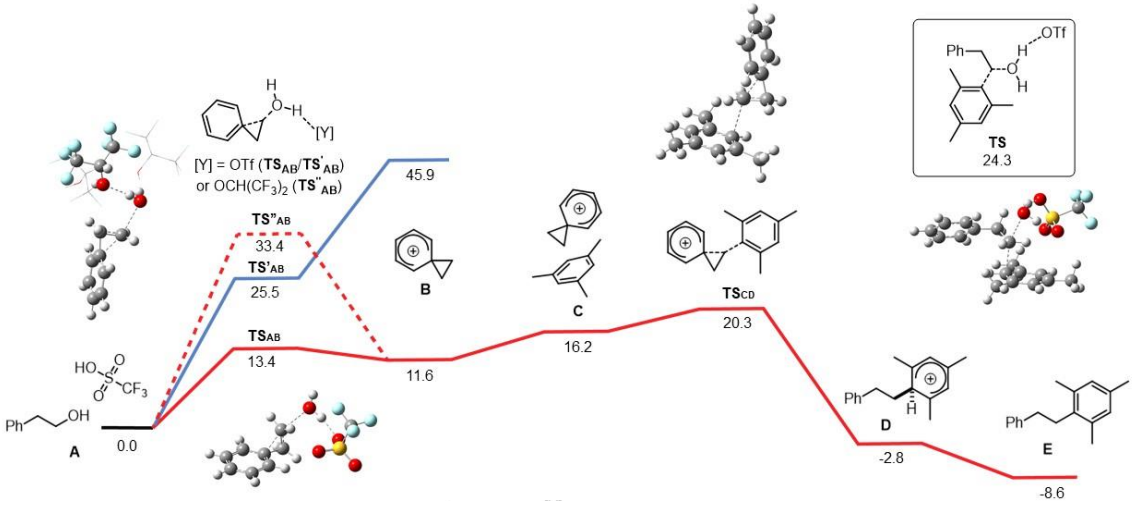



*Figure 3.3. Gibbs energy profiles (ΔG, kcal mol$^{-1}$) for the addition of mesitylene to 2-phenyl ethanol.*

To gain a deeper understanding of the Friedel-Crafts reaction of primary aliphatic alcohols in HFIP for the second step of diarylation of epoxides, we used Density Functional Theory (DFT) calculations to model the potential reaction mechanisms involved for 2-phenyl ethanol. All calculations were performed using Gaussian 16. The B3LYP exchange correlation was used with the def2-TZVP basis set.[179] The Grimme D3 correction for

[179] F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057.

dispersion was employed with the Becke-Johnson damping function.[180] The SMD continuum solvation model was applied to HFIP and toluene solvents. The Cartesian coordinates for the optimized structures are provided in the experiment part. Those calculations were carried out by Dr. Christopher Rowley at Carleton University (Canada).

The much lower reaction temperatures required for Friedel-Crafts reactions of phenyl ethanols compared to simple primary aliphatic alcohols suggests that the former react through a different mechanism, which would be consistent with the formation of a stable phenonium intermediate. We identified a concerted mechanism where TfOH transfers a proton to the hydroxyl group of phenyl ethanol while a C–C bond is formed between the α-carbon and the *ipso* carbon of the phenyl ring. At the transition state, the proton transfer is effectively complete, forming a structure where the nascent water molecule acts as a Lewis base for the carbocation. Once formed, the phenonium ion undergoes nucleophilic addition with mesitylene to form a Wheland intermediate. Deprotonation of this Wheland intermediate yields the product. The Gibbs energy profile for this mechanism is presented in Figure 3.3. By comparing the calculations in toluene *versus* HFIP, the importance of solvent becomes evident. In a continuum solvent model for toluene, the phenonium is a high-energy species (45.9 kcal/mol), due to the lack of stabilizing electrostatic interactions with the polar solvent. In a continuum model for HFIP, the phenonium is far more stable (11.6 kcal/mol), consistent with the stabilization of ionic intermediates by the higher dielectric constant of HFIP. As a potential alternative mechanism that avoids a phenonium ion, we also considered a pathway in which the attack by mesitylene is concerned with the proton transfer from TfOH to the alcohol. However, the activation energy for this pathway (24.3 kcal/mol) is higher than the one proceeding through the phenonium ion intermediate.

Based on the experimental and theoretical calculations, the mechanism of the ring-opening and 1,2-difunctionalization of epoxides that we proposed is shown in Figure 3.4. The epoxides can be opened following a $S_N2$ or $S_N1/S_N2$ pathway to generate the monoarylation product. The substituted arene plays an important role in this step: the more electron deficient the substituted arenes, the more the mechanism leans toward an $S_N2$ process. Once the monoarylation product was formed, there are two possible pathways: 1) the newly generated hydroxyl group is protonated with the assistance of HFIP and a

[180] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

subsequent direct nucleophilic addition of the arene would produce the 1,2-diarylation product. In the case of same nucleophile addition, the desired product can be generated, but in the case of different nucleophile, a by-product was formed due to the required high temperatures for the direct activation of primary alcohols; 2) the newly generated hydroxyl group is protonated by the

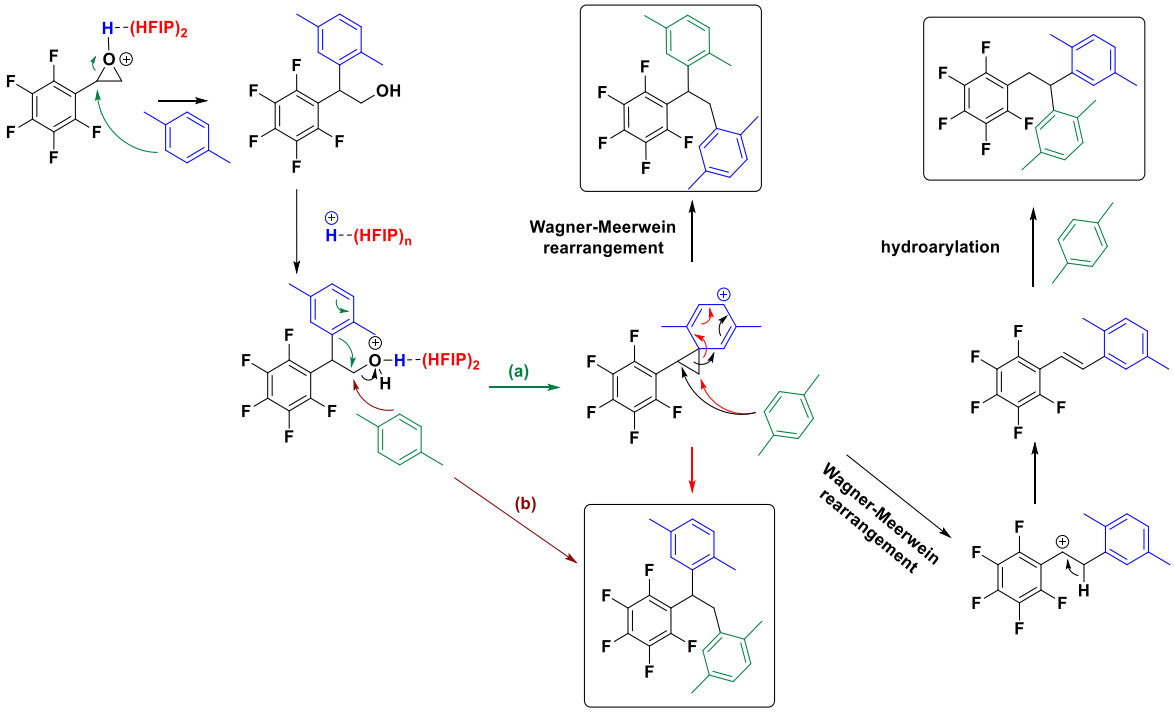



*Figure 3.4. Proposed mechanism for 1,2-difunctionalization of epoxides.*

catalyst with the assistance of HFIP and gives the phenonium ion intermediate. Then, there are two positions for the nucleophilic addition with the most substituted position favored through the Wagner-Meerwein rearrangement. Alternatively, the nucleophile could, in principle, attack the terminal position. In some cases, the styrene can be generated by Wagner-Meerwein rearrangement of the phenonium ion intermediate and hydroarylation with the arene nucleophile to form another by-product.

## 3.4. Conclusion of Chapter 3

In summary, HFIP enables a significant expansion of the Friedel-Crafts reaction to now include most classes of terminal epoxides, oxetanes and isochromans as electrophiles. As Friedel-Crafts reactions featuring epoxides produce primary aliphatic alcohols, the dehydrodarylation of epoxides has now been described, where two of the same arene or two different arenes can be introduced in one pot. This method opens direct access to phenonium ions from phenyl ethanols, which should reach beyond the Friedel-Crafts

reaction, allowing new ionic transformations to be developed. For most classes of epoxides, the reactions are stereospecific, which should be useful for stereoselective synthesis. Our mechanistic studies suggest that simple primary aliphatic alcohols react through a phenonium ion intermediate. Finally, all the reactions described herein start directly from readily available precursors without pre-activation steps.

# 4. Linear-selective reductive arylation of epoxides mediated by HFIP

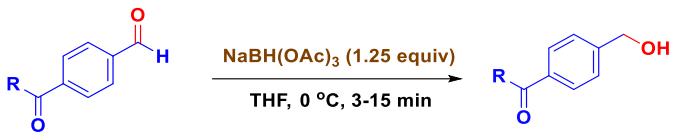
## 4.1. Scientific background and context

Primary alcohols are important building blocks for the synthesis of pharmaceuticals, agrochemicals, solvents, and fragrances. Based on the wide range of applications of primary alcohols, the development of efficient methods to synthesize them remains essential. Here, selected methods are given for the synthesis of primary alcohols.

### 4.1.1. Synthesis of primary alcohols by reduction of aldehydes

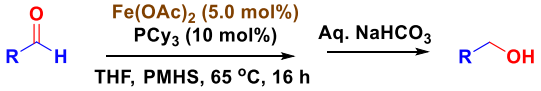
Early strategies for the synthesis of primary alcohols are the reduction of aldehydes by reducing agents, such as $LiAlH_4$, $NaBH_4$, and DIBAL-H, in polar solvent. However, although many reducing agent can reduce aldehydes to primary alcohols, most are too reactive to do so chemoselectively in the presence of other functional groups such as ketones under normal conditions. For example, chemoselective reduction of aldehydes by $NaBH_4$ is only achieved at very low temperatures[181] or by the addition of other reagents such as thiols,[182] metal salts,[183] or resins.[184] To decrease the reactivity of $NaBH_4$, several modified $NaBH_4$ analogues have been developed. $NaBH(OAc)_3$ [185] and $NaBH(OCH(CF_3)_2)_3$ [186] take advantage of steric and electron-withdrawing effects to reduce the reactivity of the B–H bond, and act as mild reducing agents for the chemoselective reduction of aldehydes. For example, Hao and co-workers[185] developed a strategy for the chemoselective reduction of aldehydes in the presence of ketones using $NaBH(OAc)_3$ as the reducing agent (Scheme 4.1).[185] Various aldehydes bearing ketone groups were examined and showed high chemoselectivity and functional group tolerance, including C–C double bonds and disulfide bonds.

[181] (a) D. E. Ward, C. K. Rhee, *Synth. Commun*. **1988**, *18*, 1927; (b) D. E. Ward, C. K. Rhee, *Can. J. Chem.* **1989**, *67*, 1206.
[182] Y. Maki, K. Kikuchi, *Tetrahedron Lett.* **1977**, 263.
[183] C. Adams, *Synth. Commun*. **1984**, *14*, 1349.
[184] B. Zeynizadeh, F. Shirini, *J. Chem. Res., Synop*. **2003**, 335.
[185] G. Sui, Qi. Lv, X. Song, H. Guo, J. Dai, L. Ren, C. Lee, W. Zhou, H. Hao, *New J. Chem.*, **2019**, *43*, 15793.
[186] Y. Kuroiwa, S. Matsumura, K. Toshima, *Synlett* **2008**, *16*, 2523.




*Scheme 4.1. Synthesis of primary alcohols by the reduction of aldehydes.*

Another method for the reduction of aldehydes to produce primary alcohols is metal catalyzed hydrosilylation of aldehydes. Since the first report of metal-catalyzed hydrosilylation of ketones in the presence of Wilkinson's catalyst,[187] a number of metal catalyzed reactions were developed for the hydrosilylation of aldehydes to access primary alcohols, including methods featuring [Au], [188] [Ag], [189] [Ni], [190] [Ru] [191] and [Fe] complexes.[192] For example, Beller and co-workers reported a method to access benzylic alcohols from aldehydes by using the $Fe(OAc)_2/PCy_3$/PMHS system (Scheme 4.2).[192] Various benzylic alcohols were prepared in excellent yields (up to 98%), and the system was found to be compatible with heteroaromatic aldehydes. Aliphatic and α, β-unsaturated aldehydes also reacted with high yields (up to 90%).




*Scheme 4.2. Metal-catalyzed hydrosilylation of aldehydes.*

### 4.1.2. Hydroboration/oxidation of alkenes

A classical method for the synthesis of primary alcohols from olefins on lab-scale is hydroboration/oxidation. The first example of a hydroboration/oxidation process to access primary alcohols was reported by Brown and co-workers.[193] Simple olefins, such as ethylene, 1- and 2-pentene, cyclohexene, and styrene were examined, and the corresponding anti-Markovnikov hydration produced alcohols in 70-90% yields. The hydroboration/oxidation process involves two steps. The first step requires a stoichiometric amount of borane reagent to produce an organoborane. In the second step, the organoborane undergoes rapid and essentially quantitative oxidation with hydrogen

[187] I. Ojima, T. Kogure, M. Nihonyanagi, Y. Nagai, *J. Chem. Soc., Chem. Commun.*, **1972**, 938.
[188] D. Lantos, M. Contel, S. Sanz, A. Bodor, I. T. Horvath, *J. Org. Chem.* **2007**, *692*, 1799.
[189] B. M. Wile, M. Stradiotto, *Chem. Commun.*, **2006**, 4104.
[190] S. Chakraborty, J. A. Krause, H. Guan, *Organometallics* **2009**, *28*, 582.
[191] B. Chatterjeea, C. Gunanathan,*Chem. Commun*., **2014**, *50*, 888.
[192] N. S. Shaikh, K. Junge, M. Beller, *Org. Lett*., **2007**, *9*, 5429.
[193] H. C. Brown, B. C. Subba Rao, J. Am. Chem. Soc., 1956, 78, 5694.

peroxide to produce the corresponding boronic ether, which can be easily hydrolyzed to provide the desired alcohols. The process involves a *cis* addition of the boron hydrogen bond (**a**: see Figure 4.1), resulting in the attachment of the boron to the less substituted carbon of the double bond, which is the key to the hydroboration/oxidation process' anti-Markovnikov selectivity. Since the original discovery, many technical advances have been made for hydroboration/oxidation. For example, a flow method for the hydroboration/oxidation of olefins to access primary alcohols was developed by Souto and co-workers.[194] This method allows primary alcohols to be produced on larger scale and shows high functional group tolerance. A THF or DMS complex of $BH_3$ was used as the borane source, giving excellent conversion of the alkenes. The flow technique is shown in Figure 4.1 **b**. Alkene (1 M) and $BH_3$ complex (1 M) are flowed into the system at the same rate and react in the reactor coil at room temperature. Then the mixture was oxidized in the second narrow reactor coil with the help of base and $H_2O_2$. Finally, the target product was obtained upon addition of organic solvents and purification by a membrane separator device.

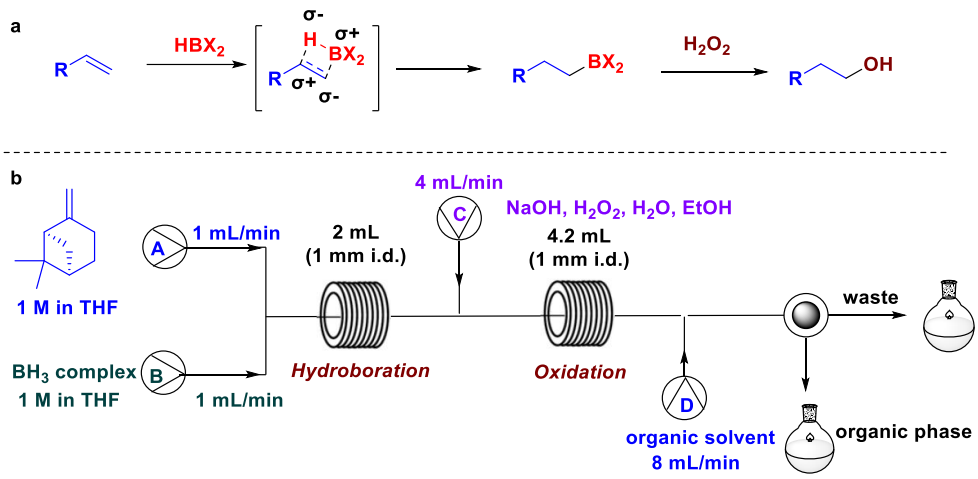


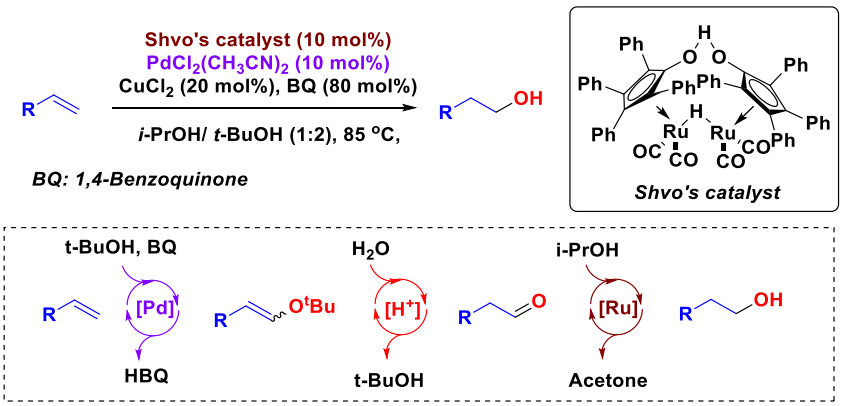

*Figure 4.1. Hydroboration/oxidation of olefins to access primary alcohols.*

### 4.1.3. Anti-Markovnikov hydration of alkenes

Another method for the synthesis of primary alcohols is the anti-Markovnikov hydration of olefins. Although the Markovnikov hydration of olefins to secondary alcohols has been reported many times, producing useful primary alcohols from the direct hydration of

[194] J. A. Souto, R. A. Stockman, S. V. Ley, *Org. Biomol. Chem.*, **2015**, *13*, 3871.

terminal alkenes is still challenging. According to Markovnikov's rule, the proton of a hydronium ion should bond to the less substituted carbon in the direct hydration of alkenes, and thus, primary alcohols are usually not obtained. However, some creative catalytic methods for anti-Markovnikov hydration have been developed in the past decade. In 2011, a triple relay catalysis strategy was developed by Grubbs and co-workers for the anti-Markovnikov hydration of olefins (Scheme 4.3).[195] This strategy begins with a Pd-catalyzed Wacker-type oxidative cycle,[196] which after acid-catalyzed hydrolysis gives an aldehyde. The aldehyde is then reduced in a third cycle into an alcohol. More specifically, in the oxidative cycle, a $Pd^{II}$ salt acts as an oxidant to produce the carbonyl compound from an olefin in the presence of water. In the reductive cycle, hydrides of Ru, Ir, and Fe are generated by transfer hydrogenation from *i*PrOH and then act as the reducing agent. The acid generated by the oxidative cycle can be employed in the reductive cycle to protonate the formed metal alkoxides and promote the formation of primary alcohols. Various styrenes were examined and found to yield the desired alcohols with good yields (63 to 84%) and high regioselectivity. Some substrates bearing an electron-withdrawing group are tolerated, but aliphatic olefins give much poorer regioselectivity than the one observed for styrenes. Mechanistic studies showed that the regioselectivity was controlled by the oxidation process. In the presence of *t*BuOH, the olefin would first undergo a Pd-catalyzed oxidation to generate a linear *t*-butyl vinyl ether, whose regioselectivity is biased by the sterically hindered *t*BuOH. The drawback of this strategy is the relatively high catalyst loadings and the use of stoichiometric BQ (1,4-Benzoquinone).

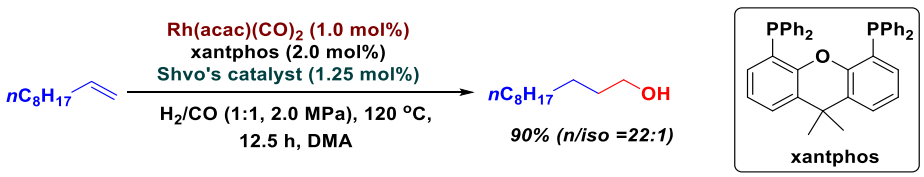



*Scheme 4.3. Anti-Markovnikov selective hydration of olefins via triple relay catalysis.*

[195] G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609.
[196] T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed.* **2006**, *118*, 495.

### 4.1.4. One-pot hydroformylation/hydrogenation of alkenes

The regioselectivity of the processes described above relies on the steric and electronic character of the alkenes.[194] Another strategy to access primary alcohols are the hydroformylation/reduction or hydroformylation/hydrogenation processes which contain two steps. The first step is the formation of aldehydes by the addition of CO to the alkenes, otherwise known as a hydroformylation[197]. In a second step, the formed aldehyde is reduced by a reducing agent such as $H_2$. Hydroformylation of olefins to produce primary alcohols is a well-established process and numerous strategies have been developed. Hydroformylation of olefins can be catalyzed by rhodium, cobalt, palladium, or ruthenium with typical organic ligands. For example, Nozaki and co-workers reported a Rh/Ru dual catalyst system to access primary alcohols by the tandem hydroformylation/hydrogeneration of terminal alkenes (Scheme 4.4).[198] This strategy employs Ru/xantphos as catalyst, which was originally developed by the van Leeuwen group as an efficient catalyst for the hydroformylation of alkenes with high *n*-regioselectivity.[199] The well-known Shvo's catalyst was employed for the hydrogenation of the formed aldehydes. The reaction was conducted in one pot using DMA (dimethylacetamide) as solvent to produce primary alcohols with excellent yields and good regioselectivity. After optimization of the reaction solvent, temperature and catalyst, the fatty alcohol undecanol was produced from 1-decene at 120 °C in the presence of $H_2$/CO (1:1, 2.0 MPa) in 90% yield with high regioselectivity. A trace of decane, acetals, internal olefins, and the corresponding format ester were formed as by-products.




*Scheme 4.4. One-pot hydroformylation–hydrogenation of 1-decene with two different catalysts.*

[197] L. C. Matsinha, S. Siangwata, G. S. Smith, B. C. E. Makhubela, *Catal. Rev*. **2019**, *61*, 111.
[198] K. Takahashi, M. Yamashita, T. Ichihara, K. Nakano, K. Nozaki, *Angew. Chem.* **2010**, *122*, 4590.
[199] G. M. Torres, R. Frauenlob, R. Franke, A. Börner, *Catal. Sci. Technol.*, **2015**, *5*, 34.

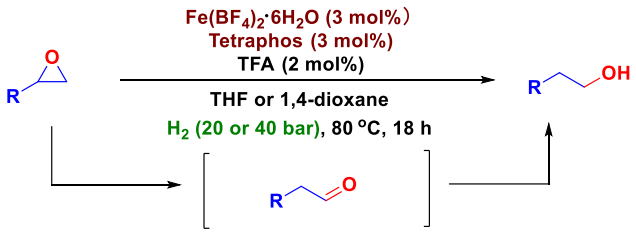
### 4.1.5. Reductive ring-opening of epoxides to deliver primary alcohols

Regioselective ring-opening nucleophilic additions to epoxides are an important way to produce primary alcohols (Scheme 4.5). The reactive nature of epoxides due to the strain of its three-membered ring makes them an attractive option to access alcohols through ring-opening reactions. As a number of regioselective ring-opening reactions of epoxides to access branch-selective products (primary alcohols) were already described in Chapter 1, we will not cover them again here. Instead we will discuss the reductive ring-opening of epoxides to give primary alcohols. To avoid redundancy, only a key example that was not already covered in Chapter 1 is described here.


*Scheme 4.5. Primary alcohols through regioselective ring-opening nucleophilic addition to epoxides.*

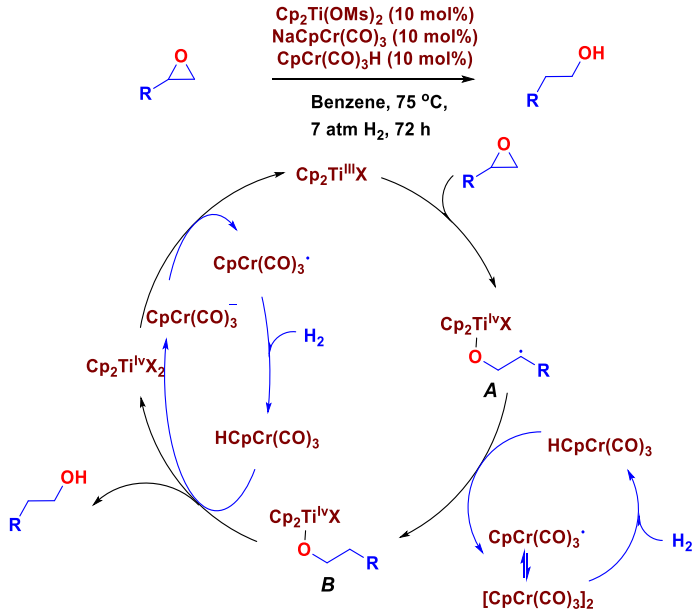
The other efficient way to access primary alcohols from epoxides is the reductive ring-opening of epoxides. For example, Beller and co-workers devised a strategy utilizing first-row transition metal Fe as catalyst for the regioselective hydrogenation of epoxides to access valuable primary alcohols (Scheme 4.6). [200] Compared with previous reports which employ noble metal complex based on Rh[201] and Ru[202] as catalyst to access primary alcohols from terminal epoxides, this strategy shows high regioselectivity and excellent yields (up to 98%). The mechanistic studies indicated that the high regioselectivity arises from the generation of an aldehyde intermediate (which is normally generate as by-product, resulting in poor selectivity for noble metal complex-catalyzed ring-opening of epoxide) through a Meinwald rearrangement in the presence of the iron/tetraphos complex. Then, the desired primary alcohols were obtained following the hydrogenation of the aldehyde intermediate in the presence of $H_2$ gas. This strategy was also examined with several natural products such as (±) camphene, (-) β-pinene, botulin and pregnenolone to access the corresponding primary alcohols in yields up to 96%.

[200] Y. Ikeda, H. Yorimitsu, H. Shinokubo, K. Oshima, *Adv. Synth. Catal.* **2004**, *346*, 1631.
[201] H. Fujitsu, S. Shirahama, E. Matsumura, K.Takeshita, I. Mochida, *J. Org. Chem.* **1981**, *46*, 2287.
[202] S. Murru, K. M. Nicholas, R. S. Srivastava, *J. Mol. Catal. A* **2012**, *363*, 460.




*Scheme 4.6. Iron-catalyzed regioselective hydrogenation of terminal epoxides to alcohols*

In another important example of reductive ring-opening of epoxides, Norton, Gansäuer and co-workers developed a strategy to access primary alcohols from the hydrogenation of epoxide by cooperative Ti/Cr catalysis (Scheme 4.7).[203] Various epoxides were shown to produce the corresponding primary alcohols with high regioselectivity. The mechanistic studies indicated that the more substituted radicals **A** can be generated by a one-electron reduction of the epoxide with the [$Ti^{III}$] catalyst and quenched to **B** by a [Cr] catalyst through a hydrogen atom transfer (HAT) process. The newly generated $CpCr(CO)_3$ radical is then quenched by $H_2$ and re-enters the catalytic cycle. The primary alcohol was formed by protonolysis of Ti(IV) alkoxide intermediate **B** with $HCpCr(CO)_3$. The $[CpCr(CO)_3]^-$ anion is a good one-electron reducing agent, which reduces [$Ti^{IV}$] to [$Ti^{III}$]. This strategy shows high functional group tolerance and excellent atom economy.

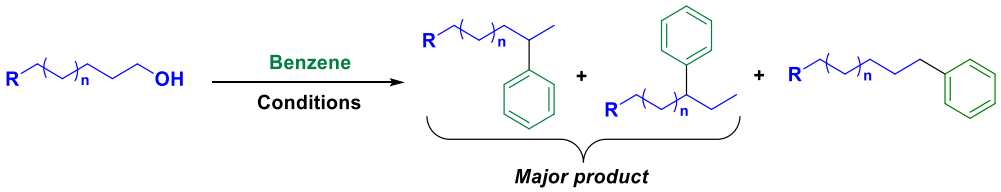



*Scheme 4.7. Primary alcohols via epoxide hydrogenation under cooperative catalysis.*

[203] C. Yao, T. Dahmen, A. Gansäuer, J. Norton, *Science* **2019**, *364*, 764.

## 4.2. Aim of this chapter

Primary aliphatic alcohols are difficult to engage in Friedel-Crafts reactions owing to the stability of the C–O bond. The Friedel-Crafts alkylation of methanol and ethanol are known but require high temperatures (300-400 °C) using zeolites as promoters. Until now, only a few examples of Friedel-Crafts alkylation of primary alcohols have been reported (Scheme 4.8).[204] In most of these cases, a branched product is the major product due to the competition of Friedel-Crafts alkylation with elimination.




*Scheme 4.8. Friedel-Crafts alkylation of primary alcohols.*

In Chapter 3, we introduced the direct Friedel-Crafts alkylation of primary alcohols and applied it to the one-pot activation of *in situ* generated primary alcohols produced by the arylative ring-opening of epoxides. In this chapter, I will present a strategy to afford primary alcohols through the reductive ring-opening of epoxides using silanes under TfOH catalysis, and then to directly substitute those alcohols to access the linear Friedel-Crafts alkylation product in one pot. Our goal was to focus in particular on highly deactivated styrene oxides, whose reduction to deliver the corresponding aliphatic alcohols was hitherto unprecedented.

## 4.3. Results and discussion

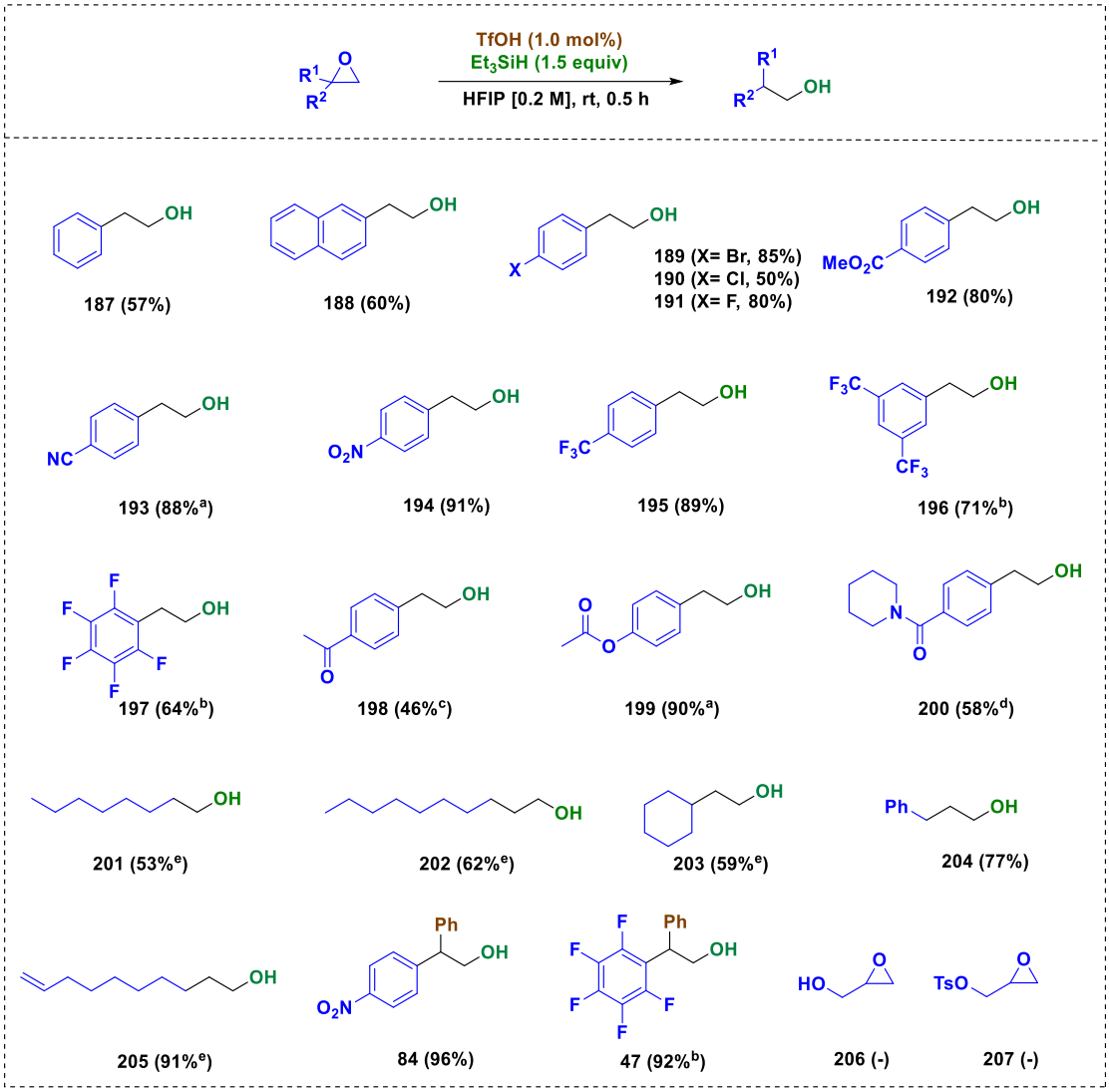
### 4.3.1. Reductive ring-opening of epoxides

As discussed in Chapter 3, primary alcohols were generated smoothly with the range of 42 to 98% yields via the ring-opening arylation of epoxides with arenes in HFIP under TfOH catalysis. Encouraged by those results, we suspected that primary alcohols can also be produced from epoxides by the use of silane as a hydride source. The conditions of this reaction were optimized by Dr. Marie Vayer. Thus, 2-(4-nitrophenyl)ethan-1-ol was prepared from 4-nitrostyrene oxide with triethylsilane (1.5 equiv.) in the presence of 1

[204] (a) O. Sieskind, P. Albrecht, *Tetrahedron Lett.* **1993**, *34*, 1197; (b) A. R. A. S. Deshmukh, V. K. Gumaste, B. M. Bhawal, *Catal. Lett.* **2000**, *64*, 247.

mol% TfOH using HFIP (0.2 M) as solvent within 30 min at room temperature in 91% yield. Traces of HFIP ether were generated as by-products.

With the optimized conditions in hand, we examined various of epoxides, including styryl and aliphatic epoxides. The transformation was compatible with epoxides bearing either electron-donating or electron-withdrawing substituents to access the corresponding primary alcohols **187**-**205** in 45 to 95% yield (Table 4.1). Similar to what was observed for the ring-opening arylation of epoxides, substrates bearing an electron-withdrawing group provided better yields than electron-rich arenes such as styrene oxide and 2-(naphthalen-2-yl)oxirane (57% and 60% yields, respectively). There are some general differences between the dehydroarylation and the reductive ring-opening of epoxides with respect to how the electronics of the substrate influences the outcome. For the dehydroarylation, the more deactivated the epoxide is, the better is the yield of the ring-opening arylation product. For the reductive ring-opening of epoxides, the substrates bearing an electron-withdrawing group also provided better yields than those that do not, but highly deactivated epoxides lead to lower yields. For example, product **194** from the corresponding epoxide was generated in 91% yield, but only 71% for product **196** and 64% for product **197** were obtained. In other words, moderate and relatively strong electron-withdrawing substituents provides an excellent yield for the reductive ring-opening of aryl epoxides by preventing the epoxide from polymerizing under the reaction conditions, but stronger electron-withdrawing substituents partially deactivates the epoxide towards reduction. One of the strengths of this reaction system is also its efficacy with alkyl-substituted oxiranes, which selectively afford the desired primary alcohols in 46 to 91% yields. The transformation exhibits chemoselectivity in the presence of an alkene functionality, providing product **205** in 91% yield. Unfortunately, unlike the arylation of epoxides, the reduction of alkyl oxiranes is not tolerant of oxygen functionalities in the alkyl chain. Thus, product **206** cannot be accessed from the corresponding epoxide as only oligomerization was observed. Nor does the reduction occur when **207** is employed as starting material. However, geminally disubstituted substituted epoxides lead to products **84** and **47** in 96% and 92% yield, respectively.




*[a] Reaction conducted with 5.0 mol% TfOH and 2.0 equiv of $Et_3SiH$; [b] at rt for 1 h; [c] at rt for 2 h; [d] reaction conducted with 30 mol% TfOH and 3.0 equiv of $Et_3SiH$; [e] NMR yield.*

*Table 4.1. Substrate scope for the reductive ring-opening of epoxides.*

### 4.3.2. Friedel-Crafts alkylation of primary alcohols

Since primary alcohols were successfully produced with our strategy, we next examined the Friedel-Crafts alkylation of primary alcohols with various arene nucleophiles, using the conditions we previously developed for 1,2-difunctionalized epoxides (Table 4.2). This was done with an eye towards eventually developing a one-pot method for the reductive arylation of epoxides. Since 4-fluorostyrene oxide was successfully reduced to give 4-fluorophenyl ethanol as described in the previously, we therefore chose 4-fluorophenyl ethanol as starting material to evaluate the Friedel-Crafts alkylation of primary alcohols with different nucleophiles. Various alkylation products were accessed

in yields ranging from 36 to 96% (**208-218**) without any formation of branched products. Interestingly, when 4-methylphenol is used as nucleophile, only the diarylation of 4-fluorophenyl ethanol (**219**) was observed with 20% yield. This observation might be rationalized by considering that once the arylation product is formed, it becomes more nucleophilic than 4-methylphenol and then reacts with another primary alcohol to yield the diarylation product. Of note, arenes containing ester groups did not undergo Friedel-Crafts reactions but instead transesterification to give products **220**, nearly quantitatively. Although, most of the nucleophiles that we examined delivered the corresponding alkylation products under our standard conditions, the nucleophiles shown in Table 4.2b were not compatible during the decomposition of the nucleophile or the formation of ether from the primary alcohol.

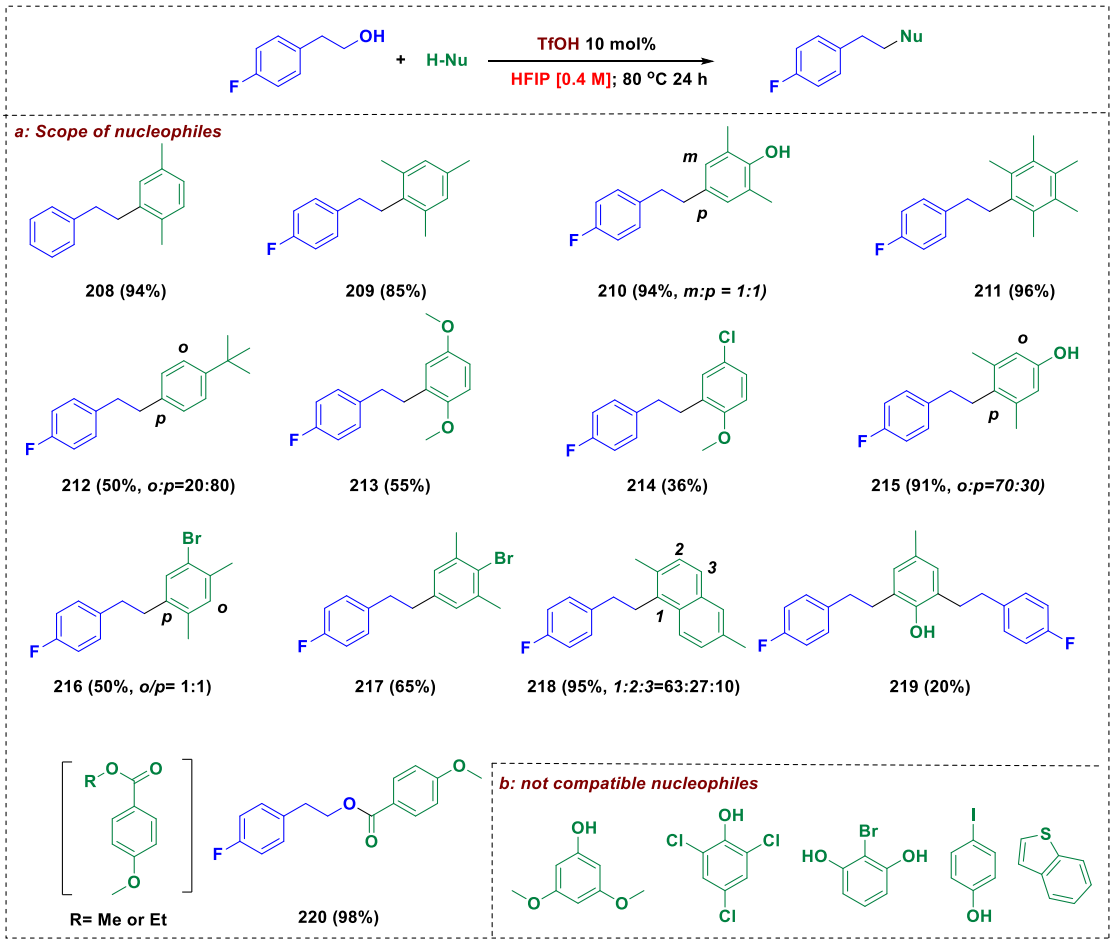
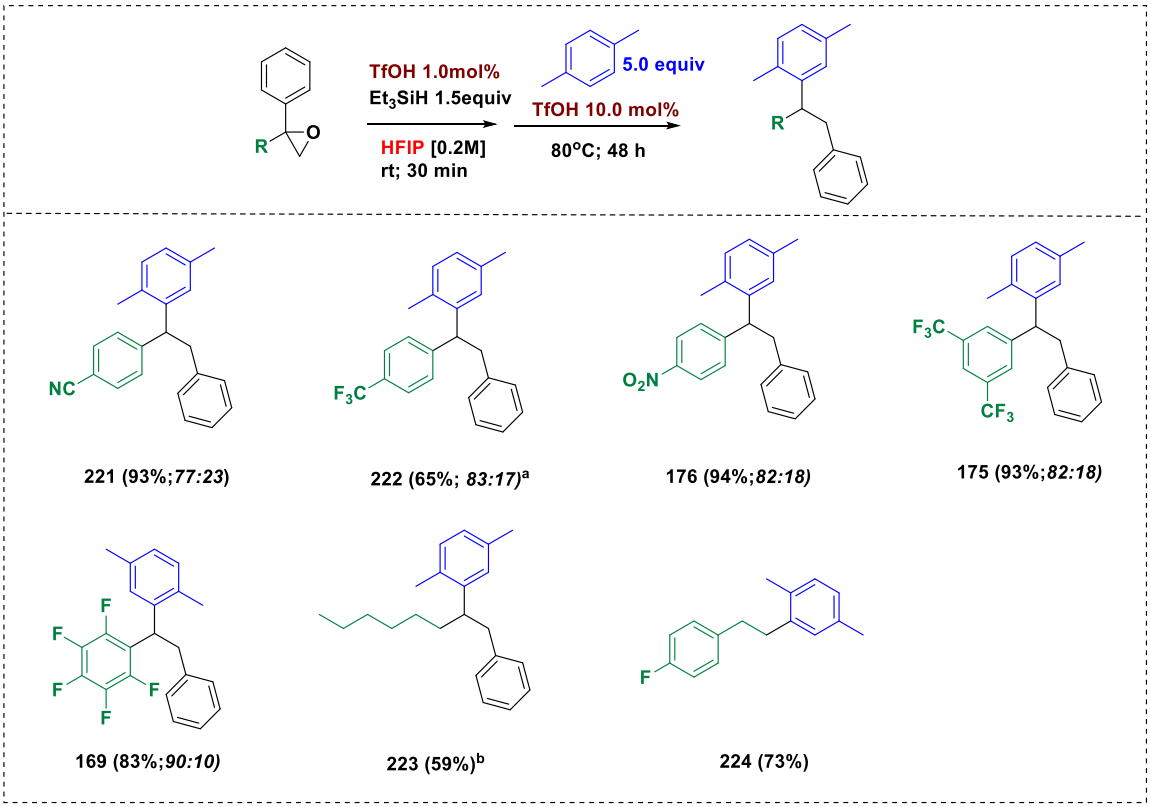



*Table 4.2. Nucleophile scope for the Friedel-Crafts alkylation of primary alcohols on a substrate relevant to the reductive ring-opening of epoxides.*

### 4.3.3. One-pot epoxide ring-opening and Friedel-Crafts alkylation

Next, we turned our attention to developing a one-pot reductive ring-opening arylation of epoxides. Due to the importance of 1,1,2-triarylethanes, the reaction was examined with disubstituted epoxides to produce valuable 1,1,2-triarylethanes with *p*-xylene under our standard conditions. First, the reaction was conducted under the conditions of reductive ring-opening. After the reaction was completed, 10 mol% TfOH and 5.0 equivalents of *p*-xylene were added to the reaction mixture which was heated 80 ºC for typically 48 h (Table 4.3). The desired 1,1,2-triarylethanes were produced in 65 to 94% yields (**169**, **175**, **176** and **221**-**224**). Small amounts of regioisomeric by-products were observed, likely because of the involvement of a phenonium ion intermediate, as already discussed in detail in Chapter 3. The reaction was also found to be compatible with aliphatic epoxides and mono-substituted styryl oxides, giving access to the corresponding products **223** (59% yield) and **224** (73% yield).



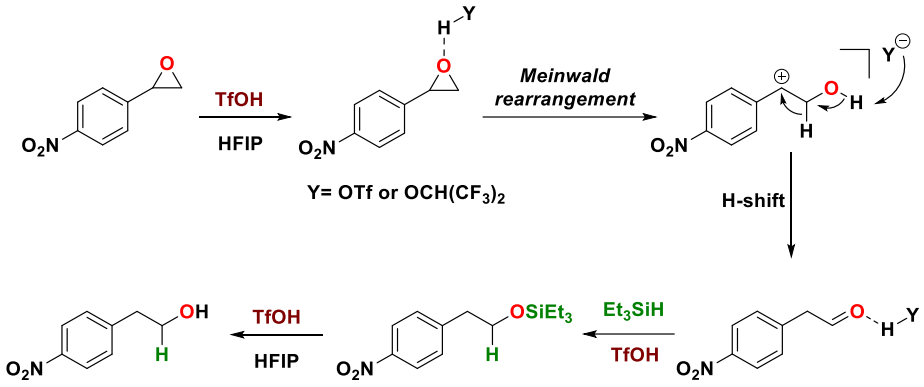

*[a] 16 h instead of 48 h; [b] reaction conducted at rt.*

*Table 4.3. Substrate scope for the one-pot reductive ring-opening arylation of epoxides.*

### 4.3.4. Mechanistic study

The mechanism of reductive ring-opening of epoxides was studied using 4-nitrostyrene oxide as a model substrate. In the absence of silane, the corresponding aldehyde was obtained in 81% yield from 4-nitrostyrene oxide and the alcohol product was prepared

from the obtained aldehyde in 54% yield. Thus, we propose that the mechanism of reductive ring-opening of epoxides occurs as shown in Scheme 4.9. First, the epoxide is protonated by TfOH and generates the corresponding aldehyde, which can be reduced by the silane in the presence of acid to access the silyl ether. The desired alcohol is produced following the acid-catalyzed deprotection of the silyl ether. If Friedel-Crafts alkylation of primary alcohols are performed following the reductive ring-opening, the mechanism is the same as discussed in detail in Chapter 3, whereby a phenonium ion is formed and the desired product is obtained following a Wagner-Meerwein rearrangement.




*Scheme 4.9. Proposed mechanism for the reductive ring-opening of epoxides.*

## 4.4. Conclusion of Chapter 4

In this chapter, we developed a highly regioselective strategy to produce primary alcohols from terminal epoxides or *bis*-substituted epoxide using triethylsilane as hydride source. Various primary alcohols were prepared, including aliphatic and styryl substituted alcohols, in moderate to excellent yields (41 to 91%). Notably, the desired primary alcohols were synthesized without the generation of any branched alcohols. The newly formed primary alcohols also underwent the Friedel-Crafts reaction to access the arylated compounds in one pot. Mechanistic studies indicated that an aldehyde was initially generated in the presence of TfOH with assistance from HFIP. The silane then acts as a hydrogen donor to reduce the aldehyde. The regioselectivity for the formation of the aldehyde is controlled by the formation of a more stable benzylic or secondary carbocation. The mechanism of the Friedel-Crafts arylation step is the same as we proposed in Chapter 3 and involves a phenonium ion intermediate. Finally, all the reactions described herein start directly from readily available precursors without pre-activation steps.

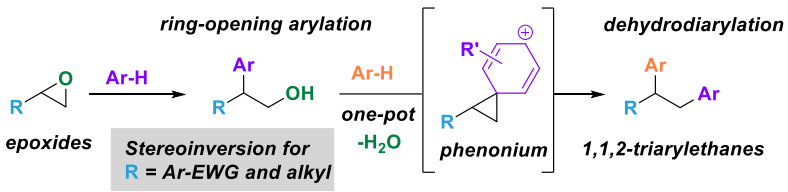
# 5. Conclusions and Outlook

Owing to the unique properties of HFIP (high hydrogen bond donor ability, low nucleophilicity, high ionizing power and ability to solvate water), HFIP hydrogen-bond clusters are probably involved when Lewis or Brønsted acid are employed as catalysts. Lewis- or Brønsted acid-assisted-Brønsted acid catalysis or hidden Brønsted acid catalysis may often be operative, which can accentuate the catalytic activity of simple compounds, making catalytic mechanisms difficult to deconvolute. In Chapter 2, re-examination of various published boronic acid catalyzed reactions, particularly those involving HFIP and the activation of alcohols (Friedel-Crafts reactions, allylic transposition, dehydrative cyclization) or oximes (Beckman rearrangement), revealed that hidden Brønsted acid catalysis is likely involved in most cases. This conclusion was supported by the fact that 1) the boronic acid catalysts could perform reactions that could only be catalyzed by strong Brønsted acid, such as TfOH; 2) simple Brønsted acids catalyzed the reaction in similar yields under otherwise identical reaction conditions; 3) the (sometimes surprisingly weak) Brønsted acids that catalyzed them in similar yield showed similar Gutmann-Beckett acidities in the relevant reaction solvent as did the boronic acid catalysts. 4) The boronic acid catalyzed reactions were quenched by 2,6-DTBP, even when carried out in an aprotic solvent. For the boronic acid catalysts used in HFIP, the transient generation of HFIP boronic esters appears to form a powerful Lewis acid that binds adventitious water to form a strong Brønsted acid catalyst. In another case, the boronic acid appears to act as a dual H-bond catalyst. In all the reactions examined involving alcohols and oximes (except for one substrate), boron does not appear to be directly involved in the catalytic mechanism. This chapter illustrates how catalysts designed with one mechanistic activation mode in mind may be operating by totally different mechanisms.

Epoxides and primary alcohols are important building blocks for organic synthesis. Efficient strategies for the regioselective ring-opening of epoxides and for the direct dehydrative substitution of primary alcohols are desirable as they can produce valuable compounds with high atom- and step-economy. Although several types of epoxide ring-opening reactions have been developed in the past, epoxides bearing strong electron-withdrawing groups have been excluded due to their deactivated nature. Most epoxide-opening reactions that can install an aryl group require the pre-activation of the arene

nucleophile or expensive catalysts. Furthermore, due to the lack of efficient methods for the catalytic dehydrative substitution of primary aliphatic alcohols, the alcohol generated by the ring-opening of terminal epoxides are difficult to directly implement in further reactions without a separate pre-activation step. In this context, a part of this thesis was also devoted to the Friedel-Crafts arylation of epoxides bearing strong electron-withdrawing groups and to the direct dehydrative Friedel-Crafts arylation of primary alcohols with the TfOH/HFIP system.

Thus, in Chapter 3, a strategy was developed for the mono- and bis-arylation of epoxides using the TfOH/HFIP catalyst system. Branch-selective ring-opening of epoxides occurs for a broad range of substrates and various nucleophilic arenes. As Friedel-Crafts reactions of terminal epoxides produce primary aliphatic alcohols, an efficient method for Friedel-Crafts arylation of primary alcohols was developed using the same catalyst system. Putting them together in one pot has allowed for the dehydrodiarylation of epoxides, a new transformation where two of the same arenes or two different arenes can be introduced (Scheme 5.1). Mechanistic studies indicated that the epoxide ring-opening occurs through an $S_N2$ or $S_N1$ mechanism, depending on the electronics of the epoxide. The $S_N1$ mechanism dominates for electron-rich styrene oxides, whereas alkyl epoxides and more deactivated styrene oxides proceed through an $S_N2$ mechanism. By raising the reaction temperature, the generated substituted phenyl ethanols can then react with another arene molecule via a phenonium ion intermediate without additional pre-activation steps.




*Scheme 5.1. Strategy toward the monoarylation and dehydrodiarylation of terminal epoxides.*

Chapter 4 describes a new method for the reduction of epoxides that is compatible with electron-poor epoxides, which was enabled by catalytic TfOH in HFIP while using triethylsilane as a reductant. By combining it with the direct Friedel-Crafts arylation of primary alcohols described in Chapter 3, a one-pot reductive dehydroarylation of epoxides can be achieved. Various primary alcohols can be prepared from a selected pool

of epoxides. Mechanistic studies show that an aldehyde is initially generated in the presence of TfOH with the assistance of HFIP, and then reduced to the corresponding primary alcohol by hydride transfer from the silane.

In summary, this thesis gives insight into the power and complexities associated with Brønsted acid catalysis in HFIP, whether accidental or by design. New insight was obtained into the mechanism of boronic acid catalysis in reactions of alcohols and of oximes. An efficient HFIP-mediated strategy for mono- and bis-functionalization of epoxides with arenes was described. Various 1,1-diaryalkanes and 1,1,2-triaryethlanes were easily prepared with high yield from simple epoxide starting materials. This strategy also provides an efficient method for the direct dehydrative Friedel-Crafts arylation of primary alcohols. With an eye towards the future, two examples of ring-opening amination of epoxides with anilines were introduced, which can be applied in future investigations for the preparation of unnatural amino alcohols and even unnatural amino acids.

# Experimental Section

# Experimental section-Chapter 2

## General information

All the reactions were performed in 10 mL glass tubes with stirring bars. Purification of reaction products was carried out by column chromatography using 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 $CDCl_3$ (7.26 ppm) as internal standard. **$^{13}$C-NMR** spectra were recorded on a Bruker UltraShield Plus 400 (100 MHz) spectrometer at ambient temperature and are reported in ppm using $CDCl_3$ (77.16 ppm) as internal standard. **NMR Yields** were calculated by using hexamethyldisiloxane as an internal standard.

**Materials**: All commercial materials were purchased from Sigma-Aldrich, Alfa Aesar and FluoroChem, and were used as received, without further purification. All acids were purchased from Sigma Aldrich, and HFIP (CAS: 920-66-1) from FluoroChem. Nitromethane (CAS: 75-52-5) was purchased from Sigma-Aldrich.

## General procedures

**General procedure A for the ring-opening of cyclopropanes (Table 2.1):** To a solution of cyclopropylbenzene (0.033 mL, 0.25 mmol) in HFIP (0.125 mL) was added 1-methoxynaphthalene (0.072 mL, 0.50 mmol, 2 equiv) and catalyst (10 mol%). The reaction tube was then capped and heated at the indicated temperature for 16 h. Then, the reaction mixture was filtered through Celite 545 and concentrated by reduced pressure distillation. The crude mixture was completely dissolved in 0.5 mL of $CDCl_3$ and a $^{1}$H NMR spectrum was recorded. The yield was calculated based on the relative integration of the resonance corresponding to the product's methylene protons (-$CH_2$-) at 2.47-2.28 ppm (m, 2H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H).

**General procedure B for activation of alcohol (Table 2.2):** To a solution of the requisite benzyl alcohol (0.50 mmol) in a solvent mixture of hexafluoroisopropanol and

nitromethane (4:1) was added the requisite arene nucleophile (2.5 mmol, 5 equiv), followed by the catalyst. The glass tube was capped and stirred at the indicated temperature for the indicated time. Then, the reaction mixture was filtered through Celite 545 and concentrated by reduced pressure distillation. The crude mixture was completely dissolved in 0.5 mL of $CDCl_3$ and a $^1H$ NMR spectrum was recorded. The yield was calculated based on the relative integration of the resonance corresponding to the product's methylene protons (-$CH_2$-) at 4.17-4.01 ppm (s, 2H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H).

**General procedure C for activation of oximes (Table 2.3):** To a solution of the requisite oxime (0.50 mmol) in a solvent mixture of hexafluoroisopropanol and nitromethane (4:1 in volume) was added the Brønsted or boronic acid and perfluoropinacol. The glass tube was capped and stirred at the indicated temperature for the indicated time. Upon completion, the reaction mixture was filtered through Celite 545 and concentrated by reduced pressure distillation. The crude mixture was completely dissolved in 0.5 mL of $CDCl_3$ and a $^1H$ NMR spectrum was recorded. In the case of substrate **32**, the yield was calculated based on the relative integration of the resonance corresponding to the product's protons (-$CH_3$) at 2.19 ppm (s, 3H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H). In the case of substrate **33**, the yield was calculated based on the relative integration of the resonance corresponding to the product's protons (-$CH_3$) at 2.08 ppm (s, 3H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H). In the case of substrate **34**, the yield was calculated based on the relative integration of the resonance corresponding to the product's proton (-CH) at 7.71-7.63 ppm (m, 2H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H). In the case of substrate **35**, the yield was calculated based on the relative integration of the resonance corresponding to the product's protons (-$CH_2$) at 3.27 ppm (dd, 2H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H).

**General procedures D for compound 41:** To a solution of the allylic alcohol **40** (0.20 mmol) in 1.0 mL nitromethane was added the Brønsted or boronic acid. The resulting

mixture was stirred for 48 h at 50 °C. Then, the reaction mixture was filtered through Celite 545 and concentrated by reduced pressure distillation. The crude mixture was completely dissolved in 0.5 mL of $CDCl_3$ and a $^1H$ NMR spectrum was recorded. The yield was calculated based on the relative integration of the resonance corresponding to the product's proton (-CH-) at 3.72-3.66 ppm (m, 1H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H).

**General procedures E for compound 43:** To a solution of the allylic alcohol **41** (84 mg, 0.40 mmol) in 1.0 mL toluene was added the Brønsted or boronic acid. The resulting mixture was stirred for 24 h at rt. Then, the reaction mixture was filtered through Celite 545 and concentrated by reduced pressure distillation. The crude mixture was completely dissolved in 0.5 mL of $CDCl_3$ and a $^1H$ NMR spectrum was recorded. The yield was calculated based on the relative integration of the resonance corresponding to the product's protons (-$CH_2$-) at 4.06 ppm (d, 2H) compared to the integration of the resonance corresponding to a methyl group of the external standard hexamethyldisiloxane at 0.06 ppm (18H).

**General procedure F for direct amidation:** To a solution of the phenyl acetic acid (0.038 g, 0.28 mmol) in 7 mL dichloromethane, the catalyst and 0.5 g of activated 4Å molecular sieves was added. The glass tube was capped and stirred for 10 min. Then, benzylamine (28 µL, 0.25 mmol) was added. The resulting mixture was stirred for 48 h at room temperature. Upon completion, the reaction mixture was filtered through Celite 545 and washed with 3M HCl solution, saturated $NaHCO_3$ solution; The organic layer was collected, dried over anhydrous $Na_2SO_4$, filtered and evaporated to yield **44**.

**Gutmann Beckett Plot**

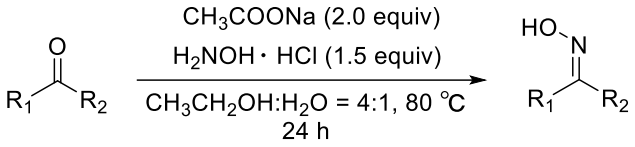
**General procedure in toluene-*$d_8$*:** A solution of the Brønsted acid or boronic acid (0.225 mmol, 3.0 equiv) with triethylphosphine oxide (10 mg, 0.075 mmol, 1.0 equiv) in 500 µL deuterated toluene-*$d_8$* was added into an NMR tube and a $^{31}P$ NMR spectrum was recorded after 15 min.

**General procedure in a mixture of hexafluoroisopropanol and nitromethane (4:1):** A solution of the Brønsted acid or boronic acid (0.225 mmol, 3.0 equiv) with triethylphosphine oxide (10 mg, 0.075 mmol, 1.0 equiv) in 500 µL HFIP/$MeNO_2$ (4:1)

was added to an NMR tube containing a sealed ampule of $d_8$-toluene as an external standard. A $^{31}P$ NMR spectrum was recorded after 15 min.

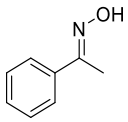
## Starting Material Preparation

### Synthesis and Characterization of Oximes (General procedure G)




Sodium acetate (1.64 g, 20.0 mmol) and hydroxylamine hydrochloride (1.04 g, 15.0 mmol) were added into a solution of the ketone (0.3 M) in ethanol/water (4:1 in volume) in 100 mL round bottom flask. The reaction mixture was then heated to 80℃ for 24 h. After that, the reaction was cooled to room temperature. The crude mixture was obtained after removal of excess ethanol and added into 20 mL of water. The resulting aqueous solution was extracted with 20 mL EtOAc for three times. The combined organic layers were washed with 20 mL water two times and 20 mL brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The pure oxime product was obtained after column chromatography.

***(E)-1-phenylethan-1-one oxime 32***

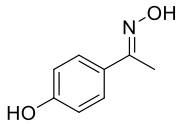



Chemical Formula: $C_8H_9NO$
Exact Mass: 135.0684

**General procedure G** was followed with acetophenone (1.20 g, 10.0 mmol), sodium acetate (547 mg, 6.7 mmol) and hydroxylamine hydrochloride (347 mg, 5.0 mmol). The reaction mixture was stirred at 80 ℃ for 24 h. Purification by FC over silica gel (EtOAc:PE = 1:7) afforded **32** (1.16 g, 85% yield) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 9.44 (s, 1H), 7.72-7.63 (m, 2H), 7.49-7.38 (m, 3H), 2.37 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 156.07, 136.53, 129.33, 128.59, 126.11, 12.48.

***(E)-1-(4-hydroxyphenyl)ethan-1-one oxime 33***

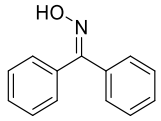


Chemical Formula: $C_8H_9NO_2$
Exact Mass: 151.0633

**General procedure G** was followed with 1-(4-hydroxyphenyl)ethan-1-one (1.36 g, 10.0 mmol), sodium acetate (547 mg, 6.7 mmol) and hydroxylamine hydrochloride (347 mg, 5.0 mmol). The reaction mixture was stirred at 80 ℃ for 24 h. Purification by FC over silica gel (EtOAc) afforded **33** (1.45 g, 98% yield) as a brown solid.

**$^1$H NMR (400 MHz, Methanol-*d*$_4$):** δ 7.49 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 2.20 (s, 3H). **$^{13}$C NMR (100 MHz, Methanol-*d*$_4$):** δ 158.10, 154.94, 128.37, 127.10, 114.71, 10.79.

***Diphenylmethanone oxime 34***

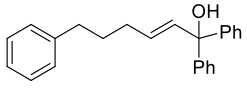


Chemical Formula: $C_{13}H_{11}NO$
Exact Mass: 197.0841

**General procedure G** was followed with benzophenone (1.83 g, 10.0 mmol), sodium acetate (547 mg, 6.7 mmol) and hydroxylamine hydrochloride (347 mg, 5.0 mmol). The reaction mixture was stirred at 80 ℃ for 24 h. Purification by FC over silica gel (EtOAc:PE = 1:10) afforded **34** (1.91 g, 97% yield) as a white solid.

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 7.55-7.45 (m, 5H), 7.49-7.35 (m, 2H), 7.38-7.31 (m, 1H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 158.21, 136.15, 132.64, 129.58, 129.29, 129.19, 128.38, 128.28, 127.92.

**Synthesis and Characterization of allylic alcohol**



Chemical Formula: $C_{24}H_{24}O$
Exact Mass: 328.1827

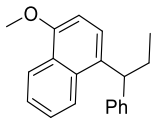
**Compound 40:** Prepared by following a literature procedure.[205]

[205] Zheng, H. C.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187-6190.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.11 (m, 15H), 6.17 (d, *J* = 15.4 Hz, 1H), 5.71 (dt, *J* = 15.4, 6.8 Hz, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.34 (s, 1H), 2.28-2.14 (m, 2H), 1.81 (p, *J* = 7.6 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.46, 142.33, 136.26, 130.58, 128.51, 128.35, 128.10, 127.15, 126.95, 125.79, 79.10, 35.50, 31.85, 30.96.

**Characterization Data**

***1-methoxy-4-(1-phenylpropyl)naphthalene 25***

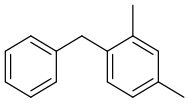



Chemical Formula: $C_{20}H_{20}O$
Exact Mass: 276.1514

**General procedure A** was followed with cyclopropylbenzene (0.033 mL, 0.25 mmol) and 1-methoxynaphthalene (0.072 mL, 0.50 mmol, 2 equiv) in the presence of 10 mol% catalyst in HFIP (1.0 mL). The reaction mixture was stirred at 80 ℃ for 16 h. Purification by FC over silica gel (EtOAc:PE = 1:7) afforded **25** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.40 (d, *J* = 1.9 Hz, 1H), 7.99-7.83 (m, 1H), 7.59-7.48 (m, 2H), 7.52-7.39 (m, 5H), 7.39-7.27 (m, 1H), 6.93 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.20-4.03 (m, 1H), 4.11 (s, 3H), 2.47-2.28 (m, 2H), 1.09 (t, *J* = 6.7 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 155.45, 145.46, 142.15, 133.34, 128.56, 128.20, 127.88, 127.39, 126.18, 125.48, 120.27, 120.16, 104.07, 55.55, 53.73, 28.61, 13.03, one carbon hidden. All characterization data agreed with that previously reported in the literature.[206]

***1-benzyl-2,4-dimethylbenzene 29***



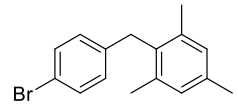
Chemical Formula: $C_{15}H_{16}$
Exact Mass: 196.1252

**General procedure B** was followed with benzyl alcohol (54 mg, 0.50 mmol) and *m*-xylene (265 mg, 2.50 mmol, 5 equiv) in the presence of 10 mol% catalyst in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at 50 ℃ for 24 h. Purification by FC over silica gel (PE) afforded **29** as a colorless oil.

[206] E. Richmond, J. Yi, V. D. Vukovic, F. Sajadi, C. N. Rowley, J. Moran, *Chem. Sci.* **2018**, *9*, 6411.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.50-7.18 (m, 10.6H), 4.29 (s, 0.65H, minor), 4.17 (s, 2H, major), 2.54 (s, 3H, major), 2.48 (s, 1.95H, minor), 2.43 (s, 3H, major); **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 140.92 (major), 140.03 (minor), 137.35 (minor), 137.09 (minor), 136.62 (major), 136.11 (major), 136.08 (major), 130.38 (major), 130.16 (major), 128.92 (major), 128.62 (minor), 128.59 (major), 128.38 (minor), 128.09 (minor), 126.86 (major), 126.58 (minor), 126.07 (major), 125.98 (minor), 39.31 (major), 35.28 (minor), 21.19 (major), 20.46 (minor), 19.83(major) (includes regioisomers). All characterization data agreed with that previously reported in the literature.[207]

***2-(4-bromobenzyl)-1,3,5-trimethylbenzene 30***

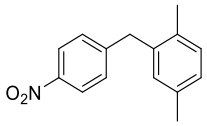



Chemical Formula: $C_{16}H_{17}Br$
Exact Mass: 288.0514

**General procedure B** was followed with 4-bromobenzyl alcohol **2b** (93 mg, 0.50 mmol) and mesitylene (300 mg, 2.50 mmol, 5 equiv) in the presence of 10 mol% catalyst in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at 50 ℃ for 24 h. Purification by FC over silica gel (PE) afforded **30** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.43-7.35 (m, 2H), 6.98-6.90 (m, 4H), 4.01 (s, 2H), 2.35 (s, 3H), 2.24 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 139.19, 136.95, 135.99, 133.18, 131.43, 129.63, 129.04, 119.45, 34.17, 20.95, 20.11. All characterization data agreed with that previously reported in the literature.[207]

***1,4-dimethyl-2-(4-nitrobenzyl)benzene 31***



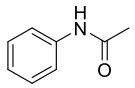

Chemical Formula: $C_{15}H_{15}NO_2$
Exact Mass: 241.1103

**General procedure B** was followed with 4-nitrobenzyl alcohol (77 mg, 0.50 mmol) and *p*-xylene (265 mg, 2.50 mmol, 5 equiv) in the presence of 20 mol% catalyst in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at 80 ℃ for 48 h. Purification by FC over silica gel (PE:EtOAc = 10:1) afforded **31** as a colorless oil.

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

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 8.20-8.12 (m, 2H), 7.36-7.29 (m, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.00 (s, 1H), 4.11 (s, 2H), 2.38 (s, 3H), 2.23 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 148.65, 146.45, 136.99, 135.85, 133.40, 130.90, 130.62, 129.44, 127.89, 123.68, 39.41, 21.00, 19.20. All characterization data agreed with that previously reported in the literature.[207]

***N-phenylacetamide 36***

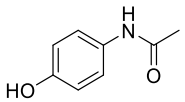


Chemical Formula: $C_8H_9NO$
Exact Mass: 135.0684

**General procedure C** was followed with acetophenone oxime (67 mg, 0.50 mmol) in the presence of 5 mol% catalyst and 5 mol% perfluoropinacol in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (PE:EtOAc = 1:1) afforded **36** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.55-7.48 (m, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 2.19 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 168.61, 137.94, 128.99, 124.33, 119.99, 24.57. All characterization data agreed with that previously reported in the literature.[208]

***N-(4-hydroxyphenyl)acetamide 37***



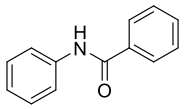
Chemical Formula: $C_8H_9NO_2$
Exact Mass: 151.0633

**General procedure C** was followed with compound **33** (75 mg, 0.50 mmol) in the presence of 5 mol% catalyst and 5 mol% perfluoropinacol in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (EtOAc) afforded **37** as a colorless oil.

**$^1$H NMR (400 MHz, Methanol-$d_4$):** δ 7.30 (d, 2H), 6.72 (d, 2H), 4.89 (s, 1H), 2.08 (s, 3H); **$^{13}$C NMR (100 MHz, Methanol-$d_4$):** δ 170.11, 153.99, 130.25, 122.29, 114.90, 22.21. All characterization data agreed with that previously reported in the literature.[208]

[208] X. B. Mo, T. D. R. Morgan, H. T. Ang, D. G. Hall, *J. Am. Chem. Soc.* **2018**, *140*, 5264.

***N-phenylbenzamide 38***

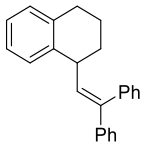


Chemical Formula: $C_{13}H_{11}NO$
Exact Mass: 197.0841

**General procedure C** was followed with benzophenone oxime (99 mg, 0.50 mmol) in the presence of 5 mol% catalyst and 5 mol% perfluoropinacol in HFIP/$MeNO_2$ (4:1) (1.0 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (PE:EtOAc = 1:1) afforded **38** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.93-7.86 (m, 3H), 7.71-7.63 (m, 2H), 7.61-7.54 (m, 1H), 7.54-7.46 (m, 2H), 7.39 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.22-7.13 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 165.81, 137.94, 135.02, 131.87, 129.13, 128.82, 127.04, 124.61, 120.24. All characterization data agreed with that previously reported in the literature.[208]

***1-(2,2-diphenylvinyl)-1,2,3,4-tetrahydronaphthalene 41***



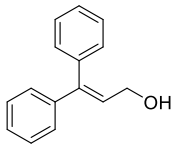
Chemical Formula: $C_{24}H_{22}$
Exact Mass: 310.1722

**General procedure D** was followed with allylic alcohol **40** (66 mg, 0.20 mmol) in the presence of 20 mol% catalyst in $MeNO_2$ (1.0 mL). The reaction mixture was stirred at 50 ℃ for 48 h. Purification by FC over silica gel (PE:EtOAc = 20:1) afforded **41** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.52-7.44 (m, 2H), 7.44-7.24 (m, 9H), 7.24-7.12 (m, 3H), 6.22 (d, *J* = 10.3 Hz, 1H), 3.69 (td, *J* = 9.6, 5.3 Hz, 1H), 2.98-2.74 (m, 2H), 2.12-1.97 (m, 2H), 1.85-1.68 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 142.44, 141.37, 140.13, 139.24, 136.90, 133.66, 129.82, 129.26, 129.25, 128.47, 128.22, 127.32, 127.15, 127.10, 126.01, 125.80, 39.47, 30.67, 29.80, 21.88. All characterization data agreed with that previously reported in the literature.[209]

[209] H. C. Zheng, S. Ghanbari, S. Nakamura, D. G. Hall, *Angew. Chem. Int. Ed.* **2012**, *51*, 6187.

***3,3-diphenylprop-2-en-1-ol 43***

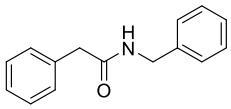



Chemical Formula: $C_{15}H_{14}O$
Exact Mass: 210.1045

**General procedure E** was followed with allylic alcohol **42** (84 mg, 0.40 mmol) in the presence of 20 mol% catalyst in toluene (1.0 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (PE:EtOAc = 8:1) afforded **43** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.23 (m, 8H), 7.19-7.15 (m, 2H), 6.24 (t, *J* = 6.7 Hz, 1H), 4.06 (d, *J* = 6.7 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 144.72, 141.87, 139.21, 129.78, 128.17, 128.14, 127.67, 127.53, 127.49, 125.58, 68.08. All characterization data agreed with that previously reported in the literature.[210]

***N-benzyl-2-phenylacetamide 44***




Chemical Formula: $C_{15}H_{15}NO$
Exact Mass: 225.1154

**General procedure F** was followed with phenyl acetic acid (0.28 mmol) and benzylamine (0.25 mmol) in the presence of 10 mol% catalyst in DCM (1.0 mL). The reaction mixture was stirred at rt for 48 h. Purification by FC over silica gel (PE:EtOAc = 1:1) afforded **44** as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.35 (m, 1H), 7.39-7.27 (m, 5H), 7.31-7.23 (m, 2H), 7.27-7.17 (m, 2H), 5.82 (s, 1H), 4.43 (d, *J* = 5.8 Hz, 2H), 3.64 (s, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 170.94, 138.15, 134.81, 129.48, 129.08, 128.68, 127.51, 127.45, 127.43, 43.83, 43.60. All characterization data agreed with that previously reported in the literature.[211]

[210] H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci.*, **2011**, *2*, 1305.
[211] R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed*. **2008**, *47*, 2876.

# Experimental section-Chapter 3

## General information

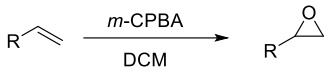
All reagents were used as received from commercial suppliers (*Alfa Aesar*, *Sigma Aldrich TCI* or *FluoroChem*) unless otherwise stated. HFIP (CAS: 920-66-1) was purchased from FluoroChem. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel $F_{254}$ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining using vanilin. Flash column chromatography (FC) was performed using silica gel 60 (230-400 mesh, Merck and co.). Yields refer to chromatographically and spectroscopically pure compounds. When stated, NMR yields were calculated by using hexamethyldisiloxane as an internal standard.

$^{1}$H NMR, $^{13}$C NMR and $^{18}$F NMR spectra were recorded using Bruker UltraShield 400, 500 or 600 at 300K. $^{1}$H NMR chemical shifts are reported in ppm using residual solvent peak as reference ($CDCl_3$: $\delta$ = 7.26 ppm or DMSO-$d_6$: $\delta$ = 2.50 ppm). Data for $^{1}$H NMR are presented as follows: chemical shift $\delta$ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant $J$ (Hz) and integration; $^{13}$C NMR spectra were recorded at 100, 125 or 150 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference ($CDCl_3$: $\delta$ = 77.16 ppm or DMSO-$d_6$: $\delta$ = 39.52 ppm). Multiplicity was defined by recorded a $^{13}$C NMR spectra using the attached proton test (APT). $^{18}$F NMR spectra were recorded at 376.5 or 471 MHz at ambient temperature. High-resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and IC), MicroTOF-Q Bruker (ESI) and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer).

**Materials:** All commercial materials were purchased from Sigma-Aldrich, TCI 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. The other starting starting materials were prepared according to known protocols.

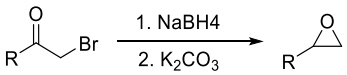
## Starting Material Preparation

**General procedure A:**




A 500 mL flask equipped with a magnetic stirring bar was charged with corresponding styrene (129 mmol). The olefin was dissolved in $CH_2Cl_2$ (300 mL) and treated with *m*-CPBA (>65.0 % purity, 48.0 g, 180 mmol). The suspension was allowed to stir at room temperature for required time. The full consumption of the olefin was checked with $^{19}F$ NMR spectrum. The reaction flask was cooled down at 0°C. The reductant sodium thiosulfate pentahydrate ($Na_2SO_3$, 20.0 g, 80.0 mmol) was added into the reaction flask and vigorously stirred for 1 h at 0°C. Hexane (500 mL) was added into the resulting suspension and filtered through Celite®. The filtrate was dried off and hexane (100 mL) was added into the resting suspension. The resulting suspension was filtered through Celite® again and the filtrate was dried off to give slightly yellow liquid. The liquid was distilled (80.0°C, 13.0 mmHg) to obtain colorless epoxide.

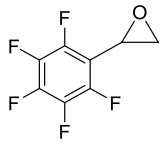
**General procedure B:**




To a stirred solution of bromoketone (7.9 mmol) in methanol (30 mL) at 0°C was added $NaBH_4$ (0.33g, 8.7 mmol) portionwise and after five minutes the reaction was the reaction allowed to warm to room-temperature. After three hours potassium carbonate (1.1 g, 7.9 mmol) was added, and the mixture stirred at room-temperature for a further 16 h. TLC analysis indicated the reaction was completed. The methanol was evaporated, and water (50 mL) was added, then the mixture was extracted with DCM (3x100 mL). the combined organic solvent was washed with brine, dried over $Na_2SO_4$ anhydrous and concentrated in vacuum to give the crude corresponding product; the product was purified by flash column chromatography over silica (with petroleum ether/EtOAc 10:1) give the pure product.

**Characterization Data For epoxide:**

***2,3,4,5,6-pentrafluorostyrene oxide***

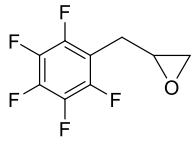


Chemical Formula: $C_8H_3F_5O$
Exact Mass: 210.0104

**General Procedure A** was followed with 2,3,4,5,6-pentafluorostyrene (2.5 g, 12.9 mmol) with *m*-CPBA (>65% purity, 5.0 g, >18.8 mmol) and gave the product as colorless oil (14.0 g, 51.6 % yield).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 4.03 (dd, J = 4.1, 2.7 Hz, 1H), 3.27 (dd, J = 5.2, 2.7 Hz, 1H), 3.20 (dd, J = 5.2, 4.2 Hz, 1H).**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.98 (ddt, J = 11.7, 7.9, 4.0 Hz), 144.98 (ddt, J = 11.7, 7.9, 4.0 Hz), 143.49 – 141.68 (m), 140.76 – 139.62 (m), 138.55 (dddd, J = 16.4, 12.7, 5.4, 2.0 Hz), 136.55 (dddd, J = 18.0, 12.8, 5.4, 2.0 Hz), 110.75 (td, J = 14.9, 4.2 Hz), 46.92 (t, J = 3.8 Hz), 45.45 – 42.81 (m). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -144.52 to -144.52 to -144.66 (m), -154.58 (t, *J* = 20.2 Hz), -162.95 to -163.15 (m).

***2-((perfluorophenyl)methyl)oxirane***

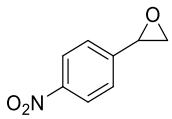


Chemical Formula: $C_9H_5F_5O$
Exact Mass: 224.0261

**General Procedure A** was followed with 1-allyl-2,3,4,5,6-pentafluorobenzene (25.0 g, 120 mmol) with *m*-CPBA (>65% purity, 5.0 g, >18.8 mmol) and gave the product as colorless oil (18.0 g, 67.0 %).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 3.16 (dq, J = 5.6, 2.8 Hz, 1H), 3.06 (dd, J = 14.4, 5.1 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.79 (t, J = 4.4 Hz, 1H), 2.53 (dd, J = 4.9, 2.6 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.98 (ddt, J = 11.7, 7.9, 4.0 Hz), 144.98 (ddt, J = 11.7, 7.9, 4.0 Hz), 143.49 – 141.68 (m), 140.76 – 139.62 (m), 138.55 (dddd, J = 16.4, 12.7, 5.4, 2.0 Hz), 136.55 (dddd, J = 18.0, 12.8, 5.4, 2.0 Hz), 110.75 (td, J = 14.9, 4.2 Hz), 49.99, 46.70, 25.44. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -143.87 to -144.14 (m), -157.42 (t, J = 20.2 Hz), -163.35 to -163.72 (m).

***2-(4-nitrophenyl)oxirane***

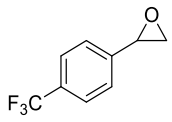


Chemical Formula: $C_8H_7NO_3$
Exact Mass: 165.0426

**General Procedure B** was followed with 2-Bromo-1-(4-nitrophenyl)ethanon (1.9 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as yellow powder (1.2 g, 92.3 %),

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ 8.24 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 3.99 (dd, J = 4.1, 2.5 Hz, 1H), 3.26 (ddd, J = 5.1, 4.1, 0.8 Hz, 1H), 2.81 (ddd, J = 5.5, 2.5, 0.8 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 147.86, 145.25, 126.24, 123.85, 51.69, 51.47.

***2-(4-(trifluoromethyl)phenyl)oxirane***

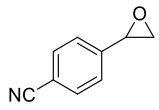


Chemical Formula: $C_9H_7F_3O$
Exact Mass: 188.0449

**General Procedure B** was followed with 2-Bromo-1-(4-(trifluoromethyl)phenyl)ethanon (2.1 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as colorless oil (0.95 g, 63.4 %).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 3.94 (dd, J = 4.1, 2.6 Hz, 1H), 3.24 – 3.18 (m, 1H), 2.82 – 2.76 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 141.8, 130.3 (q, J = 32.4 Hz), 125.7, 125.5 (q, J = 3.7 Hz), 124.1 (q, J = 272 Hz), 51.7, 51.4. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -62.61.

***4-(oxiran-2-yl)benzonitrile***

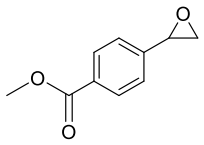


Chemical Formula: $C_9H_7NO$
Exact Mass: 145.0528

**General Procedure B** was followed with 4-(2-bromoacetyl)benzonitrile (1.8 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as colorless oil (0.53 g, 46.3%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.68 – 7.63 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 3.92 (dd, J = 4.1, 2.5 Hz, 1H), 3.22 (ddd, J = 5.2, 4.1, 0.8 Hz, 1H), 2.77 (ddd, J = 5.5, 2.5, 0.8 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 143.28, 132.37, 126.14, 118.64, 111.95, 51.62, 51.60.

***Methyl 4-(oxiran-2-yl)benzoate***

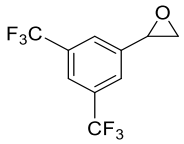


Chemical Formula: $C_{10}H_{10}O_3$
Exact Mass: 178.0630

**General Procedure B** was followed with methyl 4-(2-bromoacetyl)benzoate (2.0 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as white solide (0.73 g, 51.1%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 3.85 (s, 3H), 3.86 – 3.81 (m, 1H), 3.12 (dd, J = 5.6, 4.1 Hz, 1H), 2.72 (dd, J = 5.6, 2.5 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 166.80, 142.90, 129.99, 129.83, 125.42, 52.17, 51.96, 51.48.

***2-(3,5-bis(trifluoromethyl)phenyl)oxirane***

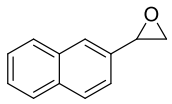


Chemical Formula: $C_{10}H_6F_6O$
Exact Mass: 256.0323

**General Procedure B** was followed with 1-(3,5-bis(trifluoromethyl)phenyl)-2-bromoethan-1-one (2.65 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as colorless oil (1.15 g, 56.8%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.74 (s, 1H), 7.66 (s, 2H), 3.91 (t, J = 3.4 Hz, 1H), 3.15 (t, J = 4.8 Hz, 1H), 2.71 (dd, J = 5.5, 2.5 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 140.66, 132.04 (q, J = 33.5 Hz), 129.83 – 124.54 (m), 124.24, 122.55 – 120.79 (m), 51.51, 51.23. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -62.77.

***2-(naphthalen-2-yl)oxirane***

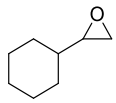


Chemical Formula: $C_{12}H_{10}O$
Exact Mass: 170.0732

**General Procedure B** was followed with 2-Bromo-2′-acetonaphthone (1.97 g, 7.9 mmol) and sodium borohydrides (0.33 g, 8.7 mmol). The product was giving as white solid (1.2 g, 85.8%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.89 – 7.81 (m, 4H), 7.54 – 7.48 (m, 2H), 7.36 (dd, J = 8.5, 1.7 Hz, 1H), 4.06 (dd, J = 4.1, 2.6 Hz, 1H), 3.26 (dd, J = 5.4, 4.1 Hz, 1H), 2.94 (dd, J = 5.4, 2.6 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 135.08, 133.34, 133.20, 128.42, 127.79, 127.78, 126.37, 126.09, 125.19, 122.67, 52.64, 51.31.

***2-cyclohexyloxirane***

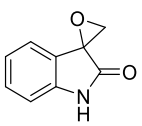


Chemical Formula: $C_8H_{14}O$
Exact Mass: 126.1045

To a solution of vinylcyclohexane (1.10 g, 10.0 mmol) was added in DCM (30 mL), m-CPBA (2.72 g, <77% purity, 11.0 mmol) was added at 0 ºC and the mixture was stirred overnight at room temperature. Then the mixture was filteded and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with 10% $Na_2SO_3$, 10% $NaHCO_3$, water and brine. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuum to obtain the product as colorless liquid (0.82 g, 66.7%).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ 2.71 (dd, J = 5.0, 3.0 Hz, 2H), 2.53 (t, J = 4.0 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.79 – 1.64 (m, 5H), 1.29 – 1.07 (m, 5H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 56.66, 45.99, 40.38, 29.71, 28.81, 26.32, 25.70, 25.54.

***spiro[indoline-3,2'-oxiran]-2-one***



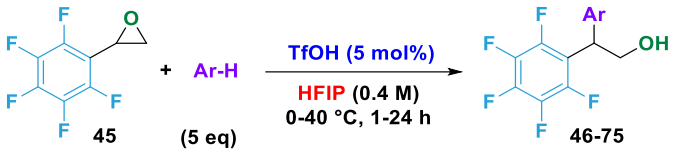
Chemical Formula: $C_9H_7NO_2$
Exact Mass: 161.0477

In a dry 100 mL round bottomed flask, a dry DMF (20 mL) solution of trimethylsulphonium iodide (1.0 g, 6.79 mmol) and sodium hydride (1.95 g, 40.77 mmol) was stirred at rt for 1h under argon atmosphere. After 1h the reaction mixture was stirred at -20 °C and then Isatin (1.0 g, 6.79 mmol) was dissolve in dry DMF (20 mL) was added dropwise. The resulting solution was stirred at rt for 2 h. Up to completed, the reaction was quenched with saturated aqueous solution of NH4Cl, extracted with EtOAc, washed with brine solution and dried over anhydrous $Na_2SO_4$. Purification by FC over silica gel (n-pentane/EtOAc 5:1) afforded the product (0.76 g, 70%) as white solid.

**$^1$H NMR (400 MHz, $(CD_3)_2SO$):** δ 10.80 (br. s, 1H), 7.31 - 7.16 (m, 1H), 7.14 - 7.13 (m, 1H), 7.01-6.98 (m, 1H), 6.94 (d, *J* = 8 Hz, 1H), 3.58 (d, *J* = 6.8 Hz, 1H), 3.35 (d, *J* = 6.8 Hz, 1H). **$^{13}$C NMR (100 MHz, $(CD_3)_2SO$):** δ 172.7, 143.4, 130.4, 122.9, 121.9, 110.6, 110.5, 56.3, 53.3.

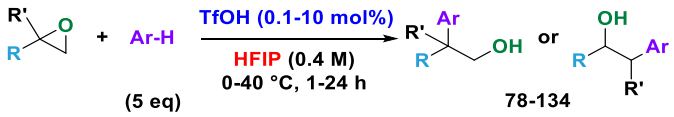
## General Procedures for the Monoarylation of Epoxides

**General procedure C** to access (pentafluorophenyl)ethanol derivatives




2,3,4,5,6-Pentafluorostyrene oxide **45** (84.0 mg, 0.40 mmol, 1.0 eq) and nucleophile (2.0 mmol, 5.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.4 M) and TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at the indicated temperature (0-40 °C) for the indicated time (1-24 h). Upon completion, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target products **46-75**. Regioisomeric ratios were calculated from $^1$H NMR spectra.

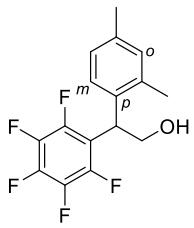
**General procedure D** for monoarylation of epoxides



Nucleophile (2.0 mmol, 5.0 eq) was charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.4 M) was added, and the solution was cool down to 0 °C. Then, epoxide (1.0 eq) and TfOH (0.1-5.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at the indicated temperature (0-40 °C) for the indicated time (1-24 h). Upon completion, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target products **78-134**. Regioisomeric ratios were calculated from $^1$H NMR spectra.

## Characterization Data of Monoarylated Products

***2-(2,4-Dimethylphenyl)-2-(perfluorophenyl)ethan-1-ol 46***

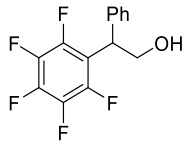



***p/o/m* 70:15:15**
Chemical Formula: $C_{16}H_{13}F_5O$
Exact Mass: 316.0887

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and *m*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **46** (122.6 mg, 97% yield, *p*/*o*/*m* 70:15:15) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.20 (d, $J$ = 8.4 Hz, 1H), 7.05–7.01 (m, 2H), 4.73 (t, $J$ = 7.9 Hz, 1H), 4.27–4.22 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 1.94 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 145.8 (dm, $J$ = 247.3 Hz), 140.1 (dm, $J$ = 252.9 Hz), 137.7 (dm, $J$ = 255.3 Hz), 138.7, 137.4, 136.7, 131.8, 127.3, 127.2 (t, $J$ = 3.0 Hz), 115.3 (m), 64.0 (t, $J$ = 3.5 Hz), 40.5 (d, $J$ = 1.3 Hz), 21.0, 19.4 (t, $J$ = 1.2 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.3 (m), -156.4 (m), -162.0 (m). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5ONa$ $[M+Na]^+$ 339.0779, found 339.0772.

***2-(Perfluorophenyl)-2-phenylethan-1-ol 47***

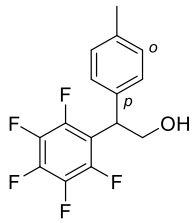



Chemical Formula: $C_{14}H_9F_5O$
Exact Mass: 288.0574

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **47** (96.5 mg, 84% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31–7.15 (m, 5H), 4.53 (t, *J* = 8.0 Hz, 1H), 4.30–4.15 (m, 2H), 1.93 (t, *J* = 5.4 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.4 (dm, *J* = 244.4 Hz), 140.1 (dm, *J* = 253.1 Hz), 138.2, 137.7 (dm, *J* = 253.0 Hz), 129.0, 127.9 (t, *J* = 1.4 Hz), 127.7, 115.3 (m), 63.6 (t, *J* = 4.0 Hz), 44.4 (q, *J* = 1.3 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.6 (m), -156.08 (t, *J* = 20.9 Hz), -161.9 (m). **HRMS (ESI):** *m/z* calcd. for $C_{14}H_9F_5ONa$ $[M+Na]^+$ 314.0466, found 314.0459.

***2-(perfluorophenyl)-2-(p-tolyl)ethan-1-ol 48***



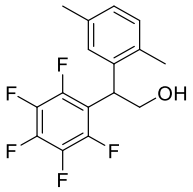

Chemical Formula: $C_{15}H_{11}F_5O$
Exact Mass: 302.0730

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and toluene (212.6 µL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **48** (97.1 mg, 80% yield, *o/p* 1:1) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.41 – 7.07 (m, 4H), 4.61 (td, J = 8.0, 2.2 Hz, 1H), 4.32 (dt, J = 22.5, 8.0 Hz, 2H), 2.46 – 2.34 (m, 3H), 2.11 (d, J = 15.7 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.86 – 145.99 (m), 144.93 – 144.20 (m), 141.04 (d, J = 4.7 Hz), 139.02

(d, J = 4.8 Hz), 138.78, 138.64 (d, J = 17.7 Hz), 138.16, 137.49, 136.82, 136.63 (d, J = 16.3 Hz), 136.23, 135.19, 130.95, 129.68, 128.88, 128.70 (d, J = 1.3 Hz), 128.44, 127.77 (d, J = 1.4 Hz), 127.55, 127.19 (t, J = 2.9 Hz), 126.50, 124.82 (t, J = 1.5 Hz), 115.73 – 114.62 (m), 63.83, 63.66, 44.38 (d, J = 1.5 Hz), 44.05 (d, J = 1.6 Hz), 40.67 (d, J = 1.6 Hz), 21.43, 21.00, 19.42. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -140.84 – -141.29 (m), -141.41 – -142.13 (m), -156.13 – -156.28 (m), -156.29 – -156.45 (m), -161.99 (dddd, J = 28.7, 22.4, 13.4, 7.1 Hz). **HRMS** (ESI): *m/z* for $C_{15}H_{11}F_5ONa$ ($[M+Na]^+$): calculated 325.0622; found 325.0625.

***2-(2,5-Dimethylphenyl)-2-(perfluorophenyl)ethan-1-ol 49***

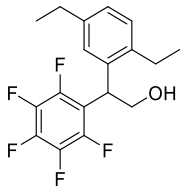



Chemical Formula: $C_{16}H_{13}F_5O$
Exact Mass: 316,0887

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **49** (108.7 mg, 86% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** *δ* 7.11–7.06 (m, 2H), 7.00 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.74 (t, *J* = 7.9 Hz, 1H), 4.30–4.20 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 1.97–1.94 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** *δ* 145.7 (dm, *J* = 246.6 Hz), 140.0 (dm, *J* = 252.9 Hz), 137.7 (dm, *J* = 252.7 Hz), 136.0 (2C), 133.6, 130.8, 128.3, 127.8 (t, *J* = 2.8 Hz), 115.1 (m), 63.9 (t, *J* = 3.6 Hz), 40.8 (d, *J* = 1.3 Hz), 21.1, 19.0 (t, *J* = 1.2 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** *δ* -141.2 (m), -156.3 (t, *J* = 21.0 Hz), -162.1 (td, *J* = 21.8, 7.2 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5ONa$ $[M+Na]^+$ 339.0779, found 339.0772.

***2-(2,5-Diethylphenyl)-2-(perfluorophenyl)ethan-1-ol 50***

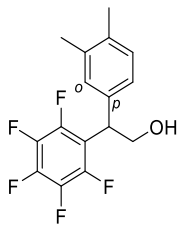


Chemical Formula: $C_{18}H_{17}F_5O$
Exact Mass: 344.1200

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,4-diethylbenzene (0.31 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **50** (82.6 mg, 60% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.20–7.07 (m, 3H), 4.82 (dd, *J* = 9.0, 6.9 Hz, 1H), 4.33–4.21 (m, 2H), 2.82–2.73 (m, 1H), 2.72–2.60 (m, 3H), 1.90 (s, 1H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.23 (t, *J* = 7.6 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.8 (dm, *J* = 247.0 Hz), 142.3, 140.1 (dm, *J* = 253.0 Hz), 139.9, 137.8 (dm, *J* = 252.1 Hz), 135.2, 129.2, 127.4, 127.0 (t, *J* = 3.1 Hz), 115.5 (m), 64.3 (t, *J* = 3.5 Hz), 40.4, 28.6, 25.0, 15.7, 15.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.1 (m), -156.3 (t, *J* = 20.9 Hz), -162.0 (dd, *J* = 21.1, 14.9 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{17}F_5ONa$ $[M+Na]^+$ 367.1092, found 367.1086.

***2-(3,4-Dimethylphenyl)-2-(perfluorophenyl)ethan-1-ol 51***

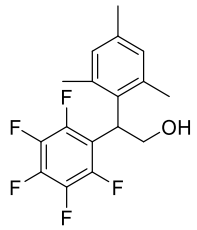


***p*/*o* 67:33**
Chemical Formula: $C_{16}H_{13}F_5O$
Exact Mass: 316.0887

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and *o*-xylene (0.24 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **51** (106.2 mg, 84% yield, *p*/*o* 67:33) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.17–7.15 (m, 0.5H, ***o***), 7.14–7.10 (m, 2H, ***o***+***p***), 7.09–7.04 (m, 2H, ***o***+***p***), 4.83 (dd, *J* = 8.5, 7.3 Hz, 0.5H, ***o***), 4.55 (t, *J* = 8.0 Hz, 1H, ***p***), 4.34–4.24 (m, 3H, ***o***+***p***), 2.32 (s, 1.5H, ***o***), 2.28 (s, 1.5H, ***o***), 2.27 (s, 3H, ***p***), 2.25 (s, 3H, ***p***), 1.97 (s, 0.5H, ***o***), 1.92 (s, 1H, ***p***). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.8 (dm, *J* = 245.6 Hz, ***o***), 145.5 (dm, *J* = 246.9 Hz, ***p***), {141.1, 139.1} (m, 2C, ***o***+***p***), {138.9, 136.8} (m, 2C, ***o***+***p***), 137.6 (***o***), 137.4 (***p***), 136.3 (***p***), 136.1 (***o***), 135.7 (***p***), 135.4 (***o***), 130.3 (***p***), 129.4 (***o***), 129.3 (t, *J* = 1.3 Hz, ***p***), 125.9 (***o***), 125.2 (t, *J* = 1.5 Hz, ***p***), 125.1 (t, *J* = 2.9 Hz, ***o***), 115.5 (m, 2C, ***o***+***p***), 64.1 (t, *J* = 3.4 Hz, ***o***), 63.8 (t, *J* = 4.1 Hz, ***p***), 44.2 (q, *J* = 1.3 Hz, ***p***), 44.1 (***o***), 21.2 (***o***), 19.9 (***p***), 19.5 (***p)***, 14.9 (t, *J* = 1.1 Hz, ***o***). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.0 (m, o), -141.7 (m, p), -156.4 (t, *J* = 20.9 Hz, ***o***), -156.5 (t, *J* = 20.9 Hz, ***p***), -162.0 (m, ***o***+***p***). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5ONa$ $[M+Na]^+$ 339.0779, found 339.0774.

***2-Mesityl-2-(perfluorophenyl)ethan-1-ol 52***

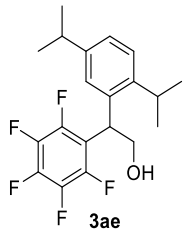



Chemical Formula: $C_{17}H_{15}F_5O$
Exact Mass: 330.1043

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **52** (125.4 mg, 95% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.85 (s, 2H), 4.90 (dd, *J* = 8.9, 7.4 Hz, 1H), 4.44 (t, *J* = 10.1 Hz, 1H), 4.06 (dd, *J* = 11.0, 7.4 Hz, 1H), 2.28 (s, 6H), 2.25 (s, 3H), 1.94 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 146.0 (dm, *J* = 246.7 Hz), 139.9 (dm, *J* = 252.8 Hz), 137.7 (dm, *J* = 252.5 Hz), 137.3, 137.1, 132.0, 130.6, 115.0 (m), 62.4 (t, *J* = 4.9 Hz), 42.2, 20.8, 20.5. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -139.9 (m), -156.8 (m), -162.5 (td, *J* = 22.0, 7.0 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{15}F_5ONa$ $[M+Na]^+$ 335.0935, found 335.0930.

***2-(2,5-Diisopropylphenyl)-2-(perfluorophenyl)ethan-1-ol 53***



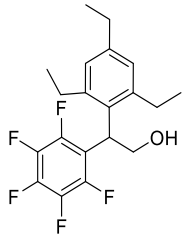

**3ae**

Chemical Formula: $C_{20}H_{21}F_5O$
Exact Mass: 372.1513

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,4-diisopropylbenzene (379.0 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **53** (113.1 mg, 76% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.26 (d, $J$ = 8.1 Hz, 1H), 7.15 (dd, $J$ = 8.1, 1.9 Hz, 1H), 7.11 (q, $J$ = 1.8 Hz, 1H), 4.91 (dd, $J$ = 9.0, 6.9 Hz, 1H), 4.32–4.19 (m, 2H), 3.27 (p, $J$ = 6.8 Hz, 1H), 2.86 (p, $J$ = 6.9 Hz, 1H), 1.78 (s, 1H), 1.28 (d, $J$ = 7.0 Hz, 3H), 1.23 (d, $J$ = 6.9 Hz, 3H), 1.22 (d, $J$ = 6.9 Hz, 3H), 1.13 (d, $J$ = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.8 (dm, $J$ = 247.6 Hz), 146.6, 144.9, 140.1 (dm, $J$ = 253.1 Hz), 139.9, 137.8 (dm, $J$ = 252.7 Hz), 134.1, 126.2, 125.9, 125.6 (t, $J$ = 3.1 Hz), 115.8 (m), 64.5 (t, $J$ = 3.5 Hz), 40.3, 33.8, 28.2, 24.6, 24.1, 24.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.2 (m), -156.3 (t, $J$ = 21.0 Hz), -162.0 (td, $J$ = 22.5, 7.6 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{20}H_{21}F_5ONa$ $[M+Na]^+$ 395.1405, found 395.1398.

***2-(Perfluorophenyl)-2-(2,4,6-triethylphenyl)ethan-1-ol 54***



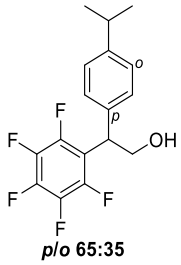

Chemical Formula: $C_{20}H_{21}F_5O$
Exact Mass: 372.1513

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,3,5-triethylbenzene (0.38 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was

stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **54** (142.9 mg, 96% yield) as a colorless oil (with traces of diarylation).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.94 (s, 2H), 4.97–4.92 (m, 1H), 4.55 (t, *J* = 10.6 Hz, 1H), 3.97 (dd, *J* = 11.4, 6.4 Hz, 1H), 2.72–2.58 (m, 6H), 2.11 (s, 1H), 1.32–1.06 (m, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 146.1 (dm, *J* = 246.6 Hz), 143.6, 143.0, 139.8 (dm, *J* = 253.4 Hz), 137.8 (dm, *J* = 250.9 Hz), 131.1, 127.2, 116.0 (m), 63.5 (t, *J* = 4.4 Hz), 41.8, 28.5, 26.1, 15.4, 15.2. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -139.8 (m), -156.9 (t, *J* = 21.2 Hz), -162.5 (m). **HRMS (ESI):** *m/z* calcd. for $C_{20}H_{21}F_5ONa$ $[M+Na]^+$ 395.1405, found 395.1399.

***2-(4-Isopropylphenyl)-2-(perfluorophenyl)ethan-1-ol 55***




***p*/*o* 65:35**

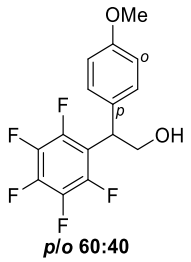
Chemical Formula: $C_{17}H_{15}F_5O$

Exact Mass: 330,1043

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and cumene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **55** (101.1 mg, 77% yield, *p*/*o*: 65/35) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.21 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 4.56 (t, *J* = 8.0 Hz, 1H), 4.34–4.22 (m, 2H), 3.23 (p, J = 6.8 Hz, 34H), 2.86 (p, *J* = 6.9 Hz, 1H), 1.64 (t, *J* = 5.8 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 148.5, 145.5 (dm, *J* = 246.5 Hz), 140.1 (dm, *J* = 252.9 Hz), 137.8 (dm, *J* = 251.1 Hz), 135.5, 128.0 (t, *J* = 1.4 Hz), 127.2, 115.5 (m), 63.9 (t, *J* = 4.1 Hz), 44.2, 33.8, 24.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.6 (m), -156.4 (dt, *J* = 21.1 Hz), -161.9 (tdd, m). **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{15}F_5ONa$ $[M+Na]^+$ 353.0935, found 353.0931.

***2-(4-Methoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 56***



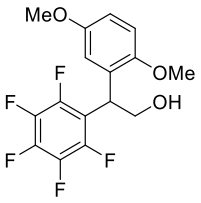

***p*/*o* 60:40**

Chemical Formula: $C_{15}H_{11}F_5O_2$
Exact Mass: 318,0679

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and anisole (0.22 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **56** (120.9 mg, 95% yield, *p*/*o* 60:40) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.20–7.12 (m, 2H, ***o***+***p***), 6.87 (td, *J* = 7.6, 1.2 Hz, 0.4H, ***o***), 6.81–6.76 (m, 1.6H, ***o***+***p***), 4.84 (dd, *J* = 8.7, 7.1 Hz, 0.4H, ***o***), 4.46 (t, *J* = 8.0 Hz, 0.6H, ***p***), 4.23–4.13 (m, 2H, ***o***+***p***), 3.71 (s, 1.2H, ***o***), 3.70 (s, 1.8H, ***p***), 1.87 (brs, 1H, ***o***+***p***). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 159.0 (***p***), 157.2 (***o***), 145.8 (dm, *J* = 248.0 Hz, ***o***), 145.4 (dm, *J* = 246.4 Hz, ***p***), {140.9, 138.9} (m, 2C, ***o***+***p***), {138.6, 136.6} (m, 2C, ***o***+***p***), 130.2 (***p***), 129.0 (t, *J* = 1.4 Hz, ***p***), 128.7 (***o***), 127.9 (t, *J* = 2.3 Hz, ***o***), 126.0 (***o***), 120.6 (***o***), 115.6 (m, ***p***), 115.2 (m, ***o***), 114.3 (***p***), 110.7 (***o***), 63.7 (t, *J* = 4.0 Hz, ***p***), 62.9 (t, *J* = 3.2 Hz, ***o***), 55.4 (***o***), 55.3 (***p***), 43.7 (***p***), 37.9 (***o***). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.6 (m, ***o***), -141.9 (m, ***p***), -156.5 (t, *J* = 20.9 Hz, ***p***), -157.1 (t, *J* = 20.9 Hz, ***o***), -162.0 (m, ***p***), -163.0 (m, ***o***). **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{11}F_5O_2Na$ $[M+Na]^+$ 341.0571, found 341.0566.

***2-(2,5-Dimethoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 57***



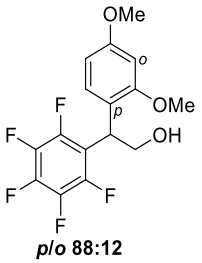

Chemical Formula: $C_{16}H_{13}F_5O_3$
Exact Mass: 348,0785

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,4-dimethoxybenzene (276 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was

stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **57** (133.7 mg, 96% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.86–6.83 (m, 1H), 6.80–6.76 (m, 2H), 4.90 (dd, $J$ = 8.6, 7.1 Hz, 1H), 4.29–4.17 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 1.99 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 160.3, 158.4, 145.8 (dm, $J$ = 246.1 Hz), 139.9 (dm, $J$ = 251.9 Hz), 137.6 (dm, $J$ = 249.8 Hz), 128.5 (t, $J$ = 3.1 Hz), 115.2, 115.1 (m), 112.3, 111.7, 63.0 (t, $J$ = 3.3 Hz), 56.1, 55.8, 38.1. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.4 (m), -157.0 (t, $J$ = 20.9 Hz), -162.9 (m). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5O_2Na$ $[M+Na]^+$ 371.0677, found 371.0671.

***2-(2,4-Dimethoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 58***

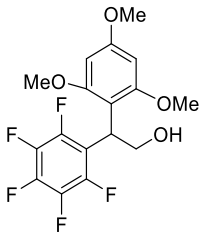



***p*/*o* 88:12**
Chemical Formula: $C_{16}H_{13}F_5O_3$
Exact Mass: 348,0785

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,3-dimethoxybenzene (0.26 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **58** (128.2 mg, 92% yield, *p*/*o* 88:12) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.17 (dd, $J$ = 8.5 Hz, 1H), 6.48 (dd, $J$ = 8.5, 2.5 Hz, 1H), 6.44 (d, $J$ = 2.5 Hz, 1H), 4.84 (dd, $J$ = 8.7, 7.2 Hz, 1H), 4.28–4.18 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 1.95 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 153.7, 151.6, 145.9 (dm, $J$ = 247.7 Hz), 140.0 (dm, $J$ = 252.3 Hz), 137.6 (dm, $J$ = 251.8 Hz), 127.4, 118.5, 115.6 (m), 104.3, 98.8, 62.4 (t, $J$ = 3.2 Hz), 55.5, 55.4, 37.5. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.8 (dd, $J$ = 22.4, 7.6 Hz), -157.4 (t, $J$ = 21.0 Hz), -163.1 (td, $J$ = 22.1, 7.7 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5O_3Na$ $[M+Na]^+$ 371.0677, found 371.0670.

***2-(Perfluorophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-ol 59***

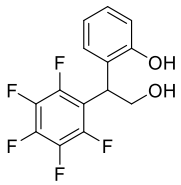



Chemical Formula: $C_{17}H_{15}F_5O_4$
Exact Mass: 378.0890

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **59** (139.1 mg, 92% yield) as a white solid.

**m.p.:** 87-90 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.11 (s, 2H), 5.00 (t, *J* = 7.6 Hz, 1H), 4.27 (dd, *J* = 10.9, 7.7 Hz, 1H), 4.09 (dd, *J* = 10.9, 7.6 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 6H), 2.31 (s, 1H). **$^{113}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 160.8, 159.3, 146.0 (dm, *J* = 246.8 Hz), 139.4 (dm, *J* = 250.7 Hz), 137.3 (dm, *J* = 246.5 Hz), 115.9 (m), 107.4, 91.1, 62.9 (t, *J* = 3.8 Hz), 55.8, 55.4, 36.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.5 (m), -158.9 (t, *J* = 20.9 Hz), -164.4 (td, *J* = 22.3, 7.4 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{15}F_5O_4Na$ $[M+Na]^+$ 401.0783, found 401.0775.

***2-(2-Hydroxy-1-(perfluorophenyl)ethyl)phenol 60***

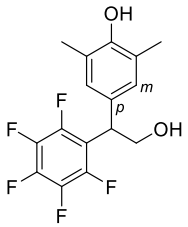



Chemical Formula: $C_{14}H_9F_5O_2$
Exact Mass: 304.0523

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and phenol (188 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **60** (51.1 mg, 42% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.17 (td, $J$ = 7.7, 1.6 Hz, 1H), 7.08 (d, $J$ = 7.7 Hz, 1H), 6.9 (t, $J$ = 7.5 Hz, 1H), 6.82 (dd, $J$ = 8.0 Hz, 1H), 6.07 (s, 1H), 4.91 (dd, $J$ = 7.9, 6.7 Hz, 1H), 4.42–4.34 (m, 1H), 4.27 (dd, $J$ = 10.4, 6.7 Hz, 1H), 2.12 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 153.9, 145.6 (dm, $J$ = 247.4 Hz), 140.1 (dm, $J$ = 252.7 Hz), 137.6 (dm, $J$ = 252.8 Hz), 128.8, 128.2 (t, $J$ = 2.0 Hz), 124.9, 121.1, 116.5, 114.5 (m), 64.5 (t, $J$ = 3.9 Hz), 38.2. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -140.6 (m), -156.04 (t, $J$ = 21.0 Hz), -162.1 (m). **HRMS (ESI):** *m/z* calcd. for $C_{14}H_9F_5O_2Na$ $[M+Na]^+$ 327.0415, found 327.0408.

***4-(2-Hydroxy-1-(perfluorophenyl)ethyl)-2,6-dimethylphenol 61***

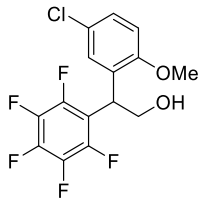



***p*/*m* 80:20**
Chemical Formula: $C_{16}H_{13}F_5O_2$
Exact Mass: 332,0836

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2,6-dimethylphenol (244.0 mg, 2.0 mmol) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **61** (106.4 mg, 80% yield, *p*/*m* 80:20) as a white solid.

**$^{1}$H NMR (400 MHz, DMSO-$d_6$, major isomer):** $\delta$ 8.17 (s, 1H), 6.81 (s, 2H), 5.03 (t, $J$ = 5.5 Hz, 1H), 4.38 (dd, $J$ = 9.3, 6.8 Hz, 1H), 4.08–3.93 (m, 2H), 2.12 (s, 6H). **$^{13}$C NMR (100 MHz, DMSO-$d_6$, major isomer):** $\delta$ 152.7, 145.5 (dm, $J$ = 243.7 Hz), 139.1 (dm, $J$ = 249.0 Hz), 137.4 (dm, $J$ = 248.9 Hz), 129.4, 127.8, 124.8, 117.3 (m), 62.8 (t, $J$ = 3.4 Hz), 43.8, 17.1. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -142.2 (dd, $J$ = 24.3, 7.3 Hz), -157.8 (t, $J$ = 22.1 Hz), -163.2 (td, $J$ = 23.3, 7.2 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{13}F_5O_2Na$ $[M+Na]^+$ 355.0728, found 355.0700.

***2-(5-Chloro-2-methoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 62***

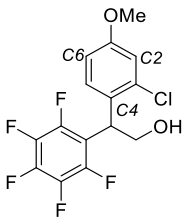



Chemical Formula: $C_{15}H_{10}ClF_5O_2$
Exact Mass: 352,0289

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mol) and 4-chloroanisole (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **62** (87.3 mg, 62% yield) as a white solid.

**m. p.:** 83-87 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.28–7.19 (m, 2H), 6.78 (dd, $J$ = 8.3, 0.7 Hz, 1H), 4.88 (dd, $J$ = 8.6, 7.2 Hz, 1H), 4.29–4.20 (m, 2H), 3.78 (s, 3H), 1.74 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 156.0, 145.9 (dm, $J$ = 247.8 Hz), 140.2 (dm, $J$ = 252.8 Hz), 137.7 (dm, $J$ = 252.4 Hz), 128.5, 128.2 (t, $J$ = 3.1 Hz), 127.9, 125.8, 114.6 (m), 112.0, 62.8 (t, $J$ = 3.2 Hz), 55.9, 37.8. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.5 (m), -156.4 (t, $J$ = 21.0 Hz), -162.5 (m). **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{10}ClF_5O_2Na$ $[M+Na]^+$ 375.0182, found 375.0176.

***2-(2-chloro-4-methoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 63***

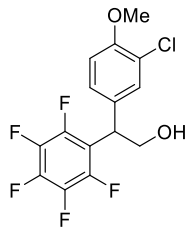



***C2:C4:C6 =1:5:5***
Chemical Formula: $C_{15}H_{10}ClF_5O_2$
Exact Mass: 352.0289

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mol) and 4-chloroanisole (245.0 µL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **63** (125.3 mg, 89% yield, regioisomer ratio: *C2:C4:C6* = 1:5:5) as a white solid.

Major product characterization data: **$^{1}$H NMR** (400 MHz, CDCl3) δ(ppm): 7.20 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.50 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 4.87 (dd, *J* = 8.7, 7.2 Hz, 1H), 4.26 (tt, *J* = 19.4, 8.7 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 1.98 (s, 1H). **$^{13}$C NMR** (100 MHz, CDCl3) δ(ppm): 160.23, 158.27, 146.71 (t, *J* = 10.1 Hz), 145.13 – 144.34 (m), 141.35 – 140.17 (m), 139.34 – 138.02 (m), 136.48 (ddd, *J* = 17.6, 9.0, 3.4 Hz), 128.40 (t, *J* = 2.4 Hz), 118.42, 115.97 – 115.04 (m), 104.17, 98.70, 62.95 (t, *J* = 3.2 Hz), 55.37 (d, *J* = 8.1 Hz), 37.44 (q, *J* = 1.3 Hz). **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ(ppm): -141.82 (dd, *J* = 22.4, 7.6 Hz), -157.38 (t, *J* = 21.0 Hz), -163.05 (td, *J* = 22.1, 7.7 Hz). **HRMS** (ESI): *m/z* for $C_{16}H_{13}F_5O_3Na$ ($[M+Na]^+$): calculated 371.0677; found 371.0670.

***2-(3-Chloro-4-methoxyphenyl)-2-(perfluorophenyl)ethan-1-ol 64***

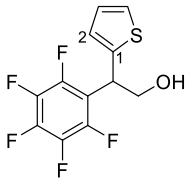



Chemical Formula: $C_{15}H_{10}ClF_5O_2$
Exact Mass: 352,0289

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2-chloroanisole (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **64** (122.5 mg, 87% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** *δ* 7.29 (d, *J* = 2.3 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.52 (t, *J* = 7.9 Hz, 1H), 4.31–4.20 (m, 2H), 3.87 (s, 3H), 1.81 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** *δ* 154.5, 145.5 (dm, *J* = 246.9 Hz), 140.3 (dm, *J* = 253.6 Hz), 137.8 (dm, *J* = 253.0 Hz), 131.4, 129.8, 127.3 (t, *J* = 3.1 Hz), 123.0, 115.0 (m), 112.4, 63.6 (t, *J* = 3.9 Hz), 56.3, 43.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** *δ* -141.7 (m), -155.7 (t, *J* = 21.0 Hz), -161.5 (m). **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{10}ClF_5O_2Na$ $[M+Na]^+$ 375.0182, found 375.0175.

***2-(Perfluorophenyl)-2-(thiophen-2-yl)ethan-1-ol 65***



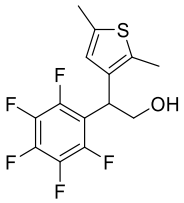

***1/2* 60:40**

Chemical Formula: $C_{12}H_7F_5OS$
Exact Mass: 294,0138

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and thiophene (0.16 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc: 8/1) afforded **65** (111.7 mg, 95% yield, *1/2* 59:41) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31 (dd, *J* = 5.0, 2.9 Hz, 1H, ***2***), 7.22 (dd, *J* = 4.9, 1.4 Hz, 1.4H, ***1***), 7.15 (d, *J* = 2.9 Hz, 1H, ***2***), 7.01 (d, *J* = 5.1 Hz, 1H, ***2***), 6.98–6.93 (m, 2.8H, ***1***), 4.85 (t, *J* = 7.8 Hz, 1.4H, ***1***), 4.70 (t, *J* = 7.9 Hz, 1H, ***2***), 4.35–4.27(m, 2.4H, ***1***+***2***), 4.26–4.19 (m, 2.4H, ***1***+***2***), 1.96 (brs, 2.4H, ***1***+***2***). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ {146.3, 144.3} (m, 2C, ***1***+***2***), {141.3, 139.3} (m, 2C, ***1***+***2***), 140.5 (***1***), {138.7, 136.6} (m, 2C, ***1***+***2***), 138.2 (***2***), 127.0 (2C, ***1***+***2***), 126.5 (***2***), 125.6 (t, *J* = 1.4 Hz, ***1***), 124.9 (***1***), 122.2 (t, *J* = 1.6 Hz, ***2***), 114.7 (m, 2C, ***1***+***2***), 64.3 (t, *J* = 3.7 Hz, ***1***), 63.7 (t, *J* = 3.7 Hz, ***2***), 39.7 (***2***), 39.5 (***1***). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.3 (m, ***1***), -141.9 (m, ***2***), -155.5 (t, *J* = 20.9 Hz, ***1***), -156.0 (t, *J* = 20.9 Hz, ***2***), -161.5 (m, ***1***), -161.8 (m, ***2***). **HRMS (ESI):** *m/z* calcd. for $C_{12}H_7F_5OSNa$ $[M+Na]^+$ 317.0030, found 317.0026.

***2-(2,5-Dimethylthiophen-3-yl)-2-(perfluorophenyl)ethan-1-ol 66***



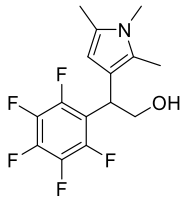

Chemical Formula: $C_{14}H_{11}F_5OS$
Exact Mass: 322.0451

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2,5-dimethylthiophene (0.23 mL, 2.0 mmol) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for

6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **66** (88.9 mg, 69% yield) as a yellow oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.63 (q, *J* = 1.3 Hz, 1H), 4.57 (t, *J* = 8.0 Hz, 1H), 4.17 (dt, *J* = 7.9, 1.4 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.80 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.3 (dm, *J* = 246.2 Hz), 140.0 (dm, *J* = 252.9 Hz), 137.7 (dm, *J* = 252.9 Hz), 136.6, 134.1, 132.9, 124.2 (t, *J* = 3.3 Hz), 114.8 (m), 63.8 (t, *J* = 3.9 Hz), 37.9 (q, *J* = 1.4 Hz), 15.2, 12.8 (t, *J* = 1.1 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.5 (m), -156.6 (t, *J* = 21.0 Hz), -161.9 (dd, *J* = 21.0, 14.7 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{14}H_{11}F_5OSNa$ $[M+Na]^+$ 345.0343, found 345.0339.

***2-(Perfluorophenyl)-2-(1,2,5-trimethyl-1H-pyrrol-3-yl)ethan-1-ol 67***

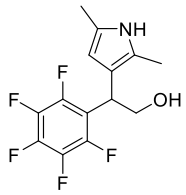



Chemical Formula: $C_{15}H_{14}F_5NO$
Exact Mass: 319,0996

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,2,5-trimethylpyrrole (0.27 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **67** (117.4 mg, 92% yield) as a yellow oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 5.89 (s, 1H), 4.50 (t, *J* = 8.1 Hz, 1H), 4.22–4.06 (m, 2H), 3.38 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.88 (dd, *J* = 7.7, 4.1 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.2 (dm, *J* = 245.1 Hz), 139.6 (dm, *J* = 251.6 Hz), 137.6 (dm, *J* = 252.0 Hz), 128.0, 125.9, 116.5 (m), 114.4, 103.6 (t, *J* = 3.6 Hz), 64.0 (q, *J* = 3.7 Hz), 36.2 (q, *J* = 1.3 Hz), 30.3, 12.4, 10.0 (t, *J* = 0.9 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.8 (dd, *J* = 22.7, 7.7 Hz), -158.0 (t, *J* = 20.9 Hz), -162.5 (m). **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{14}F_5NONa$ $[M+Na]^+$ 342.0888, found 342.0884.

***2-(2,5-Dimethyl-1H-pyrrol-3-yl)-2-(perfluorophenyl)ethanol 68***

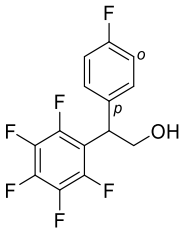



Chemical Formula: $C_{14}H_{12}F_5NO$
Exact Mass: 305,0839

General procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2,5-dimethylpyrrole (190.3 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **68** (90.3 mg, 74% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.57 (brs, 1H), 5.84 (s, 1H), 4.45 (t, $J$ = 8.1 Hz, 1H), 4.23–4.08 (m, 2H), 2.21 (s, 3H), 2.19 (s, 3H), 1.77 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.3 (dm, $J$ = 245.5 Hz), 139.7 (dm, $J$ = 251.5 Hz), 137.7 (dm, $J$ = 251.8 Hz), 126.3, 124.2, 116.4 (m), 115.5, 104.6 (t, $J$ = 2.9 Hz), 64.1 (t, $J$ = 2.8 Hz), 36.1, 13.0, 11.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.8 (dd, $J$ = 22.7, 7.7 Hz), -158.0 (t, $J$ = 20.9 Hz), -162.5 (m).

***2-(4-Fluorophenyl)-2-(perfluorophenyl)ethan-1-ol 69***




***p*/*o* 62:38**

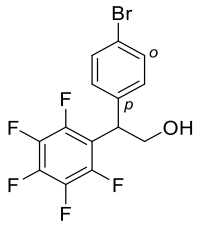
Chemical Formula: $C_{14}H_8F_6O$
Exact Mass: 306.0479

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and fluorobenzene (0.19 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **69** (64.9 mg, 53% yield, *p*/*o* 62:38) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.30-7.18 (m, 2H), 7.06–6.98 (m, 2H), 4.59 (t, $J$ = 8.0 Hz, 1H), 4.36–4.23 (m, 2H), 1.70–1.67 (m, 1H). **$^{13}$C NMR (100 MHz,**

**$CDCl_3$, major isomer):** $\delta$ 162.3 (d, $J$ = 246.8 Hz), 145.5 (dm, $J$ = 248.6 Hz), 140.5 (dm, $J$ = 253.6 Hz), 137.8 (dm, $J$ = 253.2 Hz), 134.2 (d, $J$ = 3.4 Hz), 129.7 (d, $J$ = 8.1 Hz), 116.0 (d, $J$ = 21.5 Hz), 115.3 (m), 63.8 (t, $J$ = 3.9 Hz), 43.8 (d, $J$ = 1.3 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -114.5 (m), -141.8 (m), -155.7 (t, $J$ = 20.9 Hz), -161.6 (dd, $J$ = 21.0, 14.6 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{14}H_8F_6ONa$ $[M+Na]^+$ 329.0372, found 329.0365.

***2-(4-Bromophenyl)-2-(perfluorophenyl)ethan-1-ol 70***

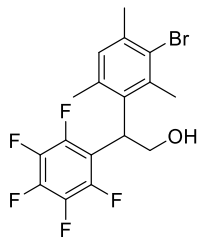



***p*/*o* 80:20**
Chemical Formula: $C_{14}H_8BrF_5O$
Exact Mass: 365.9679

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and bromobenzene (0.21 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **70** (101.0 mg, 69% yield, *p*/*o* 80:20) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.46 (d, $J$ = 8.5 Hz, 1H), 7.18 (d, $J$ = 8.5 Hz, 1H), 4.55 (t, $J$ = 7.9 Hz, 1H), 4.33□4.23 (m, 2H), 1.82 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 145.5 (dm, $J$ = 246.7 Hz), 140.4 (dm, $J$ = 253.7 Hz), 137.9 (dm, $J$ = 252.5 Hz), 137.3, 132.2, 129.7 (t, $J$ = 1.7 Hz), 121.7, 114.8 (m) 63.5 (t, $J$ = 3.9 Hz), 43.8. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.6 (m), -155.5 (m), -161.4 (m).

***2-(3-Bromo-2,4,6-trimethylphenyl)-2-(perfluorophenyl)ethan-1-ol 71***

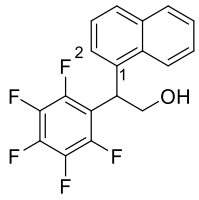



Chemical Formula: $C_{17}H_{14}BrF_5O$
Exact Mass: 408.0148

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2-bromomesitylene (0.31 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **71** (124.4 mg, 76% yield) as a white solid.

**m.p.:** 117-121 °C. **$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.94 (s, 1H), 4.95 (t, $J$ = 8.0 Hz, 1H), 4.47 (t, $J$ = 10.0 Hz, 1H), 4.07 (dd, $J$ = 11.3, 7.5 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.96 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.7 (dm, $J$ = 246.8 Hz), 139.9 (dm, $J$ = 253.4 Hz), 137.9, 137.6 (dm, $J$ = 252.7 Hz), 136.5, 136.1, 134.2, 131.4, 127.5, 114.7 (m), 62.4 (t, $J$ = 4.9 Hz), 43.1, 24.2, 20.6, 20.5. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -139.8 (m), -156.3, -162.1 (dd, $J$ = 21.4, 15.1 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{14}F_5BrONa$ $[M+Na]^+$ 431.0040, found 431.0033.

***2-(Naphthalen-2-yl)-2-(perfluorophenyl)ethan-1-ol 72***

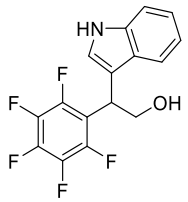



***1*/*2* 76:24**
Chemical Formula: $C_{18}H_{11}F_5O$
Exact Mass: 338.0730

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and naphthalene (256 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **72** (119.0 mg, 88% yield, *1*/*2* 77:23) as a white solid.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.84–7.80 (m, 3H), 7.77 (s, 1H), 7.59–7.47 (m, 2H), 7.41 (d, $J$ = 7.5 Hz, 1H), 4.77 (t, $J$ = 7.9 Hz, 1H), 4.48–4.34 (m, 2H), 2.03–1.87 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 145.5 (dm, $J$ = 245.7 Hz), 140.1 (dm, $J$ = 253.2 Hz), 137.8 (dm, $J$ = 252.8 Hz), 135.6, 133.4, 132.7, 128.9, 127.8, 127.7, 126.7 (t, $J$ = 1.4 Hz), 126.5, 126.3, 125.8 (t, $J$ = 1.3 Hz), 115.2 (m), 63.6 (t, $J$ = 4.0 Hz), 44.5. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.5 (m), -155.9 (t, $J$ = 20.9 Hz), -161.7 (m). **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{11}F_5ONa$ $[M+Na]^+$ 361.0622, found 361.0615.

***2-(1H-Indol-3-yl)-2-(perfluorophenyl)ethan-1-ol 73***

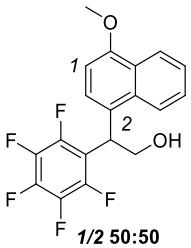



Chemical Formula: $C_{16}H_{10}F_5NO$
Exact Mass: 327.0683

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and indole (234 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **73** (108.1 mg, 83% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.16 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.39–7.35 (m, 1H), 7.26–7.17 (m, 2H), 7.10 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 4.94 (dd, *J* = 8.7, 7.2 Hz, 1H), 4.42– 4.31 (m, 2H), 1.79 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.5 (dm, *J* = 247.9 Hz), 140.0 (dm, *J* = 252.6 Hz), 137.7 (dm, *J* = 252.2 Hz), 135.9, 126.7, 122.7, 121.8 (*t*, J = 3.2 Hz), 120.1, 118.3, 115.6 (m), 112.5, 111.4, 63.6 (t, *J* = 3.4 Hz), 35.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -142.2 (m), -156.7 (t, *J* = 20.9 Hz), -162.1 (m). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{10}F_5NONa$ $[M+Na]^+$ 350.0575, found 350.0569.

***2-(4-methoxynaphthalen-1-yl)-2-(perfluorophenyl)ethan-1-ol 74***

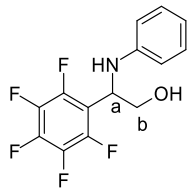



***1/2* 50:50**
Chemical Formula: $C_{19}H_{13}F_5O_2$
Exact Mass: 368.0836

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1-Methoxynaphthalene (31.6 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **74** (67.7 mg, 46% yield, *1/2* 50:50) as a white solid.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 8.37 (ddd, J = 8.4, 1.5, 0.7 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.60 (ddd, J = 8.5, 6.8, 1.5 Hz, 1H), 7.53 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 2H), 4.80 (t, J = 7.8 Hz, 1H), 4.47 – 4.42 (m, 2H), 4.03 (s, 3H), 1.96 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 155.24, 148.91 – 145.40 (m), 144.66 (dd, J = 26.0, 10.6 Hz), 139.82 – 137.83 (m), 133.66, 132.61, 128.43, 127.32, 126.35 (t, J = 1.4 Hz), 125.19, 122.98, 119.92 (m), 104.37, 63.89, 55.53, 39.27. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer)**: $\delta$ -140.47 – -142.30 (m), -156.21 (d, J = 57.5 Hz), -160.52 – -164.68 (m).

***2-(perfluorophenyl)-2-(phenylamino)ethan-1-ol 76***

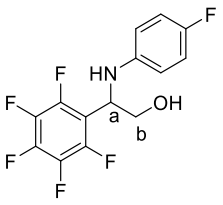



***a/b* 60:40**
Chemical Formula: $C_{14}H_{10}F_5NO$
Exact Mass: 303.0683

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and aniline (186 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 2:1) afforded **76** (82.4 mg, 68% yield, *a/b* 60:40) as a yellow oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer)** $\delta$ 7.15 – 7.03 (m, 2H), 6.76 – 6.66 (m, 1H), 6.65 – 6.57 (m, 2H), 5.07 – 4.92 (m, 1H), 4.17 (s, 1H), 3.95 (dd, J = 10.9, 7.6 Hz, 1H), 3.84 (dt, J = 10.6, 5.2 Hz, 1H), 2.18 – 2.08 (m, 1H).

***2-((4-fluorophenyl)amino)-2-(perfluorophenyl)ethan-1-ol 77***

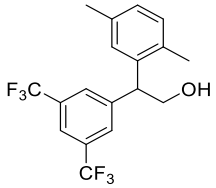



***a/b* 60:40**
Chemical Formula: $C_{14}H_9F_6NO$
Exact Mass: 321.0588

General Procedure **C** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 4-fuloroaniline (222 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 2:1) afforded **77** (96.3 mg, 75% yield, *a/b* 60:40) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer)** $\delta$ 6.87 – 6.74 (m, 1H), 6.63 – 6.47 (m, 1H), 4.91 (t, J = 6.5 Hz, 1H), 4.28 – 4.03 (m, 1H), 3.95 (dd, J = 10.9, 7.5 Hz, 1H), 3.87 – 3.78 (m, 1H), 2.14 (d, J = 5.9 Hz, 1H).

***2-(3,5-Bis(trifluoromethyl)phenyl)-2-(2,5-dimethylphenyl)ethan-1-ol 78***

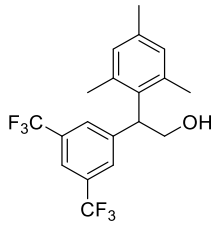



Chemical Formula: $C_{18}H_{16}F_6O$
Exact Mass: 362.1105

General Procedure **D** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (102.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **78** (130.8 mg, 90% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.76 (s, 1H), 7.69 (s, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.05–6.98 (m, 2H), 4.50 (t, *J* = 7.0 Hz, 1H), 4.24–4.12 (m, 2H), 2.35 (s, 3H), 2.24 (s, 3H), 1.76 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 144.4, 137.3, 136.2, 133.7, 131.7 (q, *J* = 33.2 Hz), 131.2, 128.2, 128.7 (m), 127.4, 123.4 (q, *J* = 272.7 Hz), 120.7 (p, *J* = 3.9 Hz), 65.4, 49.0, 21.2, 19.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.8. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{16}F_6ONa$ $[M+Na]^+$ 385.0998, found 385.0989.

***2-(3,5-Bis(trifluoromethyl)phenyl)-2-mesitylethan-1-ol 79***

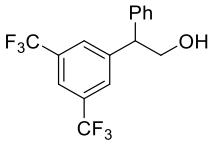



Chemical Formula: $C_{19}H_{18}F_6O$
Exact Mass: 376.1262

General Procedure **D** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (102.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **79** (134.2 mg, 92% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.72 (s, 1H), 7.66 (s, 2H), 6.88 (s, 2H), 4.79 (t, $J$ = 7.0 Hz, 1H), 4.52 (dt, $J$ = 10.7, 7.3 Hz, 1H), 4.18 (ddd, $J$ = 10.5, 6.1, 2.9 Hz, 1H), 2.28 (s, 3H), 2.12 (brs, 6H), 1.63 (dd, $J$ = 7.1, 3.4 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.2, 137.2, 133.2, 131.5 (q, $J$ = 33.0 Hz), 130.6, 127.6 (dt, $J$ = 4.6, 3.1 Hz), 123.4 (q, $J$ = 272.7 Hz), 120.0 (p, $J$ = 3.9 Hz), 63.8, 46.9, 21.5, 20.8, one C hidden. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.7. **HRMS (ESI):** *m/z* calcd. for $C_{19}H_{18}F_6ONa$ $[M+Na]^+$ 399.1154, found 399.1148.

***2-(3,5-Bis(trifluoromethyl)phenyl)-2-phenylethan-1-ol 80***



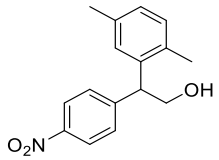

Chemical Formula: $C_{16}H_{12}F_6O$
Exact Mass: 334.0792

General Procedure **D** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (102.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **80** (96.4 mg, 72% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.77 (s, 1H), 7.75 (s, 2H), 7.40 –7.27 (m, 3H), 7.26–7.20 (m, 2H), 4.33 (t, $J$ = 6.9 Hz, 1H), 4.26–4.16 (m, 2H), 1.70 (s, 1H). **$^{13}$C NMR (100 MHz,**

**$CDCl_3$):** $\delta$ 144.4, 139.6, 131.8 (q, $J$ = 33.1 Hz), 129.2, 128.6 (m), 128.3, 127.6, 123.3 (q, $J$ = 272.7 Hz), 120.91 (p, $J$ = 3.8 Hz), 65.6, 53.1. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.8. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{12}F_6ONa$ $[M+Na]^+$ 357.0690, found 357.0677.

***2-(2,5-Dimethylphenyl)-2-(4-nitrophenyl)ethan-1-ol 81***

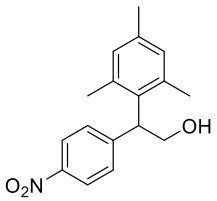



Chemical Formula: $C_{16}H_{17}NO_3$
Exact Mass: 271.1208

General Procedure **D** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **81** (78.2 mg, 72% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.14 (d, $J$ = 8.8 Hz, 2H), 7.39 (d, $J$ = 8.8 Hz, 2H), 7.09 (d, $J$ = 7.5 Hz, 1H), 7.04–6.99 (m, 2H), 4.47 (t, $J$ = 7.0 Hz, 1H), 4.22–4.13 (m, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 1.76 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 149.5, 146.7, 137.7, 136.0, 133.8, 131.1, 129.4, 128.0, 127.4, 123.7, 65.5, 49.3, 21.3, 19.3. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{17}NO_3Na$ $[M+Na]^+$ 294.1101, found 294.1095.

***2-Mesityl-2-(4-nitrophenyl)ethan-1-ol 82***

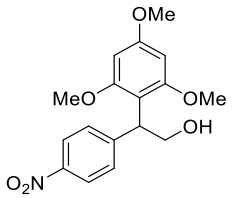



Chemical Formula: $C_{17}H_{19}NO_3$
Exact Mass: 285.1365

General Procedure **D** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **82** (105.5 mg, 93% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.12 (d, $J$ = 8.1 Hz, 2H), 7.37 (dd, $J$ = 0.9, 1.1 Hz, 2H), 6.87 (s, 2H), 4.71 (t, $J$ = 7.0 Hz, 1H), 4.56–4.49 (m, 1H), 4.10 (dd, $J$ = 10.7, 6.5 Hz, 1H), 2.27 (s, 3H), 2.13 (brs, 6H), 1.72 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 150., 146.1, 137.4, 137.1, 133.9, 130.5, 128.2, 123.5, 63.6, 47.3, 21.4, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$ 308.1257, found 308.1252.

***2-(4-Nitrophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-ol 83***

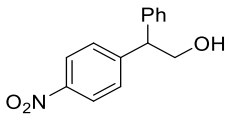



Chemical Formula: $C_{17}H_{19}NO_6$
Exact Mass: 333,1212

General Procedure **D** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 6:1) afforded **83** (111.3 mg, 84% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.07 (d, $J$ = 8.8 Hz, 2H), 7.46–7.42 (m, 2H), 6.14 (s, 2H), 4.86 (t, $J$ = 6.9 Hz, 1H), 4.35 (dd, $J$ = 10.7, 7.2 Hz, 1H), 4.23 (dd, $J$ = 10.7, 6.7 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 6H), 1.96 (s, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ(ppm) **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$: 160.6, 159.2, 151.1, 146.0, 128.8, 123.1, 109.4, 91.2, 64.1, 55.7, 55.3, 43.0. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{19}NO_6Na$ $[M+Na]^+$ 356.1105, found 356.1061.

***2-(4-Nitrophenyl)-2-phenylethan-1-ol 84***



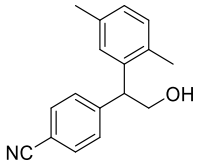

Chemical Formula: $C_{14}H_{13}NO_3$
Exact Mass: 243.0895

General Procedure **D** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and benzene (0.36 mL, 4.0 mmol, 10.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification

by FC over silica gel (*n*-pentane/EtOAc: 8:1) afforded **84** (72.2 mg, 74% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.11 (d, $J$ = 8.8 Hz, 2H), 7.39 (d, $J$ = 8.8 Hz, 2H), 7.41–7.28 (m, 2H), 7.25–7.14 (m, 3H), 4.26 (t, $J$ = 7.0 Hz, 1H), 4.19–4.13 (m, 2H), 1.63–1.58 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 149.4, 146.8, 140.0, 129.3, 129.1, 128.3, 127.5, 123.8, 65.6, 53.3. **HRMS (ESI):** *m/z* calcd. for $C_{14}H_{13}NO_3Na$ $[M+Na]^+$ 266.0788, found 266.0783.

***4-(1-(2,5-Dimethylphenyl)-2-hydroxyethyl)benzonitrile 85***

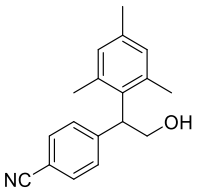



Chemical Formula: $C_{17}H_{17}NO$
Exact Mass: 251,1310

General Procedure **D** was followed with 4-(oxiran-2-yl)benzonitrile (58.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc: 5/1) afforded **85** (68.6 mg, 68% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.57 (d, $J$ = 8.4 Hz, 2H), 7.57 (d, $J$ = 8.3 Hz, 2H), 7.08 (d, $J$ = 7.6 Hz, 1H), 7.03–6.97 (m, 2H), 4.41 (t, $J$ = 7.1 Hz, 1H), 4.20–4.07 (m, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 1.80 (t, J = 5.8 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 147.3, 137.8, 135.9, 133.8, 132.3, 131.1, 129.4, 128.0, 127.4, 118.9, 110.4, 65.5, 49.5, 21.3, 19.4. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{17}NONa$ $[M+Na]^+$ 274.1202, found 274.1195.

***4-(2-Hydroxy-1-mesitylethyl)benzonitrile 86***

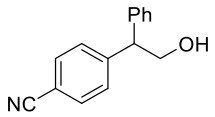



Chemical Formula: $C_{18}H_{19}NO$
Exact Mass: 265,1467

General Procedure **D** was followed with 4-(oxiran-2-yl)benzonitrile (58.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **86** (83.2 mg, 79% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.55 (d, $J$ = 8.4 Hz, 2H), 7.31 (dd, $J$ = 8.5, 1.1 Hz, 2H), 6.86 (s, 2H), 4.77–4.74 (m, 1H), 4.52–4.47 (m, 1H), 4.16–4.13 (m, 1H), 2.27 (s, 3H), 2.12 (brs, 6H), 1.88–1.84 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 148.3, 137.4, 137.0, 134.0, 132.2, 130.4, 128.2, 119.1, 109.6, 63.5, 47.3, 21.4, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{19}NONa$ $[M+Na]^+$ 288.1359, found 288.1352.

***4-(2-Hydroxy-1-phenylethyl)benzonitrile 87***

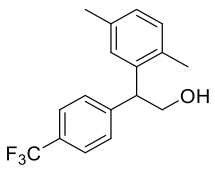



Chemical Formula: $C_{15}H_{13}NO$
Exact Mass: 223.0997

General Procedure **D** was followed with 4-(oxiran-2-yl)benzonitrile (58.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **87** (40.7 mg, 46% yield) as a white solid.

**m.p.:** 85-89 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.51 (d, $J$ = 8.4 Hz, 2H), 7.30 (d, $J$ = 8.3 Hz, 2H), 7.27–7.22 (m, 2H), 7.20–7.15 (m, 1H), 7.14–7.10 (m, 2H), 4.17 (t, $J$ = 7.0 Hz, 1H), 4.11–4.06 (m, 2H), 1.58–1.53 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 147.3, 140.1, 132.4, 129.2, 129.0, 128.3, 127.4, 118.9, 110.6, 65.6, 53.5. **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{13}NONa$ $[M+Na]^+$ 246.0889, found 246.0885.

***2-(2,5-Dimethylphenyl)-2-(4-(trifluoromethyl)phenyl)ethan-1-ol 88***

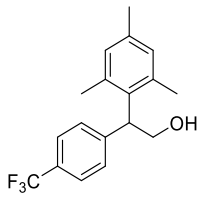



Chemical Formula: $C_{17}H_{17}F_3O$
Exact Mass: 294,1231

General Procedure **D** was followed with 2-(4-(trifluoromethyl)phenyl)oxirane (75.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **88** (60.5 mg, 52% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.55 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.10 –7.07 (m, 2H), 7.01 (dd, *J* = 7.7, 1.7 Hz, 1H), 4.32 (t, *J* = 7.1 Hz, 1H), 4.21–4.12 (m, 2H), 2.35 (s, 3H), 2.21 (s, 3H), 1.68–1.63 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.6 (q, *J* = 1.3 Hz), 138.1, 135.9, 133.9, 131.0, 128.9 (q, *J* = 32.4 Hz), 128.9, 127.8, 127.3, 125.5 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.9 Hz), 65.7, 49.3, 21.3, 19.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.4. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{17}F_3ONa$ $[M+Na]^+$ 317.1124, found 317.1118.

***2-Mesityl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol 89***

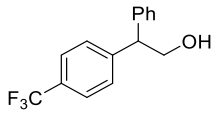



Chemical Formula: $C_{18}H_{19}F_3O$
Exact Mass: 308,1388

General Procedure **D** was followed with 2-(4-(trifluoromethyl)phenyl)oxirane (75.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **89** (84.1 mg, 68% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.52 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.87 (s, 2H), 4.82–4.76 (m, 1H), 4.52 (dt, *J* = 10.7, 7.3 Hz, 1H), 4.20 (ddd, *J* = 10.1, 7.0, 2.4 Hz, 1H), 2.28 (s, 3H), 2.15 (brs, 6H), 1.60–1.47 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 146.3 (q, *J* = 1.3 Hz), 137.6, 136.8, 134.2, 130.4, 128.2 (q, *J* = 32.4 Hz), 127.6, 125.3 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 63.7, 47.0, 21.5, 20.8. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.4. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{19}F_3ONa$ $[M+Na]^+$ 331.1280, found 331.1274.

***2-Phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-ol 90***

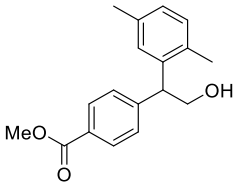



Chemical Formula: $C_{15}H_{13}F_3O$
Exact Mass: 266.0918

General Procedure **D** was followed with 2-(4-(trifluoromethyl)phenyl)oxirane (75.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **90** (59.2 mg, 56% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.60 (d, $J$ = 8.1 Hz, 2H), 7.41 (d, $J$ = 8.1 Hz, 2H), 7.37–7.33 (m, 1H), 7.32–7.24 (m, 4H), 4.29 (t, $J$ = 7.1 Hz, 1H), 4.23–4.18 (m, 2H), 1.61 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.7 (q, $J$ = 1.4 Hz), 140.5, 129.0 (q, $J$ = 32.5 Hz), 128.9, 128.7, 128.3, 127.2, 125.6 (q, $J$ = 3.8 Hz), 124.2 (q, $J$ = 272.0 Hz), 65.8, 53.4. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.5. **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{13}F_3ONa$ $[M+Na]^+$ 289.0811, found 289.0806.

***Methyl 4-(1-(2,5-dimethylphenyl)-2-hydroxyethyl)benzoate 91***



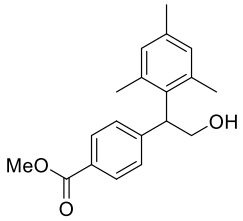

Chemical Formula: $C_{18}H_{20}O_3$
Exact Mass: 284,1412

General Procedure **D** was followed with methyl 4-(oxiran-2-yl)benzoate (71.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **91** (90.3 mg, 79% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.96 (d, $J$ = 8.3 Hz, 2H), 7.29 (d, $J$ = 8.3 Hz, 2H), 7.08–7.05 (m, 2H), 6.99 (dd, $J$ = 7.7, 1.8 Hz, 1H), 4.34 (t, $J$ = 7.1 Hz, 1H), 4.21–4.11 (m, 2H), 3.89 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H), 1.65 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$

167.0, 146.8, 138.3, 135.8, 133.9, 131.0, 129.9, 128.6 (2C), 127.7, 127.4, 65.7, 52.1, 49.5, 21.3, 19.3. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{20}ONa$ $[M+Na]^+$ 307.1305, found 307.1298.

***Methyl 4-(2-hydroxy-1-mesitylethyl)benzoate 92***

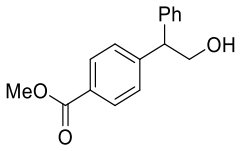



Chemical Formula: $C_{19}H_{22}O_3$
Exact Mass: 298,1569

General Procedure **D** was followed with methyl 4-(oxiran-2-yl)benzoate (71.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **92** (87.8 mg, 74% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.96–7.91 (m, 2H), 7.28–7.21 (m, 3H), 6.86 (s, 2H), 4.80 (t, *J* = 7.2 Hz, 1H), 4.54 (d, *J* = 10.0 Hz, 1H), 4.2 (dd, *J* = 10.7, 7.3 Hz, 1H), 3.90 (s, 3H), 2.27 (s, 3H), 2.14 (s, 6H), 1.45 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 167.1, 147.7, 137.6, 136.7, 134.3, 130.4 (2C), 127.8, 127.3, 63.7, 52.0, 47.1, 21.4, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{19}H_{22}ONa$ $[M+Na]^+$ 321.1461, found 321.1455.

***Methyl 4-(2-hydroxy-1-phenylethyl)benzoate 93***

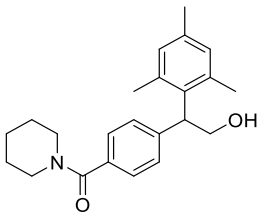



Chemical Formula: $C_{16}H_{16}O_3$
Exact Mass: 256.1099

General Procedure **D** was followed with methyl 4-(oxiran-2-yl)benzoate (71.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **93** (48.2 mg, 47% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.01–7.96 (m, 2H), 7.37–7.30 (m, 4H), 7.28–7.22 (m, 3H), 4.30–4.24 (m, 1H), 4.22–4.18 (m, 2H), 3.90 (s, 3H), 1.59 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 166.9, 146.9, 140.6, 130.0, 128.9, 128.7, 128.4, 128.3, 127.1, 65.9, 53.6, 52.1. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{16}ONa$ $[M+Na]^+$ 279.0992, found 279.0986.

***(4-(2-Hydroxy-1-mesitylethyl)phenyl)(piperidin-1-yl)methanone 94***

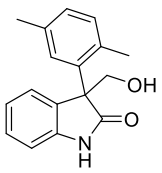



Chemical Formula: $C_{23}H_{29}NO_2$
Exact Mass: 351,2198

General Procedure **D** was followed with (4-(oxiran-2-yl)phenyl)(piperidin-1-yl)methanone (23.2 mg, 0.20 mmol) and mesitylene (0.14 mL, 0.50 mmol, 5.0 eq) in the presence of TfOH (0.9 µL, 0.020 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 40 °C for 1 h. Purification by FC over silica gel (*n*-pentane/EtOAc 100:0 to 40:60, gradient) afforded **94** (45.6 mg, 65% yield) as a colorless oil (contaminated by an impurity <5%).

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.30 (d, $J$ = 8.2 Hz, 2H), 7.19 (d, $J$ = 8.2 Hz, 2H), 6.85 (s, 2H), 4.77 (t, $J$ = 7.3 Hz, 1H), 4.51 (dd, $J$ = 10.2, 7.7 Hz, 1H), 4.18 (dd, $J$ = 10.6, 7.3 Hz, 1H), 3.69 (brs, 2H), 3.34 (brs, 2H), 2.27 (s, 3H), 2.16 (brs, 6H), 1.62–1.30 (m, 7H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 170.3, 143.5, 137.7, 136.6, 134.4, 134.0, 130.3, 127.2, 127.1, 63.8, 48.8, 47.0, 43.2, 26.6, 25.6, 24.6, 21.5, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{23}H_{30}O_2N$ $[M+H]^+$ 352.2271, found 352.2266.

***3-(2,5-Dimethylphenyl)-3-(hydroxymethyl)indolin-2-one 95***



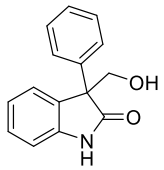

Chemical Formula: $C_{17}H_{17}NO_2$
Exact Mass: 267,1259

General Procedure **D** was followed with spiro[indoline-3,2'-oxiran]-2-one (64.5 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h.

Purification by FC over silica gel (*n*-pentane/EtOAc 1:1) afforded **95** (78.1 mg, 73% yield) as a white solid.

**m.p.:** 108-112 °C. **$^1$H NMR (400 MHz, DMSO-*d*$_6$):** $\delta$ 10.56 (s, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.19 (td, *J* = 7.6, 1.4 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.95–6.84 (m, 3H), 6.81 (dd, *J* = 7.4, 1.3 Hz, 1H), 5.08 (t, *J* = 5.1 Hz, 1H), 4.21 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.97 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.33 (s, 3H), 1.62 (s, 3H). **$^{13}$C NMR (100 MHz, DMSO-*d*$_6$):** $\delta$ 179.3, 143.5, 137.8, 135.0, 134.0, 132.9, 131.7, 129.1, 128.1, 128.0, 124.4, 121.9, 109.4, 66.5, 58.7, 21.4, 18.8. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{17}NO_2Na$ $[M+Na]^+$ 290.1152, found 290.1143.

***3-(Hydroxymethyl)-3-phenylindolin-2-one 96***

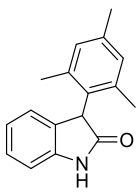


Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239,0946

General Procedure **D** was followed with spiro[indoline-3,2'-oxiran]-2-one (64.5 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 1:1) afforded **96** (49.7 mg, 52% yield) as a white solid.

**m.p.:** 145-148 °C. **$^1$H NMR (400 MHz, , DMSO-*d*$_6$):** $\delta$ 10.43 (s, 1H), 7.32–7.29 (m, 5H), 7.28–7.20 (m, 2H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.03 (t, *J* = 5.0 Hz, 1H), 4.08 (qd, *J* = 10.1, 5.1 Hz, 2H). **$^{13}$C NMR (100 MHz, , DMSO-*d*$_6$):** $\delta$ 179.0, 143.2, 138.8, 132.5, 128.9, 128.3, 127.5, 127.4, 125.7, 121.8, 109.8, 66.1, 59.4. **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$ 262.0838, found 262.0831.

***3-mesitylindolin-2-one 97***

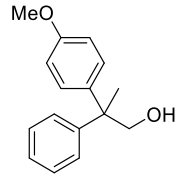


Chemical Formula: $C_{17}H_{17}NO$
Exact Mass: 251.1310

General Procedure **D** was followed with spiro[indoline-3,2'-oxiran]-2-one (64.5 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 1:1) afforded **97** (49.7 mg, 52% yield) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 9.48 (s, 1H), 7.12 (tt, *J* = 7.7, 1.3 Hz, 1H), 6.91 – 6.79 (m, 4H), 6.71 (d, *J* = 1.9 Hz, 1H), 4.98 (s, 1H), 2.45 (s, 3H), 2.19 (s, 3H), 1.67 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 179.46, 141.27, 137.86, 137.22 (d, *J* = 9.6 Hz), 130.34, 130.21, 129.40, 129.09, 127.87, 123.74, 122.55, 109.91, 48.76, 21.22, 20.85, 19.00.

***2-(4-Methoxyphenyl)-2-phenylpropan-1-ol 98***

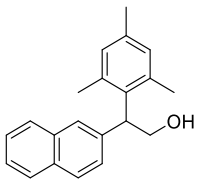



Chemical Formula: $C_{16}H_{18}O_2$
Exact Mass: 242,1307

General procedure **D** was followed with 2-methyl-2-phenyloxirane (53.7 mg, 0.40 mmol) and anisole (0.22 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 100:0 to 50:50, gradient) afforded **98** (48.4 mg, 50% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.30 (d, *J* = 6.7 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 3H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.07 (s, 2H), 3.80 (s, 3H), 1.70 (s, 3H), 1.31 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 158.1, 145.0, 138.6, 128.8, 128.5, 127.7, 126.4, 113.8, 71.1, 55.4, 48.3, 25.8.

***2-Mesityl-2-(naphthalen-2-yl)ethan-1-ol 99***

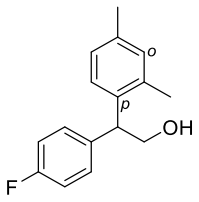



Chemical Formula: $C_{21}H_{22}O$
Exact Mass: 290,1671

General Procedure **D** was followed with 2-(naphthalen-2-yl)oxirane (68.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **99** (106.1 mg, 92% yield) as a white solid.

**m.p.:** 117-120 °C. **$^{1}$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.71–7.63 (m, 2H), 7.61 (d, $J$ = 8.6 Hz, 1H), 7.55 (d, $J$ = 1.8 Hz, 1H), 7.39–7.28 (m, 2H), 7.15–7.07 (m, 1H), 6.77 (s, 2H), 4.82 (td, $J$ = 7.4, 1.4 Hz, 1H), 4.53 (dd, $J$ = 10.7, 7.2 Hz, 1H), 4.18 (dd, $J$ = 10.7, 7.5 Hz, 1H), 2.18 (s, 3H), 2.09 (brs, 6H), 1.53 (s, 1H). **$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 139.5, 137.9, 136.5, 134.7, 133.5, 132.0, 130.4, 128.1, 127.8, 127.6, 126.5, 126.0, 125.5, 125.0, 63.9, 47.3, 21.5, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{21}H_{22}ONa$ $[M+Na]^+$ 313.1563, found 313.1556.

***2-(2,4-Dimethylphenyl)-2-(4-fluorophenyl)ethan-1-ol 100***

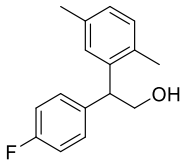



***p*/*o* 90:10**
Chemical Formula: $C_{16}H_{17}FO$
Exact Mass: 244.1263

General Procedure **D** was followed with 2-(4-fluorophenyl)oxirane (55.0 mg, 0.40 mmol) and *m*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **100** (66.6 mg, 68% yield, *p*/*o* 90:10) as a colorless oil.

**$^{1}$H NMR (400 MHz, CDCl$_3$, major isomer):** $\delta$ 7.20–7.15 (m, 3H), 7.06 (dd, $J$ = 7.8, 1.9 Hz, 1H), 7.02–6.95 (m, 3H), 4.34 (t, $J$ = 7.2 Hz, 1H), 4.20–4.04 (m, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 1.65 (s, 1H). **$^{13}$C NMR (100 MHz, CDCl$_3$, major isomer):** $\delta$ 161.6 (d, $J$ = 245.0 Hz), 137.2 (d, $J$ = 3.2 Hz), 136.9, 136.4, 136.0 (d, $J$ = 0.6 Hz), 131.9, 129.9 (d, $J$ = 7.9 Hz), 126.9, 126.4, 115.4 (d, $J$ = 21.2 Hz), 66.1 (d, $J$ = 1.0 Hz), 48.5 (d, $J$ = 0.5 Hz), 20.9, 19.6. **$^{19}$F NMR (376.5 MHz, CDCl$_3$, major isomer):** $\delta$ -116.4 (m). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{17}FONa$ $[M+Na]^+$ 267.1156, found 267.1151.

***2-(2,5-Dimethylphenyl)-2-(4-fluorophenyl)ethan-1-ol 101***

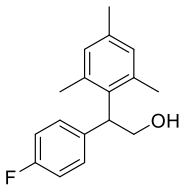



Chemical Formula: $C_{16}H_{17}FO$
Exact Mass: 244,1263

General Procedure **D** was followed with 2-(4-fluorophenyl)oxirane (55.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **101** (50.1 mg, 52% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.20–7.15 (m, 2H), 7.10–7.05 (m, 2H), 7.02–6.96 (m, 3H), 4.35 (t, *J* = 7.2 Hz, 1H), 4.18–4.06 (m, 2H), 2.35 (s, 3H), 2.20 (s, 3H), 1.59 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 161.8 (d, *J* = 245.0 Hz), 139.0 (d, *J* = 0.6 Hz), 137.2 (d, *J* = 3.2 Hz), 135.8, 134.1, 131.1, 130.1 (d, *J* = 7.9 Hz), 127.7, 127.3, 115.5 (d, *J* = 21.2 Hz), 66.2 (d, *J* = 1.0 Hz), 48.9 (d, *J* = 0.5 Hz), 21.4, 19.4. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -116.3 (m). **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{17}FONa$ $[M+Na]^+$ 267.1156, found 267.1150.

***2-(4-Fluorophenyl)-2-mesitylethan-1-ol 102***



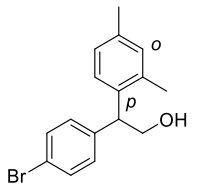

Chemical Formula: $C_{17}H_{19}FO$
Exact Mass: 258,1420

General Procedure **D** was followed with 2-(4-fluorophenyl)oxirane (55.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **102** (61.7 mg, 60% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.16–7.05 (m, 2H), 7.05–6.90 (m, 2H), 6.87 (s, 2H), 4.73 (dt, *J* = 7.6, 4.4 Hz, 1H), 4.47 (dd, *J* = 10.6, 7.4 Hz, 1H), 4.17 (dd, *J* = 10.7, 7.3 Hz, 1H), 2.28 (s, 3H), 2.17 (brs, 6H), 1.69 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 161.2 (d, *J* =

244.4 Hz), 137.7 (d, *J* = 3.3 Hz), 137.6, 136.5, 134.8 (d, *J* = 0.5 Hz), 130.3, 128.7 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.0 Hz), 64.0, 46.5 (d, *J* = 0.5 Hz), 21.3, 20.7. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -117.3 (m). **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{19}FONa$ $[M+Na]^+$ 281.1312, found 281.1308.

***2-(4-bromophenyl)-2-(2,4-dimethylphenyl)ethan-1-ol 103***

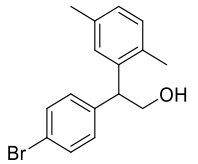


Chemical Formula: $C_{16}H_{17}BrO$
Exact Mass: 304.0463

General Procedure **D** was followed with 2-(4-Bromophenyl)oxirane (79.6 mg, 0.4 mmol) and *m*-xylene (246.6 µL, 2.0 mmol) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **103** (36.7 mg, 35% yield, *o/p* 10:90) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** δ 7.31 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 7.8 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.96 (t, J = 1.5 Hz, 1H), 6.92 (s, 1H), 4.21 (t, J = 7.2 Hz, 1H), 3.99 (ddd, J = 14.1, 7.3, 3.2 Hz, 2H), 2.21 (s, 3H), 2.11 (s, 3H), 1.54 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** δ 140.54, 136.94, 136.54, 135.63, 131.95, 131.67, 130.25, 127.16, 126.97, 120.49, 65.84, 48.70, 20.96, 19.70. **HRMS** (ESI): *m/z* for $C_{16}H_{17}BrONa$ ($[M+Na]^+$): calculated 327.0355; found 327.0350.

***2-(4-bromophenyl)-2-(2,5-dimethylphenyl)ethan-1-ol 104***



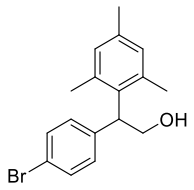
Chemical Formula: $C_{16}H_{17}BrO$
Exact Mass: 304.0463

General Procedure **D** was followed with 2-(4-Bromophenyl)oxirane (79.6 mg, 0.4 mmol) and *p*-xylene (246.6 µL, 2.0 mmol) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by

FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **104** (47.3 mg, 43% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.37 – 7.24 (m, 2H), 7.02 – 6.92 (m, 4H), 6.89 (dd, J = 7.7, 1.8 Hz, 1H), 4.22 (t, J = 7.1 Hz, 1H), 4.00 (ddd, J = 17.3, 9.2, 4.6 Hz, 1H), 2.25 (s, 3H), 2.10 (s, 3H), 1.60 – 1.56 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 140.41, 138.48, 135.74, 133.93, 131.67, 130.97, 130.30, 127.67, 127.20, 120.51, 65.79, 21.31, 19.34. **HRMS** (ESI): *m/z* for $C_{16}H_{17}BrONa$ ($[M+Na]^+$): calculated 327.0355; found 327.0349.

***2-(4-bromophenyl)-2-mesitylethan-1-ol 105***

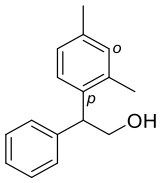



Chemical Formula: $C_{17}H_{19}BrO$
Exact Mass: 318.0619

General Procedure **D** was followed with 2-(4-Bromophenyl)oxirane (79.6 mg, 0.4 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **105** (50.3 mg, 44% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.36 – 7.23 (m, 2H), 7.01 – 6.88 (m, 2H), 6.76 (s, 2H), 4.59 (t, J = 7.3 Hz, 1H), 4.34 (d, J = 5.8 Hz, 1H), 4.05 (dd, J = 10.7, 7.2 Hz, 1H), 2.17 (s, 3H), 2.05 (s, 6H), 1.55 (d, J = 9.3 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 141.10, 137.60, 136.62, 134.40, 131.42, 130.30 (d, J = 10.4 Hz), 129.06, 119.69, 63.77, 46.59, 21.44, 20.79. **HRMS** (ESI): *m/z* for $C_{17}H_{19}BrONa$ ($[M+Na]^+$): calculated 341.0511; found 341.0505.

***2-(2,4-Dimethylphenyl)-2-phenylethan-1-ol 106***

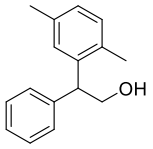



***p/o* 90:10**
Chemical Formula: $C_{16}H_{18}O$
Exact Mass: 226,1358

General Procedure **D** was followed with styrene oxide (48.0 mg, 0.40 mmol) and *m*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **106** (61.5 mg, 68% yield, *p*/*o* 90:10) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.33–7.27 (m, 2H), 7.24–7.20 (m, 4H), 7.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H), 4.37 (t, *J* = 7.2 Hz, 1H), 4.14 (dd, *J* = 7.3, 5.3 Hz, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 1.65 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 141.3, 137.1, 136.3, 136.2, 131.9, 128.6, 128.5, 126.9, 126.6, 126.5, 66.1, 49.3, 21.0, 19.7. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1250, found 249.1245.

***2-(2,5-dimethylphenyl)-2-phenylethan-1-ol 107***

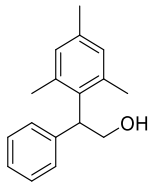



Chemical Formula: $C_{16}H_{18}O$
Exact Mass: 226.1358

General Procedure **D** was followed with styrene oxide (48.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **107** (44.1 mg, 50% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31 – 7.17 (m, 2H), 7.13 (dtd, J = 8.3, 3.4, 2.8, 1.9 Hz, 3H), 7.05 (d, J = 1.7 Hz, 1H), 7.01 – 6.91 (m, 1H), 6.93 – 6.81 (m, 1H), 4.29 (t, J = 7.2 Hz, 1H), 4.06 (t, J = 6.9 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.48 (d, J = 6.6 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$)**: $\delta$ 141.14, 138.95, 135.59, 134.06, 130.85, 128.63, 128.54, 127.43, 127.21, 126.66, 66.09, 49.54, 21.31, 19.36. **HRMS** (ESI): *m/z* for $C_{16}H_{18}ONa$ ($[M+Na]^+$): calculated 249.1250; found 249.1244.

***2-Mesityl-2-phenylethan-1-ol 108***

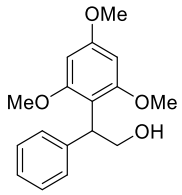



Chemical Formula: $C_{17}H_{20}O$
Exact Mass: 240,1514

General Procedure **D** was followed with styrene oxide (48.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **108** (50.8 mg, 53% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.35–7.09 (m, 5H), 6.92 (s, 2H), 4.85 (t, $J$ = 7.5 Hz, 1H), 4.56 (dt, $J$ = 10.6, 7.6 Hz, 1H), 4.26 (ddd, $J$ = 11.0, 7.7, 3.6 Hz, 1H), 2.33 (s, 3H), 2.23 (brs, 6H), 1.55 (dd, $J$ = 8.1, 3.8 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 141.8, 137.8, 136.4, 134.8, 130.3, 128.4, 127.2, 125.9, 63.8, 46.9, 21.5, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{20}ONa$ $[M+Na]^+$ 263.1406, found 263.1403.

***2-Phenyl-2-(2,4,6-trimethoxyphenyl)ethan-1-ol 109***



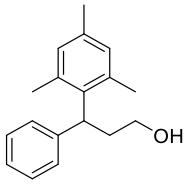

Chemical Formula: $C_{17}H_{20}O_4$
Exact Mass: 288,1362

General Procedure **D** was followed with styrene oxide (48.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **109** (103.8 mg, 90% yield) as a white solid.

**m.p.:** 107-110 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.33–7.28 (m, 2H), 7.26–7.20 (m, 2H), 7.16–7.10 (m, 1H), 6.14 (s, 2H), 4.81 (t, $J$ = 7.3 Hz, 1H), 4.28 (dd, $J$ = 7.3, 2.4 Hz, 2H), 3.79 (s, 3H), 3.72 (s, 6H), 1.89 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 160.1, 159.5,

142.6, 128.1, 128.0, 125.8, 110.7, 91.7, 64.9, 55.8, 55.3, 43.3. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1246.

***3-Mesityl-3-phenylpropan-1-ol 111***

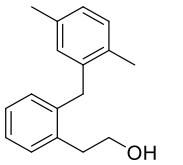



Chemical Formula: $C_{18}H_{22}O$
Exact Mass: 254,1671

General procedure **C** was followed with 2-phenyloxetane (26.8 mg, 0.20 mmol) and mesitylene (0.14 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (0.9 µL, 0.010 mmol, 5.0 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 0 °C for 90 min. Purification by FC over silica gel (*n*-pentane/EtOAc 100:0 to 60:40, gradient) afforded **111** (38.4 mg, 76% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.30-7.24 (m, 2H), 7.21-7.15 (m, 3H), 6.85 (s, 1H), 4.71 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.77-3.51 (m, 1H), 2.64 (td, *J* = 13.4, 6.9 Hz, 1H), 2.45–2.31 (m, 1H), 2.28 (s, 3H), 2.19 (brs, 6H), 1.30 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 144.2, 137.7, 137.2, 135.9, 130.2, 128.3, 127.1, 125.6, 61.8, 40.1, 34.5, 21.4, 20.9. **HRMS (ESI$^+$):** *m/z* calcd. for $C_{18}H_{22}ONa$ $[M+Na]^+$ 277.1563, found 277.1574.

***2-(2-(2,5-Dimethylbenzyl)phenyl)ethanol 113***



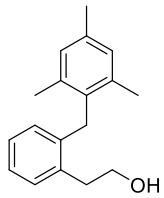

Chemical Formula: $C_{17}H_{20}O$
Exact Mass: 240,1514

General procedure **C** was followed with isochroman (53.7 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (10.6 µL, 0.12 mmol, 30 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (*n*-pentane/EtOAc 100:0 to 60:40, gradient) afforded **113** (56.7 mg, 59% yield) as a colorless oil. The diarylated product **167** (16.7 mg, 13% yield) was also isolated.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.26 (m, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.16 (td, *J* = 7.5, 1.4 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H),

6.72 (s, 1H), 3.98 (s, 2H), 3.84 (t, *J* = 6.9 Hz, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 1.47 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.8, 138.5, 136.8, 136.6, 133.4, 130.2, 130.2, 130.0, 129.9, 127.1, 126.9, 126.5, 63.1, 36.3, 36.2, 21.1, 19.3. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{20}ONa$ $[M+Na]^+$ 263.1406, found 263.1403.

***2-(2-(2,4,6-Trimethylbenzyl)phenyl)ethanol 114***

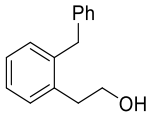



Chemical Formula: $C_{18}H_{22}O$
Exact Mass: 254,1671

General procedure **C** was followed with isochroman (26.8 mg, 0.20 mmol) and mesitylene (0.14 mL, 1.0 mmol, 5 eq) in the presence of TfOH (5.3 µL, 0.06 mmol, 30 mol%) in HFIP (0.2 mL). The reaction mixture was stirred at rt for 3 h. Purification by FC over silica gel (*n*-pentane/EtOAc 100:0 to 60:40, gradient) afforded **114** (44.8 mg, 88% yield) as a white solid. The diarylated product **168** (5.5 mg, 8% yield) was also isolated.

**m.p.:** 84-87 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.24 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.04 (td, *J* = 7.7, 1.2 Hz, 1H), 6.93 (s, 2H), 6.57 (d, *J* = 7.7 Hz, 1H), 4.00 (s, 2H), 3.97 (t, *J* = 6.9 Hz, 2H), 3.09 (t, *J* = 6.9 Hz, 2H), 2.33 (s, 3H), 2.16 (s, 6H), 1.62 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.2, 137.2, 136.4, 135.9, 133.5, 129.7, 129.0, 127.0, 127.0, 126.1, 62.9, 36.2, 31.8, 21.1, 20.1. **HRMS (ESI$^+$):** *m/z* calcd. for $C_{18}H_{22}ONa$ $[M+Na]^+$ 277.1563, found 277.1561.

***2-(2-Benzylphenyl)ethanol 115***

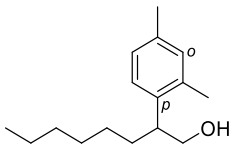



Chemical Formula: $C_{15}H_{16}O$
Exact Mass: 212.1201

General procedure **C** was followed with isochroman (26.8 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5 eq) in the presence of TfOH (5.3 µL, 0.06 mmol, 30 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at rt for 24 h. Purification by FC over silica gel (*n*-pentane/ EtOAc 100:0 to 60:40, gradient) afforded **115** (17.4 mg, 41% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.22–7.10 (m, 6H), 7.10–7.06 (m, 1H), 7.04 (d, $J$ = 7.4 Hz, 2H), 3.99 (s, 2H), 3.65 (t, $J$ = 6.9 Hz, 2H), 2.80 (t, $J$ = 6.9 Hz, 2H), 1.56 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 140.9, 139.2, 136.9, 131.0, 130.2, 128.8, 128.6, 126.9 (2C) 126.2, 63.2, 39.1, 36.1. **HRMS (ESI):** *m/z* calcd. for $C_{15}H_{16}ONa$ $[M+Na]^+$ 235.1093, found 235.1092.

***2-(2,4-Dimethylphenyl)octan-1-ol 116***

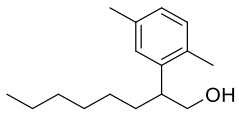



***p*/*o* 86:14**
Chemical Formula: $C_{16}H_{26}O$
Exact Mass: 234,1984

General Procedure **D** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and *m*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **116** (53.1 mg, 57% yield, *p*/*o* 86:14) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.00 (d, $J$ = 7.7 Hz, 1H), 7.04–6.99 (m, 2H), 3.75–3.66 (m, 2H), 3.15–3.06 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.74–1.65 (m, 1H), 1.60–1.50 (m, 1H), 1.30–1.19 (m, 9H), 0.88–0.84 (m, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 137.5, 137.0, 135.6, 131.3, 127.1, 125.7, 67.4, 42.6, 32.4, 31.7, 29.6, 27.3, 22.7, 20.9, 19.9, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{26}ONa$ $[M+Na]^+$ 257.1876, found 257.1870.

***2-(2,5-Dimethylphenyl)octan-1-ol 117***



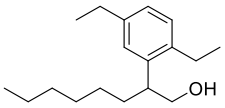

Chemical Formula: $C_{16}H_{26}O$
Exact Mass: 234,1984

General Procedure **D** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by

FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **117** (81.7 mg, 87% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.06 (d, $J$ = 7.6 Hz, 1H), 6.99 (d, $J$ = 1.9 Hz, 1H), 6.93 (dd, $J$ = 7.8, 1.9 Hz, 1H), 3.75–3.67 (m, 2H), 3.16–3.07 (m, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 1.73–1.66 (m, 1H), 1.58–1.53 (m, 1H), 1.34 (s, 1H), 1.30–1.17 (m, 8H), 0.88–0.83 (m, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ(ppm): **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 140.5, 135.7, 134.0, 130.4, 126.9, 126.5, 67.3, 42.9, 32.4, 31.7, 29.5, 27.4, 22.7, 21.2, 19.5, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{16}H_{26}ONa$ $[M+Na]^+$ 257.1876, found 257.1869.

***2-(2,5-Diethylphenyl)octan-1-ol 118***

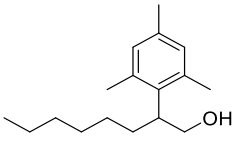



Chemical Formula: $C_{18}H_{30}O$
Exact Mass: 262,2297

General Procedure **D** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and 1,4-diethylbenzene (0.31 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **118** (74.8 mg, 71% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.01 (d, $J$ = 8.5 Hz, 1H), 7.04–7.00 (m, 2H), 3.80–3.67 (m, 2H), 3.21–3.09 (m, 1H), 2.74–2.56 (m, 4H), 1.77–1.65 (m, 1H), 1.61–1.53 (m, 1H), 1.30–1.16 (m, 15H), 0.85 (t, $J$ = 6.7 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 142.0, 140.5, 139.9, 128.9, 125.9, 125.4, 67.7, 42.3, 32.7, 31.7, 29.6, 28.6, 27.5, 25.6, 22.6, 16.0, 15.6, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{30}ONa$ $[M+Na]^+$ 285.2189, found 285.2183.

***2-Mesityloctan-1-ol 119***



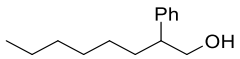

Chemical Formula: $C_{17}H_{28}O$
Exact Mass: 248,2140

General Procedure **D** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification

by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **119** (75.8 mg, 76% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.85 (s, 1H), 6.81 (s, 1H), 3.92–3.84 (m, 2H), 3.42–3.35 (m, 1H), 2.35 (s, 6H), 2.25 (s, 3H), 1.77–1.70 (m, 2H), 1.38 (d, $J$ = 3.1 Hz, 1H), 1.30–1.17 (m, 8H), 0.89–0.83 (m, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.4, 136.3, 135.6, 135.0, 131.2, 129.4, 65.6, 43.9, 31.8, 30.9, 29.7, 28.4, 22.7, 22.1, 21.4, 20.7, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{28}ONa$ $[M+Na]^+$ 271.2032, found 271.2027.

***2-Phenyloctan-1-ol 120***

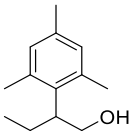



Chemical Formula: $C_{14}H_{22}O$
Exact Mass: 206.1671

General Procedure **D** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and benzene (0.18 mL, 2.0 mmol) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **120** (25.7 mg, 31% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.36–7.30 (m, 2H), 7.27–7.18 (m, 3H), 3.79–3.67 (m, 2H), 2.82–2.72 (m, 1H), 1.71–1.65 (m, 1H), 1.61–1.53 (m, 2H), 1.44–1.10 (m, 8H), 0.85 (t, $J$ = 6.9 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 142.5, 128.7, 128.1, 126.7, 67.7, 48.7, 32.1, 31.7, 29.4, 27.3, 22.6, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{14}H_{22}ONa$ $[M+Na]^+$ 229.1563, found 229.1559.

***2-Mesitylbutan-1-ol 121***



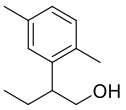

Chemical Formula: $C_{13}H_{20}O$
Exact Mass: 192,1514

General Procedure **D** was followed with 2-ethyloxirane (29.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification

by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **121** (57.3 mg, 75% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.87 (s, 1H), 6.82 (s, 1H), 3.90 (td, *J* = 9.7, 8.9, 7.5 Hz, 2H), 3.39–3.30 (m, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.15 (s, 3H), 1.85–1.74 (m, 2H), 1.58 (s, 1H), 0.88 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.6, 136.3, 135.6, 134.8, 131.2, 129.4, 65.5, 45.7, 23.7, 22.2, 21.4, 20.7, 12.9. **HRMS (ESI):** *m/z* calcd. for $C_{13}H_{20}ONa$ $[M+Na]^+$ 215.1406, found 215.1406.

***2-(2,5-dimethylphenyl)butan-1-ol 122***

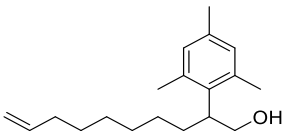



Chemical Formula: $C_{12}H_{18}O$
Exact Mass: 178.1358

General Procedure **D** was followed with 2-ethyloxirane (29.0 mg, 0.40 mmol) and mesitylene (246.6 µL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **122** (36.4 mg, 52% yield) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.97 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 1.9 Hz, 1H), 6.85 (dd, J = 7.7, 1.9 Hz, 1H), 3.64 (dd, J = 7.0, 5.0 Hz, 2H), 2.96 (ddt, J = 9.0, 7.4, 5.9 Hz, 1H), 2.22 (d, J = 3.1 Hz, 6H), 1.67 (dtd, J = 14.8, 7.4, 5.6 Hz, 1H), 1.56 – 1.40 (m, 1H), 1.38 (d, J = 2.8 Hz, 1H), 0.76 (t, J = 7.4 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ(ppm): 140.25, 135.63, 134.18, 130.37, 126.94, 126.22, 66.99, 44.62, 25.24, 21.22, 19.53, 11.95. **HRMS** (ESI): *m/z* for $C_{12}H_{18}ONa$ ($[M+Na]^+$): calculated 201.1250; found 201.1249.

***2-Mesityldec-9-en-1-ol 123***



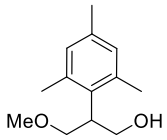

Chemical Formula: $C_{19}H_{30}O$
Exact Mass: 274.2297

General Procedure **D** was followed with 2-(oct-7-en-1-yl)oxirane (62.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol,

5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 1 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **123** (101.2 mg, 92% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.87 (s, 1H), 6.82 (s, 1H), 5.81 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.05–4.91 (m, 2H), 3.95–3.80 (m, 2H), 3.47–3.32 (m, 1H), 2.36 (s, 6H), 2.27 (s, 3H), 2.11–1.99 (m, 2H), 1.84–1.67 (m, 2H), 1.61 (s, 1H), 1.41–1.19 (m, 8H). **$^{113}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 139.2, 138.4, 136.3, 135.6, 135.0, 131.2, 129.4, 114.2, 65.6, 43.9, 33.8, 30.9, 29.9, 29.0 (2C), 28.4, 22.1, 21.4, 20.7. **HRMS (ESI):** *m/z* calcd. for $C_{19}H_{30}ONa$ $[M+Na]^+$ 297.2194, found 297.2186.

***2-Mesityl-3-methoxypropan-1-ol 124***

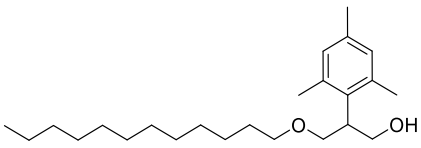



Chemical Formula: $C_{13}H_{20}O_2$
Exact Mass: 208,1463

General Procedure **D** was followed with glycidyl methyl ether (35.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 3 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **124** (45.8 mg, 55% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.83 (s, 2H), 4.25 (dd, *J* = 10.7, 8.5 Hz, 1H), 3.95 (dd, *J* = 9.6, 8.9 Hz, 1H), 3.80 (ddd, *J* = 10.7, 4.7, 1.1 Hz, 1H), 3.74–3.66 (m, 1H), 3.62 (dd, *J* = 8.9, 1.1 Hz, 1H), 3.40 (s, 3H), 2.94 (s, 1H), 2.42–2.25 (m, 6H), 2.24 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 137.6, 136.2, 132.9, 130.9, 129.5, 75.5, 65.6, 59.1, 44.8, 21.7 (2C), 20.6. **HRMS (ESI):** *m/z* calcd. for $C_{13}H_{20}O_2Na$ $[M+Na]^+$ 231.1356, found 231.1350.

***3-(dodecyloxy)-2-mesitylpropan-1-ol 125***

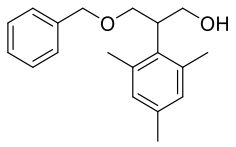



Chemical Formula: $C_{24}H_{42}O_2$
Exact Mass: 362.3185

General Procedure **D** was followed with glycidyl lauryl ether (97.0 mg, 0.4 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **125** (84.1 mg, 58% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 6.80 – 6.66 (m, 2H), 4.21 (dd, J = 10.6, 8.5 Hz, 1H), 3.90 (t, J = 9.2 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.61 (dd, J = 9.2, 4.5 Hz, 1H), 3.56 (dd, J = 8.5, 1.1 Hz, 1H), 3.39 (t, J = 6.7 Hz, 2H), 2.74 – 2.69 (m, 1H), 2.40 – 2.19 (m, 6H), 2.15 (s, 3H), 1.54 – 1.45 (m, 2H), 1.19 (s, 18H), 0.81 (t, J = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 137.57, 136.15, 135.73, 133.05, 130.86, 129.46, 73.66, 71.61, 65.91, 44.87, 31.94, 29.68, 29.67, 29.65, 29.62, 29.60, 29.47, 29.37, 26.17, 22.71, 21.83, 21.62, 20.63, 14.13. **HRMS** (ESI): *m/z* for $C_{24}H_{42}O_2Na$ ($[M+Na]^+$): calculated 385.3077; found 385.3065.

***3-(benzyloxy)-2-mesitylpropan-1-ol 126***

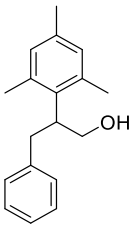



Chemical Formula: $C_{19}H_{24}O_2$
Exact Mass: 284.1776

General Procedure **D** was followed with 2-((benzyloxy)methyl)oxirane (65.6 mg, 0.4 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 4 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **126** (31.1 mg, 27% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.44 – 7.28 (m, 5H), 6.83 (dd, J = 15.2, 8.8 Hz, 2H), 4.57 (s, 2H), 4.29 (dd, J = 10.6, 8.1 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.82 (ddd, J = 10.9, 4.4, 1.2 Hz, 1H), 3.79 – 3.64 (m, 2H), 2.66 (s, 2H), 2.43 – 2.18 (m, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 137.84, 136.24, 132.91, 130.89, 129.49, 128.53, 127.85, 127.71, 73.39, 72.73, 65.64, 44.92, 21.63, 20.64. **HRMS** (ESI): *m/z* for $C_{19}H_{24}O_2Na$ ($[M+Na]^+$): calculated 307.1674; found 307.1664.

***1-Mesityl-3-phenylpropan-2-ol 127***

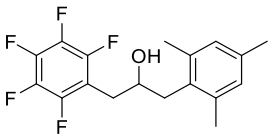



Chemical Formula: $C_{18}H_{22}O$
Exact Mass: 254,1671

General Procedure **D** was followed with 2-benzyloxirane (67.1 mg, 0.50 mmol) and mesitylene (0.35 mL, 2.5 mmol, 5.0 eq) in the presence of TfOH (0.44 µL, 5.0 µmol, 1.0 mol%) in HFIP (1.25 mL). The reaction mixture was stirred at 0 °C for 30 min. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **127** (101.6 mg, 80% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.27–7.20 (m, 2H), 7.19–7.14 (m, 1H), 7.13–7.06 (m, 2H), 6.85 (s, 1H), 6.79 (s, 1H), 4.09–3.85 (m, 2H), 3.68–3.58 (m, 1H), 3.03 (dd, *J* = 7.2, 5.6 Hz, 2H), 2.47 (s, 3H), 2.25 (s, 3H), 2.13 (s, 3H), 1.24 (brs, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 141.1, 138.4, 136.2, 136.0, 134.7, 131.4, 129.5, 129.0, 128.5, 126.1, 65.2, 46.6, 37.7, 21.9, 21.8, 20.8. **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{22}ONa$ $[M+Na]^+$ 277.1563, found 277.1557.

***2-Mesityl-3-(perfluorophenyl)propan-1-ol 128***



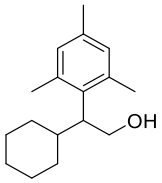

Chemical Formula: $C_{18}H_{17}F_5O$
Exact Mass: 344,1200

General Procedure **D** was followed with 2-((perfluorophenyl)methyl)oxirane (90.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **128** (67.7 mg, 49% yield) as a white solid.

**m.p.:** 107-111 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.86 (s, 2H), 4.10–4.05 (m, 1H), 3.03–2.89 (m, 3H), 2.82 (dd, *J* = 14.0, 3.8 Hz, 1H), 2.29 (s, 6H), 2.25 (s, 3H), 1.54 (d, *J* = 3.7 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.4 (dm, *J* = 245.2 Hz), 139.8 (dm, *J* = 251.9

Hz), 137.4 (dm, *J* = 250.2 Hz), 137.1, 136.1, 131.1, 129.3, 112.3 (m), 70.7, 36.8, 30.3 (q, *J* = 1.4 Hz), 20.8, 20.4. **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ(ppm): -142.6 (m), -156.9 (t, *J* = 20.8 Hz), -162.7 (m). **HRMS (ESI):** *m/z* calcd. for $C_{18}H_{17}F_5ONa$ $[M+Na]^+$ 367.1092, found 367.1085.

***2-Cyclohexyl-2-mesitylethan-1-ol 129***

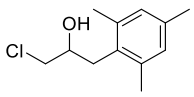



Chemical Formula: $C_{17}H_{26}O$
Exact Mass: 246.1984

General Procedure **D** was followed with 2-cyclohexyloxirane (50.5 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 3 h. Purification by FC over silica gel (*n*-pentane/EtOAc: 8/1) afforded **129** (57.8 mg, 59% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** *δ* 6.84 (s, 1H), 6.80 (s, 1H), 4.05–3.90 (m, 2H), 3.09 (td, *J* = 10.0, 5.9 Hz, 1H), 2.33 (s, 6H), 2.24 (s, 3H), 2.05–2.00 (m, 1H), 1.84–1.76 (m, 2H), 1.67□1.56 (m, 2H), 1.34–1.19 (m, 2H), 1.19–0.98 (m, 4H), 0.81–0.70 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** *δ* 139.5, 136.3, 135.6, 134.2, 131.1, 129.4, 63.9, 49.9, 38.5, 33.0, 31.8, 26.6 (2C), 26.5, 22.5, 21.4, 20.7. **HRMS (ESI):** *m/z* calcd. for $C_{17}H_{26}ONa$ $[M+Na]^+$ 269.1876, found 269.1868.

***3-Chloro-2-mesitylpropan-1-ol 130***

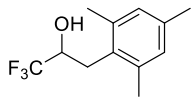



Chemical Formula: $C_{12}H_{17}ClO$
Exact Mass: 212.0968

General Procedure **D** was followed with 2-(chloromethyl)oxirane (37.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **130** (35.4 mg, 42% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.87 (s, 2H), 4.03 (p, $J$ = 2.9 Hz, 1H), 3.67–3.55 (m, 2H), 2.90 (qd, J = 14.1, 6.8 Hz, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 2.16 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 137.1, 136.1, 131.0, 129.3, 71.6, 50.0, 34.0, 20.8, 20.4. **HRMS (ESI):** *m/z* calcd. for $C_{12}H_{17}ClONa$ $[M+Na]^+$ 235.0886, found 235.0858.

***3,3,3-Trifluoro-2-mesitylpropan-1-ol 131***

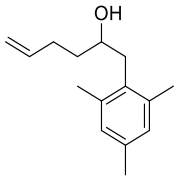



Chemical Formula: $C_{12}H_{15}F_3O$
Exact Mass: 232,1075

General Procedure **D** was followed with 2-(trifluoromethyl)oxirane (45.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane/EtOAc 5:1) afforded **131** (70.0 mg, 75% yield) as a white solid.

**m.p.:** 93-96 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.89 (s, 2H), 4.04 (dddd, $J$ = 10.1, 6.7, 4.6, 3.3 Hz, 1H), 3.08–2.95 (m, 2H), 2.33 (s, 6H), 2.27 (s, 3H), 1.94 (d, $J$ = 4.5 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 137.4, 136.6, 129.6, 129.4, 125.1 (q, $J$ = 282.0 Hz), 70.6 (q, J = 30.6 Hz), 29.0 (q, $J$ = 1.8 Hz), 20.8, 20.2. **$^{19}$F NMR** (376.5 MHz, $CDCl_3$) δ(ppm): -80.1. **HRMS (ESI):** *m/z* calcd. for $C_{12}H_{15}F_3ONa$ $[M+Na]^+$ 255.0973, found 255.0961.

***1-mesitylhex-5-en-2-ol 134***




Chemical Formula: $C_{15}H_{22}O$
Exact Mass: 218.1671

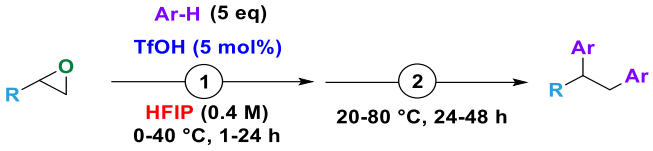
General Procedure **D** was followed with 2-(3-Buten-1-yl)oxirane (39.2 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 2 h. Purification by FC over silica gel (*n*-pentane/EtOAc 8:1) afforded **134** (15.7 mg, 18% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 6.85 (d, *J* = 15.5 Hz, 2H), 5.81 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.04 – 4.93 (m, 2H), 3.91 (qd, *J* = 10.6, 7.5 Hz, 2H), 3.44 (p, *J* = 7.5 Hz, 1H), 2.36 (d, *J* = 2.1 Hz, 6H), 2.27 (s, 3H), 2.03 (p, *J* = 6.7 Hz, 1H), 1.88 (q, *J* = 7.6 Hz, 2H).

## Dehydrodiarylation of Epoxides

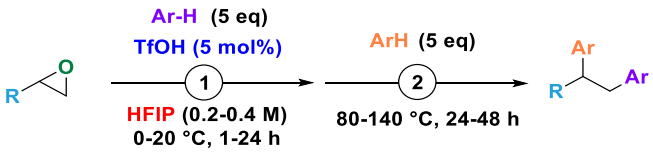
### General Procedures for the Dehydrodiarylation of Epoxides

**General procedure E** to access 1,1,2-triaryethanes using only one nucleophile




Epoxide (0.40 mmol) and nucleophile (2.0 mmol, 5.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.4 M) and TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at the indicated temperature (0-40 °C) for the indicated time (1-24 h) until completion of first step. Then, the reaction mixture was heated (if necessary) at the indicated temperature (20-80 °C) and stirred for the indicated time (24-48 h). Upon completion, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target products. Regioisomeric ratios were calculated from $^1$H NMR spectra.

**General procedure F** to access 1,1,2-triaryethanes using two different nucleophiles

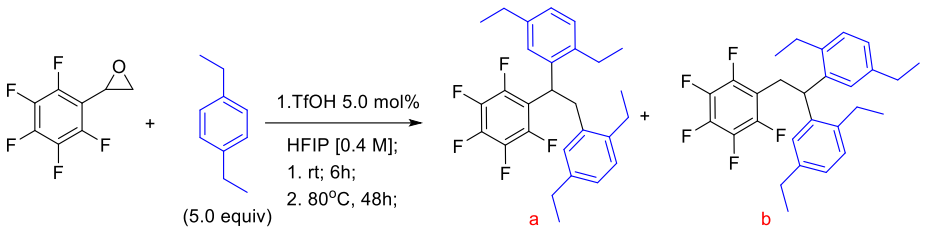



Epoxide (0.40 mmol) and nucleophile (2.0 mmol, 5.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.4 M) and then TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at the indicated temperature (0-20 °C) for the indicated time (1-24 h) until completion of first step. Then, the second nucleophile was added to the reaction mixture, which was heated at the indicated temperature (80-140 °C) and

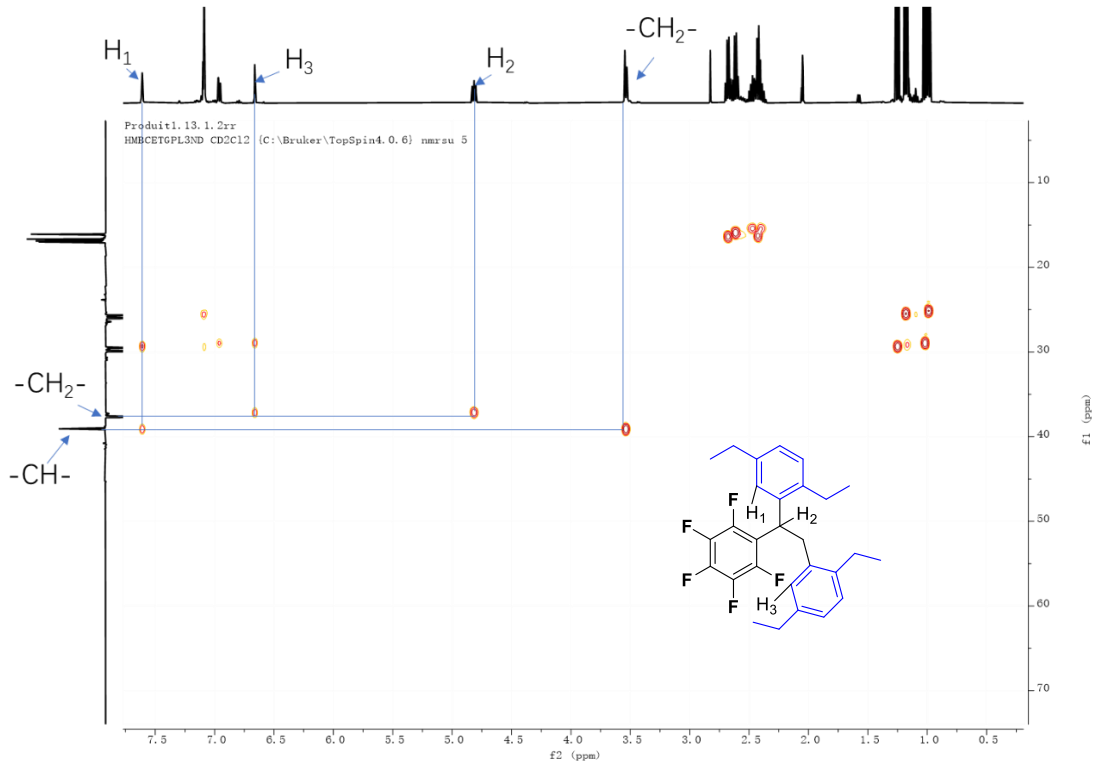
stirred for the indicated time (24-48 h). Upon completion, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target products. Regioisomeric ratios were calculated from $^1H$ NMR spectra.

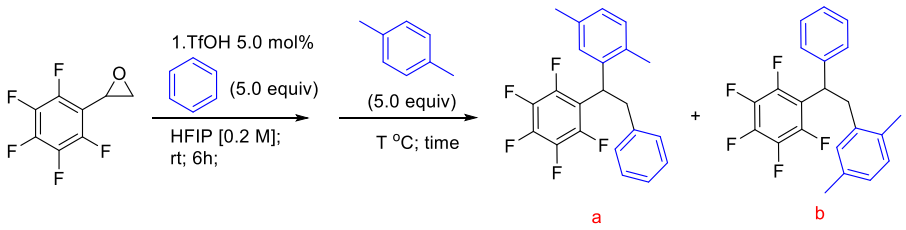
## Characterization Data of Dehydrodiarylated Products

### Structure analysis

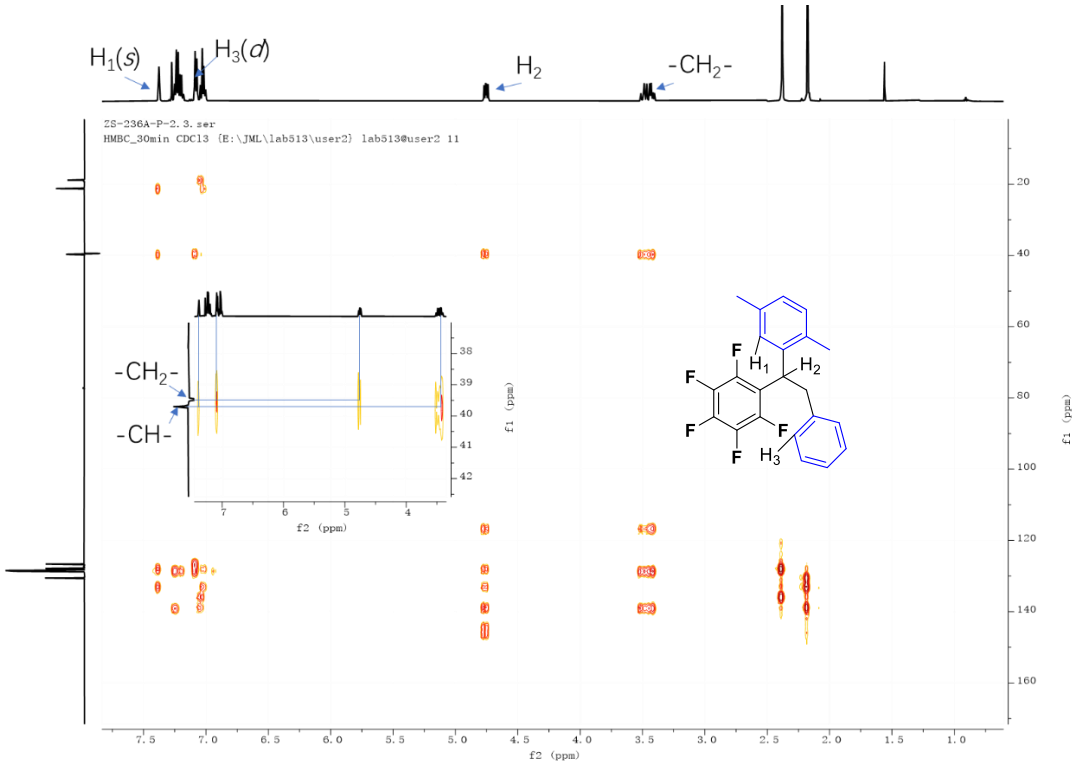



2D NMR (HMBC):



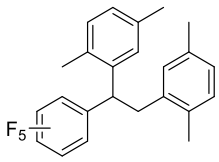



2D NMR (HMBC):




## Characterization Data

### *2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,4-dimethylbenzene) 135*

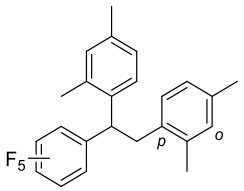


Chemical Formula: $C_{24}H_{21}F_5$
Exact Mass: 404.1563

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **135** (122.6 mg, 76% yield) as a white solid.

**m.p.:** 79-83 °C. **$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.49 (s, 1H), 7.09–7.01 (m, 3H), 6.95 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.73–6.67 (m, 1H), 4.80 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.60–3.41 (m, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 145.4 (dm, *J* = 246.2 Hz), 139.7 (dm, *J* = 252.3 Hz), 139.0, 137.5 (dm, *J* = 251.8 Hz), 136.9, 135.8, 135.2, 133.2, 133.0, 130.5, 130.3, 130.2, 128.2 (t, *J* = 3.2 Hz), 127.9, 127.4, 117.2 (m), 37.9, 36.9 (t, *J* = 2.5 Hz), 21.3, 20.9, 18.8 (t, *J* = 1.1 Hz), 18.7. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -140.8 (m), -157.0 (t, *J* = 21.0 Hz), -162.5 (td, *J* = 22.0, 7.4 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{21}F_5Na$ $[M+Na]^+$ 427.1456, found 427.1449.

***4,4'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,3-dimethylbenzene) 136***

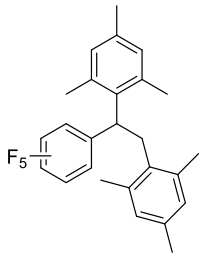



Chemical Formula: $C_{24}H_{21}F_5$
Exact Mass: 404.1563

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and *m*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **136** (102.5 mg, 64% yield, *p*/*o* 83:17) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$, major isomer):** $\delta$ 7.58 (dt, *J* = 8.1, 1.7 Hz, 1H), 7.13 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.01–6.98 (m, 2H), 6.88–6.82 (m, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.80 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.55–3.38 (m, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H); **$^{13}$C NMR (126 MHz, $CDCl_3$, major isomer):** $\delta$ 145.3 (dm, *J* = 246.5 Hz), 139.7 (dm, *J* = 252.4 Hz), 137.5 (dm, *J* = 252.0 Hz), 136.8, 136.2 (2C), 136.0, 133.9, 131.4, 131.3, 129.3, 128.4, 127.5 (t, *J* = 3.4 Hz), 127.0, 126.6, 117.3 (m), 37.5, 36.5 (t, *J* = 2.5 Hz), 20.9 (2C), 19.3 (t, *J* = 1.1 Hz), 19.2. **$^{19}$F NMR (471 MHz, $CDCl_3$, major isomer):** $\delta$ -141.0 (m), -156.9 (m), -162.3 (m). **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{21}F_5Na$ $[M+Na]^+$ 427.1456; found 427.1456.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,3,5-trimethylbenzene) 137***

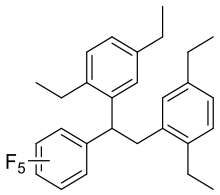



Chemical Formula: $C_{26}H_{25}F_5$
Exact Mass: 432.1876

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, at 60 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **137** (138.8 mg, 80% yield) as a white solid.

**m.p.:** 157-161 °C. **$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 6.76 (s, 2H), 6.73 (s, 2H), 4.85–4.79 (m, 1H), 3.76–3.66 (m, 1H), 3.50–3.43 (m, 1H), 2.26 (s, 3H), 2.23 (s, 3H), 1.93 (brs, 12H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 149.9 (dm, $J$ = 246.6 Hz), 139.6 (dm, $J$ = 252.4 Hz), 137.6 (dm, $J$ = 251.5 Hz), 137.3, 136.9, 136.5, 135.7, 134.5, 133.5, 130.2, 129.0, 117.8 (m), 38.6, 31.4 (t, $J$ = 4.7 Hz), 20.8, 20.7, 19.8 (t, $J$ = 1.8 Hz), 19.4. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -138.1 (m), -157.5 (t, $J$ = 21.1 Hz), -162.8 (td, $J$ = 22.1, 7.1 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{25}F_5Na$ $[M+Na]^+$ 455.1769, found 455.1764.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,4-diethylbenzene) 138***

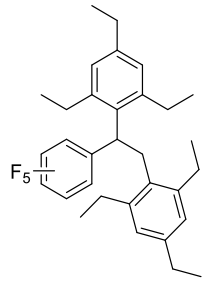



Chemical Formula: $C_{28}H_{29}F_5$
Exact Mass: 460.2189

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,4-diethylbenzene (0.31 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, at 80 $^o$C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **138** (91.4 mg, 50% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.60 (d, *J* = 2.1 Hz, 1H), 7.22–7.11 (m, 3H), 7.03 (dd, *J* = 7.8, 1.9 Hz, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 4.86 (dd, *J* = 8.9, 7.0 Hz, 1H), 3.60–3.52 (m, 2H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.62–2.41 (m, 4H), 1.36 (t, *J* = 7.6 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.4 (dm, *J* = 245.7 Hz), 142.0, 141.4, 139.7 (dm, *J* = 252.4 Hz), 139.5 (2C), 138.1, 137.5 (dm, *J* = 252.2 Hz), 136.1, 129.1, 128.6 (2C), 127.4 (t, *J* = 3.7 Hz), 126.9, 126.6, 117.6 (m), 38.0, 36.5 (d, *J* = 2.2 Hz), 28.8, 28.4, 24.8, 24.6, 15.9, 15.8, 15.5, 15.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -140.7 (m), -157.2 (t, *J* = 21.1 Hz), -162.7 (td, *J* = 22.2, 7.5 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{28}H_{29}F_5Na$ $[M+Na]^+$ 483.2082, found 483.2076.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,3,5-triethylbenzene) 140***

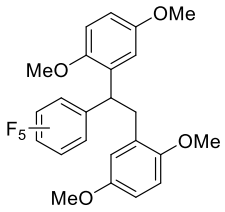



Chemical Formula: $C_{32}H_{37}F_5$
Exact Mass: 516.2815

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,3,5-triethylbenzene (0.38 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **140** (159.6 mg, 77% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.78 (s, 4H), 4.88–4.79 (m, 1H), 3.69–3.53 (m, 2H), 2.85–2.45 (m, 7H), 2.36–2.03 (m, 5H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.5 Hz, 6H), 0.76 (t, *J* = 7.4 Hz, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.9 (dm, *J* = 247.6 Hz), 142.8 (2C), 142.6, 139.5 (dm, *J* = 252.2 Hz), 137.7 (dm, *J* = 250.1 Hz), 133.5, 132.2, 125.5 (2C), 119.0 (m), 38.8, 30.9 (t, *J* = 4.6 Hz), 28.7, 28.5, 25.3, 24.6, 15.9, 15.4, 15.1, two C hidden. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -137.7 (dd, *J* = 21.7, 6.7 Hz), -157.7 (t, *J* = 21.1 Hz), -162.9 (td, *J* = 21.7, 6.4 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{32}H_{37}F_5Na$ $[M+Na]^+$ 539.2708, found 539.2701.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,4-dimethoxybenzene) 141***

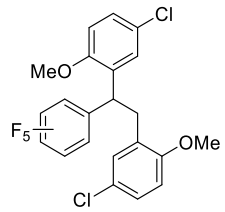



Chemical Formula: $C_{24}H_{21}F_5O_4$
Exact Mass: 468.1360

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,4-dimethoxybenzene (276 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **141** (92.6 mg, 50% yield) as a white solid.

**m.p.:** 91-95 °C. **$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.19 (d, $J$ = 2.8 Hz, 1H), 6.80–6.64 (m, 4H), 6.58 (d, $J$ = 3.0 Hz, 1H), 5.06 (dd, $J$ = 10.8, 5.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.51–3.33 (m, 2H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 153.5, 153.2, 151.9, 151.5, 145.5 (dm, $J$ = 247.1 Hz), 139.3 (dm, $J$ = 250.8 Hz), 137.1 (dm, $J$ = 249.9 Hz), 130.5, 128.4, 117.3 (m), 116.6, 114.9 (t, $J$ = 2.6 Hz), 112.0, 111.8, 111.2, 111.1, 55.9, 55.8, 55.7, 55.6, 34.3, 32.1. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -141.6 (m), -158.3 (t, $J$ = 21.0 Hz), -164.1 (td, $J$ = 22.3, 7.8 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{21}F_5O_4Na$ $[M+Na]^+$ 491.1252, found 491.1244.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(4-chloro-1-methoxybenzene) 142***

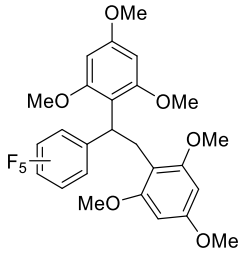



Chemical Formula: $C_{22}H_{15}Cl_2F_5O_2$
Exact Mass: 476.0369

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 4-chloroanisole (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **142** (74.6 mg, 40% yield) as a colorless oil.

**$^{1}$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.51 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.71 (dd, *J* = 9.9, 8.7 Hz, 2H), 4.96 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.44–3.30 (m, 2H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 156.1, 155.6, 145.4 (dm, *J* = 246.3 Hz), 139.6 (dm, *J* = 251.9 Hz), 137.1 (dm, *J* = 251.7 Hz), 130.5, 130.1, 128.7, 127.9 (2C), 127.7, 125.4, 125.1, 116.3 (m), 111.4 (2C), 55.6, 55.5, 34.0, 31.7. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -141.8 (m), -157.2 (t, *J* = 21.1 Hz), -163.5 (dd, *J* = 21.4, 14.5 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{15}Cl_2F_5O_2Na$ $[M+Na]^+$ 499.0262, found 499.0254.

***2,2'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(1,3,5-trimethoxybenzene) 143***

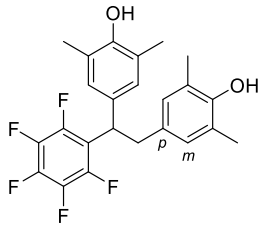



Chemical Formula: $C_{26}H_{25}F_5O_6$
Exact Mass: 528.1571

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **143** (161.6 mg, 77% yield) as a white solid.

**m.p.:** 54-58 °C. **$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 5.99 (d, *J* = 2.3 Hz, 4H), 5.00 (dd, *J* = 10.4, 5.1 Hz, 1H), 3.77–3.72 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.57 (s, 6H), 3,56 (s, 6H), 3.27–3.19 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 159.8, 159.5, 159.4, 159.3, 146.0 (dm, *J* = 247.0 Hz), 138.8 (dm, *J* = 248.9 Hz), 137.0 (dm, *J* = 247.5 Hz), 119.0 (m), 111.3, 109.7, 90.6, 90.0, 55.7, 55.4, 55.3, 55.2, 31.9, 24.5 (t, *J* = 4.5 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -140.2 (m), -160.7 (t, *J* = 21.1 Hz), -165.7 (dd, *J* = 21.3, 15.2 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{25}F_5O_6Na$ $[M+Na]^+$ 551.1464, found 551.1454.

***4,4'-(1-(Perfluorophenyl)ethane-1,2-diyl)bis(2,6-dimethylphenol) 144***

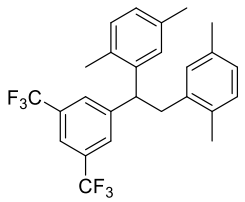



Chemical Formula: $C_{24}H_{21}F_5O_2$
Exact Mass: 436.1462

General Procedure **E** was followed with 2,3,4,5,6-pentafluorostyrene oxide (84.0 mg, 0.40 mmol) and 2,6-dimethylphenol (244 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **144** (139.6 mg, 80% yield, *p*/*m*: 80:20) as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$, major isomer):** $\delta$ 6.96 (s, 2H), 6.73 (s, 2H), 4.60–4.53 (m, 2H), 4.45 (s, 1H), 3.35–3.28 (m, 2H), 2.23 (s, 6H), 2.16 (s, 6H). **$^{13}$C NMR (125 MHz, $CDCl_3$, major isomer):** $\delta$ 151.2, 150.6, 145.0 (dm, $J$ = 245.5 Hz), 139.6 (dm, $J$ = 251.4 Hz), 137.4 (dm, $J$ = 250.2 Hz), 132.8, 130.8, 128.6, 127.8, 123.1, 122.9, 117.9 (t, $J$ = 16.9 Hz), 42.2, 37.7 (t, $J$ = 3.0 Hz), 16.0, 15.9. **$^{19}$F NMR (471 MHz, $CDCl_3$, major isomer):** $\delta$ -141.8 (dd, $J$ = 23.5, 7.8 Hz), -157.4 (t, $J$ = 21.1 Hz), -162.5 (td, $J$ = 22.4, 7.7 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{21}F_5O_2Na$ $[M+Na]^+$ 459.1354, found 459.1348.

***2,2'-(1-(3,5-Bis(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(1,4-dimethylbenzene) 146***

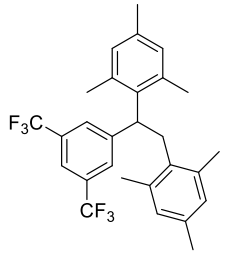



Chemical Formula: $C_{26}H_{24}F_6$
Exact Mass: 450.1782

General Procedure **E** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (51.0 mg, 0.20 mmol) and *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (0.90 µL, 0.010 mmol, 5.0 mol%) in HFIP (0.50 mL). The reaction mixture was stirred at 0 °C for 6 h and then, at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **146** (81.2 mg, 90% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.68 (d, $J$ = 2.2 Hz, 1H), 7.36–7.28 (m, 3H), 7.07–6.98 (m, 3H), 6.93 (dd, $J$ = 7.7, 1.9 Hz, 1H), 6.45 (d, $J$ = 1.9 Hz, 1H), 4.39 (dd, $J$ = 9.6, 5.4 Hz, 1H), 3.38 (dd, $J$ = 13.2, 5.5 Hz, 1H), 3.19 (dd, $J$ = 13.3, 9.7 Hz, 1H), 2.43 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 146.7, 140.4, 136.9, 135.9, 135.2, 133.1, 132.9, 131.1 (q, $J$ = 33.0 Hz), 130.8, 130.7, 130.3, 128.5 (m), 127.8, 127.5, 127.3, 123.4 (q, $J$ = 272.7 Hz), 120.1 (p, $J$ = 3.9 Hz), 47.7, 39.5, 21.3, 20.7, 19.3, 18.7. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -62.8. **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{24}F_6Na$ $[M+Na]^+$ 473.1674, found 473.1671.

***2,2'-(1-(3,5-Bis(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(1,3,5-trimethylbenzene) 147***

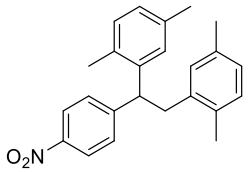



Chemical Formula: $C_{28}H_{28}F_6$
Exact Mass: 478.2095

General Procedure **E** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (51.0 mg, 0.20 mmol) and mesitylene (0.14 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (0.9 µL, 0.010 mmol, 5.0 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **147** (88.4 mg, 92% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.74 (s, 1H), 7.68 (s, 2H), 6.77 (s, 2H), 6.75 (s, 2H), 4.69 (dd, $J$ = 10.3, 3.5 Hz, 1H), 3.61 (dd, $J$ = 13.2, 3.6 Hz, 1H), 3.41 (dd, $J$ = 13.2, 10.4 Hz, 1H), 2.25 (s, 6H), 1.95 (s, 6H), 2.07–1.67 (brs, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 147.9, 137.6, 136.8, 136.5, 135.8, 135.6, 131.3 (q, $J$ = 32.9 Hz), 131.3, 129.3, 129.1, 127.5 (m), 123.5 (q, $J$ = 272.7 Hz), 119.7 (p, $J$ = 3.9 Hz), 44.2, 30.6, 21.4, 20.8 (2C), 20.7, 19.5. **$^{19}$F NMR (471 MHz, $CDCl_3$):** $\delta$ -62.7. **HRMS (ESI):** *m/z* calcd. for $C_{28}H_{28}F_6Na$ $[M+Na]^+$ 501.1987, found 501.1980.

***2,2'-(1-(4-Nitrophenyl)ethane-1,2-diyl)bis(1,4-dimethylbenzene) 148***

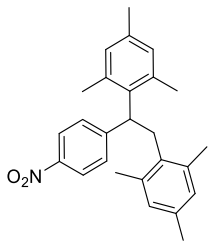


Chemical Formula: $C_{24}H_{25}NO_2$
Exact Mass: 359.1885

General Procedure **E** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and then, at 80 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **148** (87.0 mg, 61% yield, 90:10 with **148'**) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.02 (d, $J$ = 8.7 Hz, 2H), 7.25–7.26 (m, 1H), 7.10 (d, $J$ = 8.7 Hz, 2H), 7.00 (s, 2H), 6.97 (d, $J$ = 7.7 Hz, 1H), 6.90 (dd, $J$ = 7.6, 1.9 Hz, 1H), 6.55 (d, $J$ = 1.9 Hz, 1H), 4.40 (dd, $J$ = 9.4, 5.6 Hz, 1H), 3.32 (dd, $J$ = 13.4, 5.7 Hz, 1H), 3.24 (dd, $J$ = 13.4, 9.4 Hz, 1H), 2.39 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 151.9, 146.3, 141.1, 137.2, 135.7, 135.1, 133.1, 133.0, 130.6 (2C), 130.1, 129.3, 127.5 (2C), 127.1, 123.2, 47.8, 39.3, 21.3, 20.9, 19.2, 18.8. **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{25}NO_2Na$ $[M+Na]^+$ 382.1778, found 382.1770.

***2,2'-(1-(4-Nitrophenyl)ethane-1,2-diyl)bis(1,3,5-trimethylbenzene) 149***



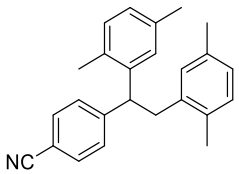
Chemical Formula: $C_{26}H_{29}NO_2$
Exact Mass: 387,2198

General Procedure **E** was followed with 2-(4-nitrophenyl)oxirane (66.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **149** (116.8 mg, 75% yield, 93:7 with **149'**) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.13 (d, $J$ = 8.8 Hz, 2H), 7.41 (d, $J$ = 8.8 Hz, 2H), 6.74 (s, 2H), 6.71 (s, 2H), 4.65 (dd, $J$ = 10.5, 3.1 Hz, 1H), 3.62 (dd, $J$ = 13.2, 3.1 Hz, 1H), 3.36

(dd, *J* = 13.2, 10.5 Hz, 1H), 2.23 (s, 6H), 1.92 (brs, 9H), 1.69 (brs, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 153.4, 145.9, 137.0, 136.7, 136.6, 136.4, 135.5, 133.6, 131.1, 129.0 (2C), 128.1, 123.4, 44.5, 30.3, 21.3, 20.8 (2C), 20.6, 19.5. **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{29}NO_2Na$ $[M+Na]^+$ 410.2091, found 410.2085.

***4-(1,2-Bis(2,5-dimethylphenyl)ethyl)benzonitrile 150***

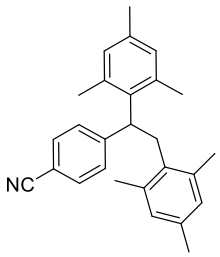



Chemical Formula: $C_{25}H_{25}N$
Exact Mass: 339.1987

General Procedure **E** was followed with 4-(oxiran-2-yl)benzonitrile (58.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **150** (90.2 mg, 67% yield) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.46 (d, *J* = 8.3 Hz, 2H), 7.27 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 7.02–7.00 (m, 2H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.91 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.55 (d, *J* = 1.9 Hz, 1H), 4.35 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.31 (dd, *J* = 13.4, 5.7 Hz, 1H), 3.23 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.40 (s, 3H), 2.18 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 149.7, 141.2, 137.4, 135.6, 135.1, 133.2, 133.1, 131.8, 130.7, 130.6, 130.1, 129.3, 127.5, 127.5, 127.1, 119.1, 109.8, 48.0, 39.3, 21.4, 20.9, 19.3, 18.8. **HRMS (ESI):** *m/z* calcd. for $C_{25}H_{25}NNa$ $[M+Na]^+$ 362.1879, found 362.1875.

***4-(1,2-Dimesitylethyl)benzonitrile 151***

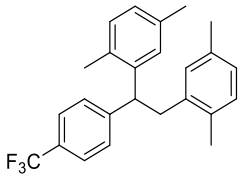



Chemical Formula: $C_{27}H_{29}N$
Exact Mass: 367.2300

General Procedure **E** was followed with 4-(oxiran-2-yl)benzonitrile (58.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, to 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **151** (113.3 mg, 77% yield) as a colorless oil.

**$^{1}$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.45 (d, $J$ = 8.2 Hz, 2H), 7.26 (d, $J$ = 8.2 Hz, 2H), 6.62 (s, 2H), 6.62–6.57 (m, 2H), 4.53 (dd, $J$ = 10.7, 3.1 Hz, 1H), 3.49 (dd, $J$ = 13.3, 3.1 Hz, 1H), 3.23 (dd, $J$ = 13.2, 10.6 Hz, 1H), 2.12 (s, 6H), 1.82 (brs, 9H), 1.59 (brs, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 151.1, 137.7, 136.8, 136.7, 136.3, 135.5, 133.7, 132.0, 131.1, 129.0 (2C), 128.1, 119.2, 109.3, 44.5, 30.1, 21.2, 20.8 (2C), 20.6, 19.6. **HRMS (ESI):** *m/z* calcd. for $C_{27}H_{29}NNa$ $[M+Na]^+$ 390.2192, found 390.2185.

***2,2'-(1-(4-(Trifluoromethyl)phenyl)ethane-1,2-diyl)bis(1,4-dimethylbenzene) 152***

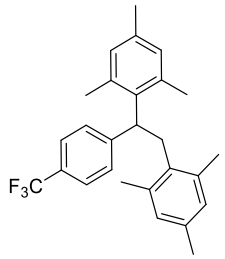



Chemical Formula: $C_{25}H_{25}F_3$
Exact Mass: 382.1908

General Procedure **E** was followed with 2-(4-(trifluoromethyl)phenyl)oxirane (75.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at rt for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **152** (59.0 mg, 39% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.43 (d, $J$ = 8.1 Hz, 2H), 7.28 (s, 1H), 7.09 (d, $J$ = 8.0 Hz, 2H), 7.04–6.87 (m, 3H), 6.89 (dd, $J$ = 7.7, 1.9 Hz, 1H), 6.54 (d, $J$ = 1.9 Hz, 1H), 4.37 (dd, $J$ = 9.0, 6.0 Hz, 1H), 3.31 (dd, $J$ = 13.4, 6.0 Hz, 1H), 3.24 (dd, $J$ = 13.4, 9.0 Hz, 1H), 2.39 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 148.2 (q, $J$ = 1.4 Hz), 141.7, 137.6, 135.5, 135.0, 133.2, 133.1, 130.7, 130.5, 130.0, 128.8, 128.2 (q, $J$ = 32.3 Hz), 127.6, 127.3, 126.9, 124.9 (q, $J$ = 3.8 Hz), 124.3 (q, $J$ = 271.8 Hz), 47.6, 39.4, 21.3, 20.9, 19.3, 18.9. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.3. **HRMS (ESI):** *m/z* calcd. for $C_{25}H_{25}F_3Na$ $[M+Na]^+$ 405.1801, found 405.1794.

***2,2'-(1-(4-(Trifluoromethyl)phenyl)ethane-1,2-diyl)bis(1,3,5-trimethylbenzene) 153***

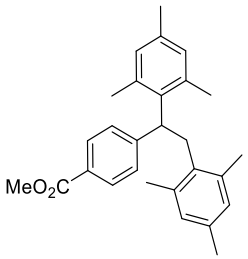



Chemical Formula: $C_{27}H_{29}F_3$
Exact Mass: 410.2221

General Procedure **E** was followed with 2-(4-(trifluoromethyl)phenyl)oxirane (75.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at rt for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **153** (92.8 mg, 57% yield) as a white solid.

**m.p.:** 143-147 °C. **$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.53 (d, $J$ = 8.2 Hz, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 6.74 (s, 2H), 6.74–6.67 (m, 2H), 4.65 (ddd, $J$ = 11.1, 3.3, 1.7 Hz, 1H), 3.63 (dd, $J$ = 13.3, 3.1 Hz, 1H), 3.36 (dd, $J$ = 13.2, 10.7 Hz, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 1.96 (brs, 6H), 1.93 (s, 3H), 1.70 (brs, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 149.5 (q, $J$ = 1.4 Hz), 137.7, 137.1, 136.8, 136.0, 135.3, 134.1, 131.0, 128.9 (2C), 127.8 (q, $J$ = 32.4 Hz), 127.4, 125.1 (q, $J$ = 3.8 Hz), 124.4 (q, $J$ = 271.8 Hz), 44.2, 30.1, 21.3, 20.8 (2C), 20.6, 19.5. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.2. **HRMS (ESI):** *m/z* calcd. for $C_{27}H_{29}F_3Na$ $[M+Na]^+$ 433.2114, found 433.2110.

***Methyl 4-(1,2-dimesitylethyl)benzoate 154***



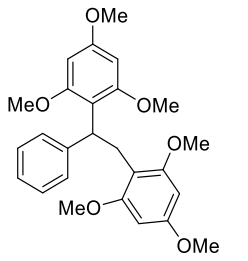

Chemical Formula: $C_{28}H_{32}O_2$
Exact Mass: 400.2402

General Procedure **E** was followed with methyl 4-(oxiran-2-yl)benzoate (71.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6

h and then, at rt for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **154** (131.8 mg, 82% yield, 89:11 with **4'ff**) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.96 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.74 (s, 2H), 6.71 (s, 2H), 4.66 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.92 (s, 3H), 3.65 (dd, *J* = 13.3, 3.1 Hz, 1H), 3.35 (dd, *J* = 13.2, 10.7 Hz, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 1.94 (brs, 9H), 1.71 (brs, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 167.2, 150.9, 137.7, 137.3, 136.9, 135.9, 135.3, 134.2, 131.0, 129.5, 128.9, 127.4, 127.3, 52.0, 44.4, 30.2, 21.2, 20.9, 20.8 (2C), 20.6, 19.5. **HRMS (ESI):** *m/z* calcd. for $C_{28}H_{23}O_2Na$ $[M+Na]^+$ 423.2295, found 423.2289.

***2,2'-(1-Phenylethane-1,2-diyl)bis(1,3,5-trimethoxybenzene) 156***

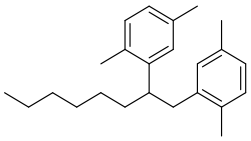


Chemical Formula: $C_{26}H_{30}O_6$
Exact Mass: 438.2042

General Procedure **E** was followed with styrene oxide (48.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (0.036 µL, 0.4 µmol, 0.1 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) was added to the reaction mixture which was stirred at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **156** (81.0 mg, 46% yield) as a yellow oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.37 (dd, *J* = 7.2, 1.1 Hz, 2H), 7.22 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.15–7.06 (m, 1H), 6.02 (s, 2H), 6.01 (s, 2H), 4.90 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.59 (s, 6H), 3.59–3.54 (m, 1H), 3.53 (s, 6H), 3.34 (dd, *J* = 12.5, 5.3 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 159.7, 159.3, 159.1, 158.5, 146.5, 128.1, 127.2, 124.6, 115.2, 111.0, 91.3, 90.2, 55.8, 55.5, 55.3, 55.2, 38.6, 24.8. **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{31}O_6$ $[M+H]^+$ 439.2115, found 439.2125.

***2,2'-(Octane-1,2-diyl)bis(1,4-dimethylbenzene) 157***

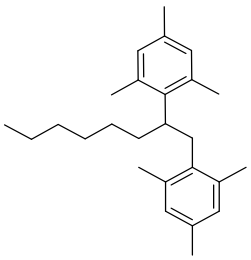


Chemical Formula: $C_{24}H_{34}$
Exact Mass: 322.2661

General Procedure **E** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at 80 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **157** (65.2 mg, 51% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.08 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.9 Hz, 2H), 6.74 (d, *J* = 1.9 Hz, 1H), 3.13–3.02 (m, 1H), 2.82 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.71 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.05 (s, 3H), 1.65 (dddd, *J* = 8.9, 7.0, 5.6, 2.4 Hz, 2H), 1.33–1.04 (m, 8H), 0.83 (t, *J* = 7.0 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 144.0, 139.0, 135.2, 134.8, 133.0 (2C), 130.9, 129.9, 129.8, 126.7, 126.5, 126.2, 41.0 (2C), 35.4, 31.8, 29.5, 27.6, 22.7, 21.3, 20.9, 19.2, 19.1, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{34}Na$ $[M+Na]^+$ 345.2553, found 345.2647.

***2,2'-(Octane-1,2-diyl)bis(1,3,5-trimethylbenzene) 158***

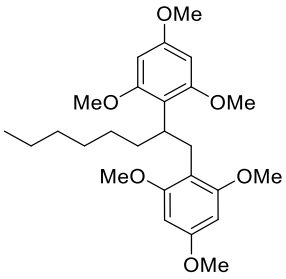


Chemical Formula: $C_{26}H_{38}$
Exact Mass: 350.2974

General Procedure **E** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at rt for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **158** (108.4 mg, 77% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.81 (d, $J$ = 2.0 Hz, 1H), 6.77 (s, 2H), 6.70 (d, $J$ = 2.0 Hz, 1H), 3.34–3.22 (m, 1H), 3.02 (dd, $J$ = 13.6, 8.1 Hz, 1H), 2.97 (dd, $J$ = 13.6, 6.1 Hz, 1H), 2.54 (s, 3H), 2.24 (s, 6H), 2.12 (s, 6H), 2.06–1.93 (m, 1H), 1.87 (s, 3H), 1.78–1.65 (m, 1H), 1.30-1.05 (m, 8H), 0.85 (t, $J$ = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.2, 137.4, 136.6, 136.4, 135.5, 134.9, 134.8, 131.0, 129.0, 128.8, 41.2, 34.4, 33.9, 31.8, 29.7, 28.6, 22.7, 21.7, 21.4, 20.8, 20.7, 20.1, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{38}Na$ $[M+Na]^+$ 373.2866, found 373.2860.

***2,2'-(Octane-1,2-diyl)bis(1,3,5-trimethoxybenzene) 159***

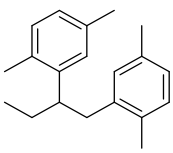



Chemical Formula: $C_{26}H_{38}O_6$
Exact Mass: 446.2668

General Procedure **E** was followed with 2-hexyloxirane (51.0 mg, 0.40 mmol) and 1,3,5-trimethoxybenzene (336.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **159** (114.3 mg, 64% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.16–5.97 (m, 4H), 3.92–3.72 (m, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 3.65 (s, 6H), 3.49–3.39 (m, 4H), 2.90 (dd, $J$ = 7.3, 4.0 Hz, 2H), 2.06–1.71 (m, 1H), 1.68–1.42 (m, 1H), 1.40–0.93 (m, 8H), 0.83 (t, $J$ = 7.0 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 160.6, 159.2, 158.7, 158.5, 115.4, 112.2, 91.3, 91.1, 90.4, 56.5, 55.6, 55.3, 55.2, 35.1, 33.0, 31.9, 29.5, 28.4, 26.7, 22.7, 14.1. **HRMS (ESI):** *m/z* calcd. for $C_{26}H_{38}O_6Na$ $[M+Na]^+$ 469.2561, found 469.2554.

***2,2'-(Butane-1,2-diyl)bis(1,4-dimethylbenzene) 160***

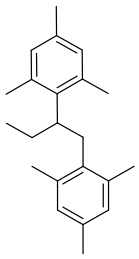


Chemical Formula: $C_{20}H_{26}$
Exact Mass: 266.2035

General Procedure **E** was followed with 2-ethyloxirane (29.0 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) with TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at 60 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **160** (49.8 mg, 47% yield) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.09 (d, $J$ = 1.8 Hz, 1H), 6.99 (dd, $J$ = 13.5, 7.6 Hz, 2H), 6.91 (dd, $J$ = 7.7, 1.9 Hz, 2H), 6.80 (d, $J$ = 1.9 Hz, 1H), 3.12–2.95 (m, 1H), 2.83 (dd, $J$ = 13.5, 8.1 Hz, 1H), 2.75 (dd, $J$ = 13.4, 6.4 Hz, 1H), 2.35 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 1.87–1.69 (m, 1H), 1.68–1.59 (m, 1H), 0.75 (t, $J$ = 7.4 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 143.7, 139.1, 135.3, 134.8, 133.2, 133.0, 131.0, 130.0, 129.9, 126.7, 126.6, 126.3, 42.7, 40.8, 28.0, 21.3, 21.0, 19.4, 19.1, 12.2. **HRMS (ESI):** *m/z* calcd. for $C_{20}H_{26}Na$ $[M+Na]^+$ 289.1927, found 289.1922.

***2,2'-(Butane-1,2-diyl)bis(1,3,5-trimethylbenzene) 161***

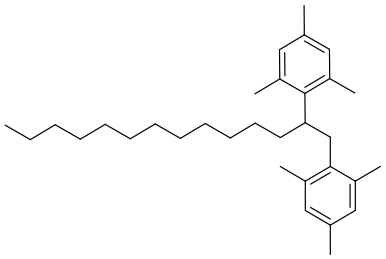


Chemical Formula: $C_{22}H_{30}$
Exact Mass: 294.2348

General Procedure **E** was followed with 2-ethyloxirane (29.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, at rt for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **161** (81.4 mg, 69% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.84 (s, 1H), 6.80 (s, 2H), 6.73 (s, 1H), 3.30–3.19 (m, 1H), 3.10–3.00 (m, 2H), 2.55 (s, 3H), 2.26 (s, 6H), 2.16 (s, 6H), 2.01 (ddd, $J$ = 13.4, 10.1, 7.4 Hz, 1H), 1.94 (s, 3H), 1.79 (ddd, $J$ = 13.4, 7.5, 5.9 Hz, 1H), 0.79 (t, $J$ = 7.4 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 137.9, 137.5, 136.6, 136.4, 135.6, 134.9, 134.8, 131.1, 129.0, 128.9, 43.0, 33.7, 26.8, 21.6, 21.5, 20.8, 20.7, 20.2, 13.1. **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{30}Na$ $[M+Na]^+$ 317.2240, found 317.2236.

***2,2'-(Tetradecane-1,2-diyl)bis(1,3,5-trimethylbenzene) 162***

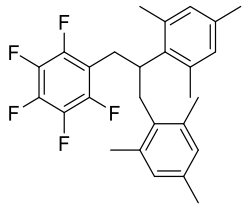


Chemical Formula: $C_{32}H_{50}$
Exact Mass: 434,3913

General Procedure **E** was followed with 1,2-epoxytetradecane (85.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 1 h and, then, at rt for 8 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **162** (108.8 mg, 88% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.81 (s, 1H), 6.77 (s, 2H), 6.70 (s, 1H), 3.33–3.23 (m, 1H), 3.07–2.93 (m, 2H), 2.54 (s, 3H), 2.24 (s, 6H), 2.12 (s, 6H), 2.04–1.94 (m, 1H), 1.87 (s, 3H), 1.77–1.65 (m, 1H), 1.35–1.07 (m, 20H), 0.90 (t, $J$ = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 138.3, 137.5, 136.7, 136.5, 135.6, 134.9, 134.8, 131.2, 129.1, 129.0, 41.3, 34.5, 34.0, 32.1, 30.2, 29.8 (4C), 29.7, 29.5, 28.7, 22.9, 21.8, 21.5, 20.9, 20.8, 20.3, 14.3. **HRMS (ESI):** *m/z* calcd. for $C_{32}H_{50}Na$ $[M+Na]^+$ 457.3805, found 457.3792.

***2,2'-(3-(Perfluorophenyl)propane-1,2-diyl)bis(1,3,5-trimethylbenzene) 163***

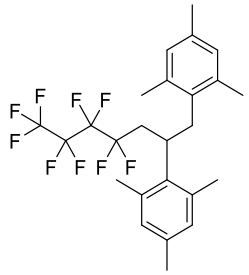



Chemical Formula: $C_{27}H_{27}F_5$
Exact Mass: 446.2033

General Procedure **E** was followed with 2-((perfluorophenyl)methyl)oxirane (90.0 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 60 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **163** (146.9 mg, 82% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.83 (d, $J$ = 2.0 Hz, 1H), 6.73 (s, 2H), 6.59 (d, $J$ = 2.0 Hz, 1H),), 3.58 (tt, $J$ = 7.9, 4.0 Hz, 1H), 3.25–3.19 (m, 3H), 2.99 (dd, $J$ = 13.8, 5.2 Hz, 1H), 2.68 (s, 3H), 2.20 (s, 6H), 1.98 (s, 6H), 1.65 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.2 (dm, $J$ = 243.5 Hz), 139.5 (dm, $J$ = 252.7 Hz), 139.0, 137.2 (dm, $J$ = 251.2 Hz), 137.2, 136.5, 136.4, 135.7, 135.6, 135.3, 134.1, 131.2, 129.1, 129.0, 114.8 (m), 40.9, 32.3, 26.7, 21.4, 20.8, 20.7, 19.7. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -143.0 (m), -157.3 (t, $J$ = 20.9 Hz), -162.8 (m). **HRMS (ESI):** *m/z* calcd. for $C_{27}H_{27}F_5Na$ $[M+Na]^+$ 469.1925, found 469.1921.

***2,2'-(4,4,5,5,6,6,7,7,7-Nonafluoroheptane-1,2-diyl)bis(1,3,5-trimethylbenzene) 164***

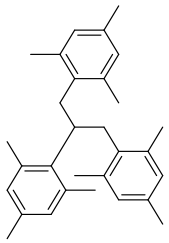


Chemical Formula: $C_{25}H_{27}F_9$
Exact Mass: 498.1969

General Procedure **E** was followed with 2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)oxirane (110.4 mg, 0.40 mmol) and mesitylene (0.28 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **164** (145.5 mg, 73% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.85 (d, $J$ = 2.0 Hz, 1H), 6.78 (s, 2H), 6.70 (d, $J$ = 2.0 Hz, 1H), 3.88 (ddd, $J$ = 10.2, 5.0, 1.6 Hz, 1H), 3.26 (dd, $J$ = 13.7, 10.1 Hz, 1H), 3.05 (dd, $J$ = 13.7, 5.1 Hz, 1H), 2.83–2.67 (m, 1H), 2.65–2.48 (m, 4H), 2.25 (s, 6H), 2.11 (s, 6H), 1.86 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 137.2, 136.8, 136.5, 135.9, 135.7, 135.6, 133.5, 131.1, 129.3, 129.1, 121.7–106.3 (m, $\boldsymbol{C}F_2\boldsymbol{C}F_2\boldsymbol{C}F_2\boldsymbol{C}F_3$), 34.7 (t, $J$ = 20.9 Hz), 34.3, 32.3 (t, $J$ = 1.7 Hz), 21.4, 20.8, 20.7, 20.6, 19.9. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -81.1 (t, $J$ = 9.9 Hz), -115.0 (m), -124.4 (q, $J$ = 9.6 Hz), -125.9 (tq, $J$ = 11.8, 6.6 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{25}H_{27}F_9Na$ $[M+Na]^+$ 521.1861, found 521.1850.

***2,2',2''-(Propane-1,2,3-triyl)tris(1,3,5-trimethylbenzene) 166***

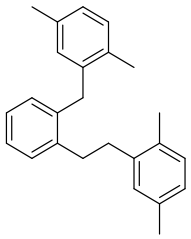


Chemical Formula: $C_{30}H_{38}$
Exact Mass: 398,2974

General Procedure **E** was followed with glycidyl methyl ether (35.2 mg, 0.40 mmol) and mesitylene (0.56 mL, 4.0 mmol, 10 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 3 h and then, at 50 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **166** (74.9 mg, 47% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 6.84 (d, $J$ = 2.0 Hz, 1H), 6.73 (s, 4H), 6.84 (d, $J$ = 2.0 Hz, 1H), 3.35–3.25 (m, 1H), 3.17 (dd, $J$ = 13.4, 6.9 Hz, 2H), 2.98 (dd, $J$ = 13.4, 7.3 Hz, 2H), 2.73 (s, 3H), 2.23 (s, 3H), 2.22 (s, 6H), 1.96 (s, 12H), 1.52 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 136.3, 135.1, 134.6, 134.5, 133.1, 133.0, 132.8, 129.0, 127.0, 126.7, 40.2, 29.9, 20.0, 18.7, 18.5 (2C), 17.6. **HRMS (ESI):** *m/z* calcd. for $C_{30}H_{38}Na$ $[M+Na]^+$ 421.2866, found 421.2854.

***2-(2-(2,5-Dimethylbenzyl)phenethyl)-1,4-dimethylbenzene 167***

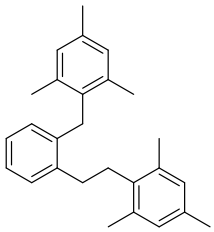


Chemical Formula: $C_{25}H_{28}$
Exact Mass: 328,2191

General procedure **E** was followed with isochroman (53.7 mg, 0.40 mmol) and *p*-xylene (212.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (10.6 µL, 0.12 mmol, 30 mol%) in HFIP (1.0 mL). In that case, the reaction mixture was stirred from the beginning at 40 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **167** (115.3 mg, 88% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.29 (d, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 7.4 Hz, 1H), 7.17–7.13 (m, 1H), 7.10 (d, $J$ = 7.6 Hz, 1H), 7.05 (d, $J$ = 7.6 Hz, 1H), 6.99 (d, $J$ = 7.8 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 1H), 6.93–6.89 (m, 2H), 6.74 (s, 1H), 3.95 (s, 2H), 2.89–2.80 (m, 4H), 2.31 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 140.5, 140.1, 138.6, 138.1, 135.6, 133.5, 132.8, 130.3 (2C), 130.1, 129.9, 129.7, 129.4, 127.1, 126.9, 126.5, 126.4, 36.3, 34.9, 34.1, 21.2, 21.1, 19.3, 18.8, one C hidden. **HRMS (ESI):** *m/z* calcd. for $C_{25}H_{28}Na$ $[M+Na]^+$ 351.2083, found 351.2080.

***1,3,5-Trimethyl-2-(2-(2,4,6-trimethylbenzyl)phenethyl)benzene 168***

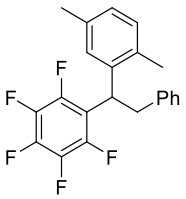


Chemical Formula: $C_{27}H_{32}$
Exact Mass: 356,2504

General procedure **E** was followed with isochroman (53.7 mg, 0.40 mmol) and mesitylene (240.4 mg, 2.0 mmol, 5.0 eq) in the presence of TfOH (10.6 µL, 0.12 mmol, 30 mol%) in HFIP (1.0 mL). In that case, the reaction mixture was stirred from the beginning at 40 °C for 24 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **168** (123.8 mg, 87% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.29 (d, $J$ = 7.5 Hz, 1H), 7.18 (t, $J$ = 7.4 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 6.94 (s, 2H), 6.90 (s, 2H), 6.56 (d, $J$ = 7.7 Hz, 1H), 3.99 (s, 2H), 3.05–2.89 (m, 4H), 2.38 (s, 6H), 2.34 (s, 3H), 2.30 (s, 3H), 2.17 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 140.4, 137.5, 137.4, 136.2, 135.9, 135.6, 135.5, 133.7, 129.2, 129.1, 129.0, 126.7, 126.5, 126.2, 32.6, 31.6, 30.7, 21.1, 21.0, 20.1, 20.0. **HRMS (ESI):** *m/z* calcd. for $C_{27}H_{32}Na$ $[M+Na]^+$ 379.2396, found 379.2386.

***1-(2-(2,5-Dimethylphenyl)-1-phenylethyl)-2,3,4,5,6-pentafluorobenzene 169***

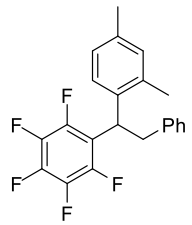



Chemical Formula: $C_{22}H_{17}F_5$
Exact Mass: 376.1250

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) was added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **169** (60.3 mg, 80% yield, *a:b* 94:6) as a colorless oil.

**$^{1}$H NMR (500 MHz, $CDCl_3$, major isomer):** $\delta$ 7.37 (s, 1H), 7.27–7.16 (m, 3H), 7.09–7.05 (m, 2H), 7.04–6.98 (m, 2H), 4.74 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.48 (dd, *J* = 13.5, 10.2 Hz, 1H), 3.41 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$, major isomer):** $\delta$ 145.3 (dm, *J* = 246.3 Hz), 139.7 (dm, *J* = 252.4 Hz), 137.4 (dm, *J* = 251.6 Hz), 139.1, 138.8, 135.8, 133.0, 130.5, 128.6, 128.4, 128.0 (t, *J* = 3.1 Hz), 127.9, 126.6, 116.6 (m), 39.7, 39.5, 21.3, 18.9. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -140.7 (dd, *J* = 22.6, 7.5 Hz), -156.7 (t, *J* = 21.0 Hz), -162.4 (td, *J* = 22.2, 7.5 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{17}F_5Na$ $[M+Na]^+$ 399.1143, found 399.1139.

***1-(2-(2,4-Dimethylphenyl)-1-phenylethyl)-2,3,4,5,6-pentafluorobenzene 170***



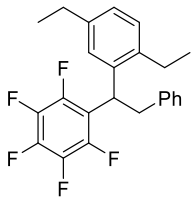

Chemical Formula: $C_{22}H_{17}F_5$
Exact Mass: 376.1250

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then *m*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) was added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **170** (57.6 mg, 77% yield, *a:b* 92:8) as a colorless oil.

**$^{1}$H NMR (500 MHz, $CDCl_3$, major isomer):** $\delta$ 7.47 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.25–7.17 (m, 3H), 7.10–7.05 (m, 3H), 6.97 (d, *J* = 2.0 Hz, 1H), 4.74 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.47 (dd, *J* = 13.5, 9.8 Hz, 1H), 3.42 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.32 (d, *J* = 2.4 Hz, 3H), 2.18 (s, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$, major isomer):** $\delta$ 145.2 (dm, *J* = 245.8 Hz), 139.6 (dm, *J* = 252.4 Hz), 139.0, 137.4 (dm, *J* = 252.4 Hz), 136.8, 136.1, 136.0, 131.5, 128.7,

128.5, 127.3 (t, *J* = 3.2 Hz), 127.0, 126.6, 116.8 (m), 39.5 (t, *J* = 2.6 Hz), 39.2, 20.9, 19.3 (t, *J* = 2.6 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -140.9 (dd, *J* = 22.6, 7.4 Hz), -156.7 (t, *J* = 21.0 Hz), -162.4 (td, *J* = 22.3, 7.6 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{17}F_5Na$ $[M+Na]^+$ 399.1143, found 399.1137.

***1-(2-(2,5-Diethylphenyl)-1-phenylethyl)-2,3,4,5,6-pentafluorobenzene 171***

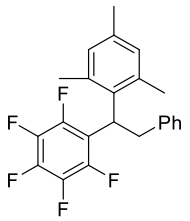



Chemical Formula: $C_{24}H_{21}F_5$
Exact Mass: 404.1563

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then 1,4-diethylbenzene (0.16 mL, 1.0 mmol, 5.0 eq) was added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **171** (46.2 mg, 57% yield, *a:b* 89:11) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.44 (d, *J* = 1.9 Hz, 1H), 7.26–7.18 (m, 3H), 7.13–7.08 (m, 4H), 4.87 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.55–3.48 (dd, *J* = 13.6, 10.5 Hz, 1H), 3.42 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.72–2.64 (m, 3H), 2.55 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 145.3 (dm, *J* = 245.9 Hz), 142.0, 139.7 (dm, *J* = 252.4 Hz), 139.2, 139.1, 138.0, 137.5 (dm, *J* = 252.1 Hz), 128.7, 128.6, 128.5, 127.2 (t, *J* = 3.6 Hz), 126.9, 126.6, 117.0 (m), 39.8 (t, *J* = 2.5 Hz), 39.1, 28.7, 24.7 (t, *J* = 1.2 Hz), 15.7, 15.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -140.6 (m), -156.7 (t, *J* = 21.1 Hz), -162.3 (m). **HRMS (ESI):** *m/z* calcd. for $C_{24}H_{21}F_5Na$ $[M+Na]^+$ 427.1456, found 427.1451.

***1,2,3,4,5-Pentafluoro-6-(2-mesityl-1-phenylethyl)benzene 172***

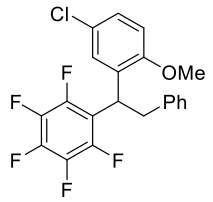



Chemical Formula: $C_{23}H_{19}F_5$
Exact Mass: 390.1407

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then mesitylene (0.14 mL,1.0 mmol, 5.0 mL) was added to the reaction mixture which was stirred at 140 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afford **172** (46.5 mg, 60% yield, *a:b* = 80:20) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.30–7.22 (m, 3H), 7.07–7.03 (m, 2H), 6.83 (s, 2H), 4.97 (t, *J* = 7.7 Hz, 1H), 3.64 (ddt, *J* = 13.8, 7.1, 2.2 Hz, 1H), 3.44 (ddt, *J* = 13.8, 9.1, 2.2 Hz, 1H), 2.29 (s, 3H), 2.15 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 145.9 (dm, *J* = 247.2 Hz), 139.6 (dm, *J* = 252.3 Hz), 139.4, 137.5 (dm, *J* = 251.3 Hz), 136.7, 136.5, 134.6, 130.3, 129.0, 128.2, 126.5, 116.5 (m), 40.3, 37.8 (t, *J* = 4.2 Hz), 20.8, 20.7, 20.2 (t, *J* = 1.8 Hz), one C hidden. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -138.4 (m), -157.6 (t, *J* = 21.1 Hz), -162.8 (td, *J* = 22.1, 7.0 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{23}H_{19}F_5Na$ $[M+Na]^+$ 413.1299, found 413.1304.

***1-(2-(5-Chloro-2-methoxyphenyl)-1-phenylethyl)-2,3,4,5,6-pentafluorobenzene 173***



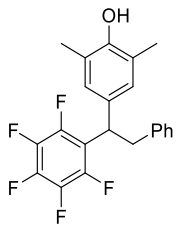

Chemical Formula: $C_{21}H_{14}ClF_5O$
Exact Mass: 412.0653

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) with TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h then 4-chloroanisole (122 µL, 1.0 mmol, 5.0 eq) was added and the reaction mixture was stirred at 80 °C for 48 h. Purification by flash column chromatography over silica (*n*-pentane, 100%) afford **173** (34.0 mg, 42% yield, *a:b* 75:25) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.47 (d, *J* = 1.6 Hz, 1H), 7.27–7.14 (m, 4H), 7.12–7.07 (m, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 4.94 (t, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 3.39 (d, *J* = 8.3 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 155.5, 145.4 (dm, *J* = 247.5 Hz), 139.7 (dm, *J* = 251.8 Hz), 138.6, 137.3 (dm, *J* = 251.4 Hz), 130.6, 128.6, 128.4, 128.0, 127.9 (t, *J* = 3.2 Hz), 126.7, 125.5, 116.1 (m), 111.5, 55.6, 37.5 (q, *J*

= 2.4 Hz), 36.0. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.5 (m), -156.9 (t, $J$ = 21.0 Hz), -163.1 (td, $J$ = 22.3, 7.8 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{21}H_{14}ClF_5ONa$ $[M+Na]^+$ 435.0546, found 435.0539.

***2,6-Dimethyl-4-(1-(perfluorophenyl)-2-phenylethyl)phenol 174***

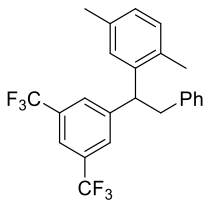



Chemical Formula: $C_{22}H_{17}F_5O$
Exact Mass: 392.1200

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then 2,6-dimethylphenol (122 mg, 1.0 mmol, 5.0 eq) was added and the reaction mixture was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **174** (47.1 mg, 60% yield, *a:b* 88:12) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.24–7.18 (m, 2H), 7.18–7.13 (m, 1H), 7.13–7.09 (m, 2H), 6.97 (s, 2H), 4.60 (t, $J$ = 8.5 Hz, 1H), 4.56 (s, 1H), 3.46 (d, $J$ = 7.8 Hz, 2H), 2.23 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 151.2, 145.0 (dm, $J$ = 246.3 Hz), 139.7 (dm, $J$ = 252.0 Hz), 139.2, 137.5 (dm, $J$ = 252.7 Hz), 132.6, 128.5 (2C), 127.7, 126.5, 123.2, 117.7 (m), 42.1, 38.6 (t, $J$ = 2.9 Hz), 16.0 (t, $J$ = 3.0 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -141.9 (dd, $J$ = 22.9, 7.8 Hz), -157.1 (t, $J$ = 21.1 Hz), -162.4 (td, $J$ = 22.3, 7.7 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{17}F_5ONa$ $[M+Na]^+$ 415.1092, found 415.1082.

***2-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-phenylethyl)-1,4-dimethylbenzene 175***

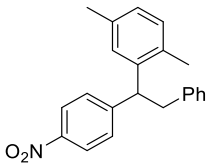



Chemical Formula: $C_{24}H_{20}F_6$
Exact Mass: 422.1469

General Procedure **F** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)oxirane (51.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 0 °C for 6 h and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) was added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **175** (40.5 mg, 48% yield, *a:b* = 85:15) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.69 (s, 1H), 7.45 (d, *J* = 1.6 Hz, 2H), 7.26–7.19 (m, 5H), 7.11–7.00 (s, 1H), 6.97–6.92 (m, 2H), 4.49 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.44 (dd, *J* = 13.4, 6.2 Hz, 1H), 3.26 (dd, *J* = 13.4, 9.2 Hz, 1H), 2.41 (s, 3H), 2.08 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 146.5, 140.3, 139.0, 135.9, 133.0, 131.2 (q, *J* = 33.0 Hz), 130.7, 129.0, 128.5 (m), 128.4, 127.7, 127.4, 126.5, 123.4 (q, *J* = 272.8 Hz), 120.2 (p, *J* = 3.9 Hz), 48.9, 42.3, 21.3, 19.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -62.8. **HRMS (ESI):** *m/z* calcd. for $C_{28}H_{28}F_6Na$ $[M+Na]^+$ 501.1987, found 501.1980.

***1,4-Dimethyl-2-(2-(4-nitrophenyl)-2-phenylethyl)benzene 176***

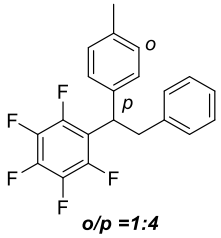



Chemical Formula: $C_{22}H_{21}NO_2$
Exact Mass: 331.1572

General Procedure **F** was followed with 2-(4-nitrophenyl)oxirane (33.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) was added and the reaction mixture was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **176** (19.7 mg, 30% yield, *a:b* = 83:17) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 8.05 (d, *J* = 8.8 Hz, 2H), 7.26–7.15 (m, 5H), 7.11–7.07 (m, 1H), 7.02–6.90 (m, 4H), 4.46 (dd, *J* = 9.4, 6.0 Hz, 1H), 3.45–3.38 (m, 1H), 3.28 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.37 (s, 3H), 2.07 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 151.7, 146.3, 140.9, 139.3, 135.8, 133.1, 130.7, 129.2, 129.0, 128.3, 127.6, 127.5, 126.4, 123.4, 49.0, 42.2, 21.3, 19.3. **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{21}NO_2Na$ $[M+Na]^+$ 354.1465, found 354.1460.

***1,2,3,4,5-pentafluoro-6-(1-phenyl-2-(p-tolyl)ethyl)benzene 180***




***o/p =1:4***

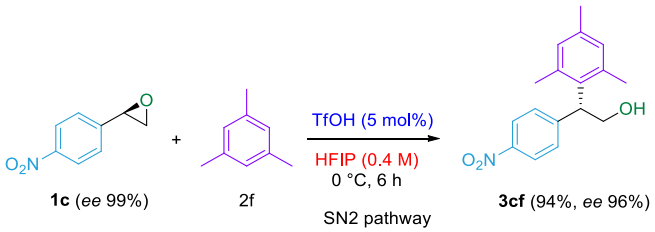
Chemical Formula: $C_{21}H_{15}F_5$
Exact Mass: 362.1094

General Procedure **F** was followed with 2,3,4,5,6-pentafluorostyrene oxide (42.0 mg, 0.20 mmol) and benzene (0.09 mL, 1.0 mmol, 5.0 eq) in the presence of TfOH (1.8 µL, 0.020 mmol, 5.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 6 h, then toluene (79.9 µL, 1.0 mmol, 5.0 eq) was added and the reaction mixture was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane, 100%) afforded **180** (32.7 mg, 45% yield, *a(o:p):b* = 5(1:4):2) as a colorless oil.

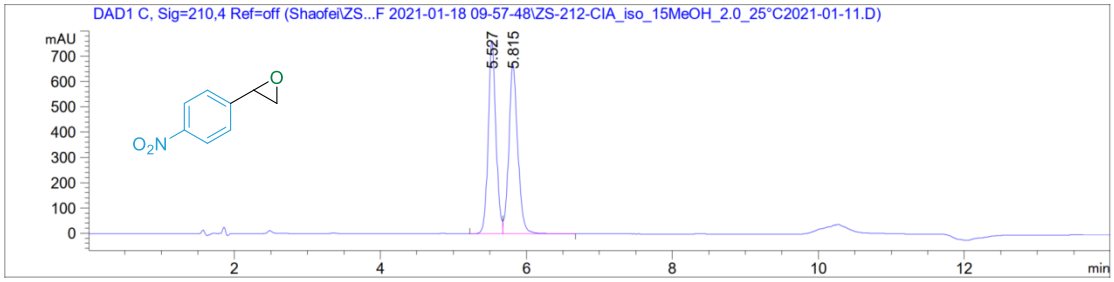
Major product characterization data: **$^1$H NMR (400 MHz, $CDCl_3$):** δ7.33 – 7.23 (m, 5H), 7.19 – 7.12 (m, 4H), 4.74 (dd, J = 9.5, 7.4 Hz, 1H), 3.60 – 3.50 (m, 2H), 2.37 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ146.19 (d, J = 12.4 Hz), 143.82, 140.87, 139.09 (d, J = 1.5 Hz), 138.63 (d, J = 17.5 Hz), 136.94, 136.24, 130.67, 129.42, 128.53, 128.51, 127.67 – 127.32 (m), 126.59 (d, J = 1.3 Hz), 117.35 (d, J = 16.1 Hz), 42.38 (d, J = 1.3 Hz), 38.42 (t, J = 3.0 Hz), 21.03. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** δ -141.45 – -142.02 (m), -156.70 – -157.09 (m), -161.15 – -162.94 (m). **HRMS** (ESI): *m/z* for $C_{21}H_{15}F_5Na$ ([M+Na]$^+$): calculated 385.0986; found 385.0980.

## Stereochemical studies

*(R)-2-(4-nitrophenyl)oxirane*

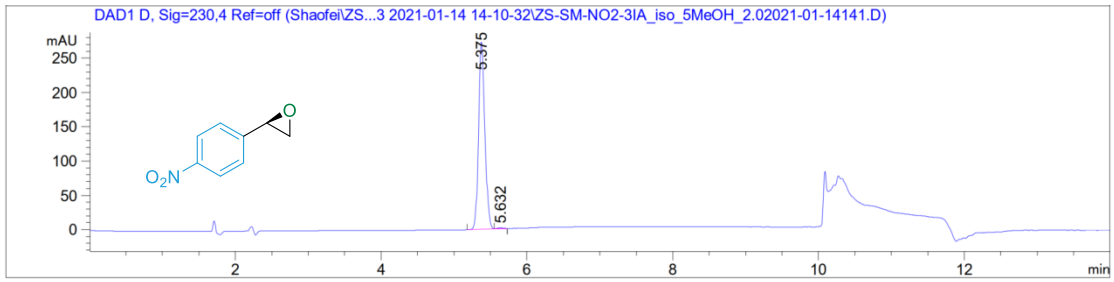



**1c** (*ee* 99%) 2f **3cf** (94%, *ee* 96%)



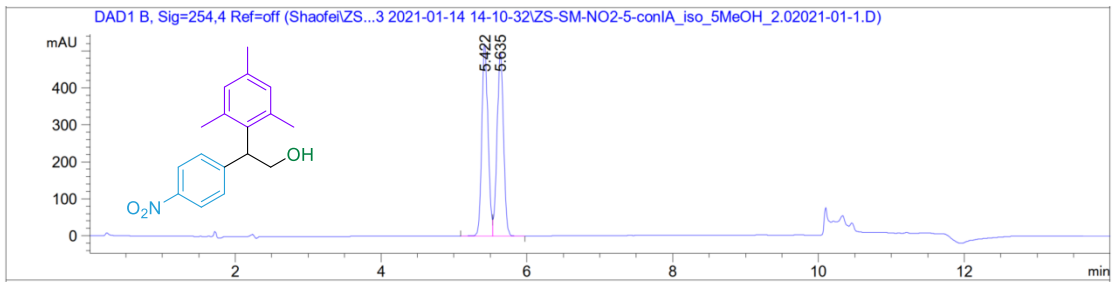

Signal 3: DAD1 C, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.527 | BV | 0.1121 | 5646.03418 | 765.13287 | 49.5263 |
| 2 | 5.815 | VB | 0.1300 | 5754.03271 | 671.10718 | 50.4737 |
| Totals : | | | | 1.14001e4 | 1436.24005 | |



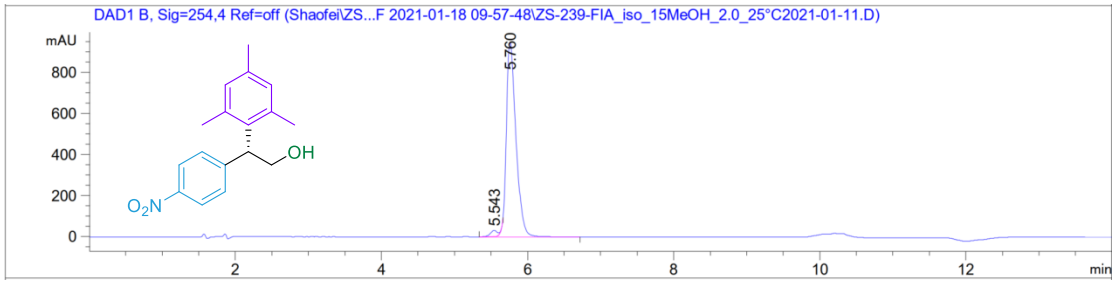

Signal 4: DAD1 D, Sig=230,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.375 | BV R | 0.0927 | 1659.19153 | 273.81107 | 99.5856 |
| 2 | 5.632 | VB E | 0.0975 | 6.90460 | 1.19297 | 0.4144 |
| Totals : | | | | 1666.09613 | 275.00403 | |




Signal 2: DAD1 B, Sig=254,4 Ref=off

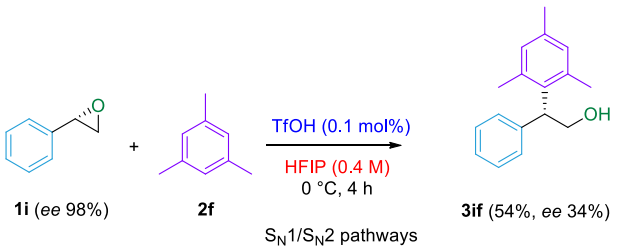
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.422 | VV R | 0.0929 | 3082.88232 | 520.52814 | 50.1227 |
| 2 | 5.635 | VB | 0.0961 | 3067.79224 | 496.30051 | 49.8773 |
| Totals : | | | | 6150.67456 | 1016.82864 | |

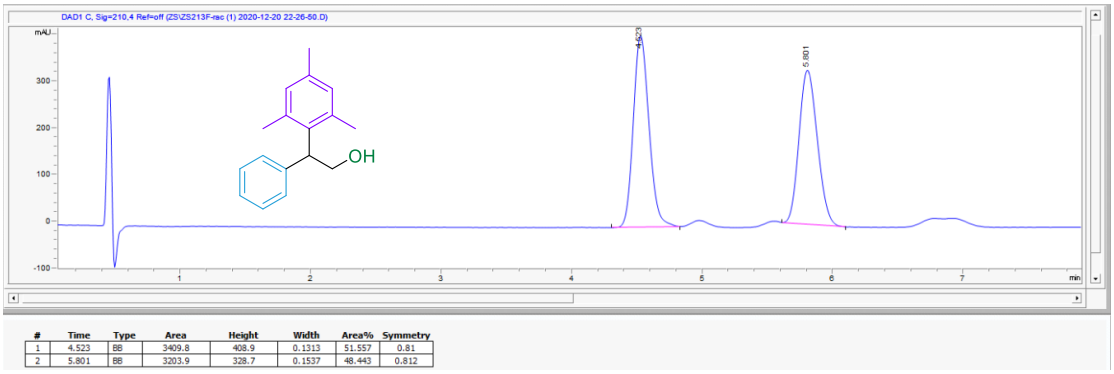


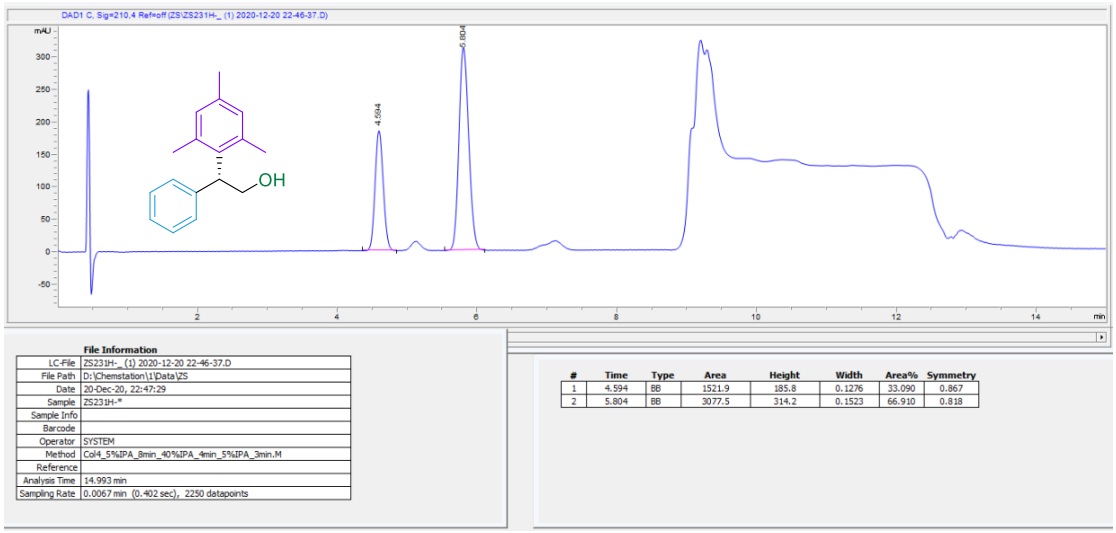

Signal 2: DAD1 B, Sig=254,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.543 | BV E | 0.1008 | 208.24751 | 30.81831 | 2.3611 |
| 2 | 5.760 | VB R | 0.1358 | 8611.71582 | 949.27063 | 97.6389 |
| Totals : | | | | 8819.96333 | 980.08894 | |

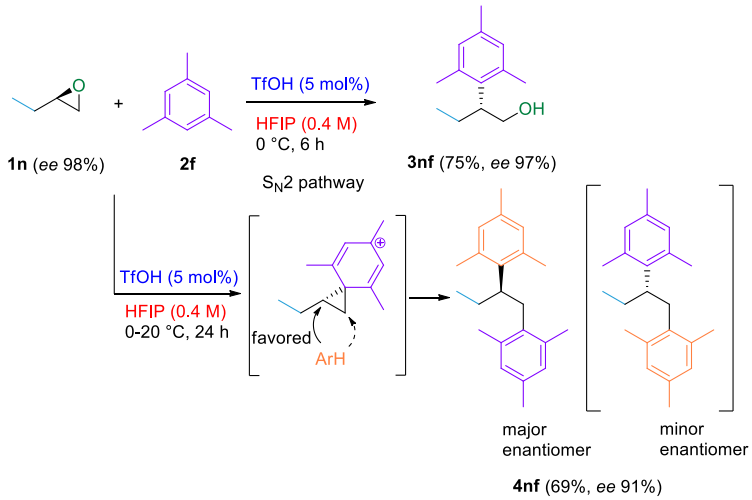
*(S)-2-phenyloxirane*

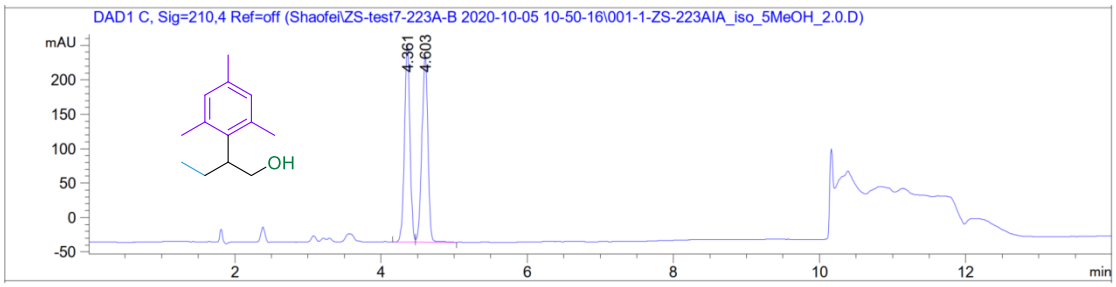




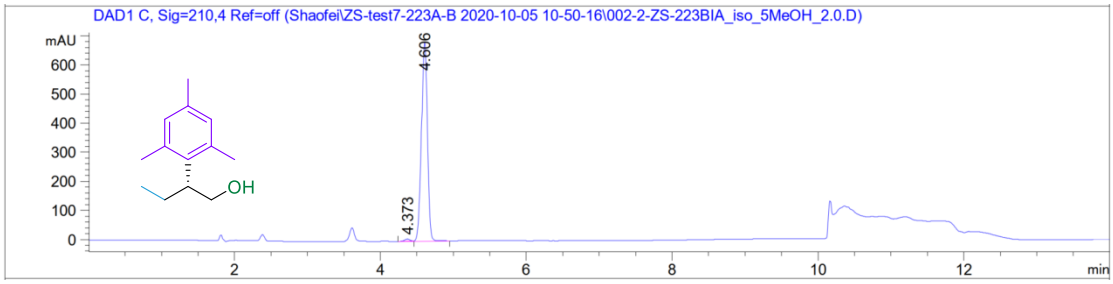

*(R)-2-ethyloxirane*



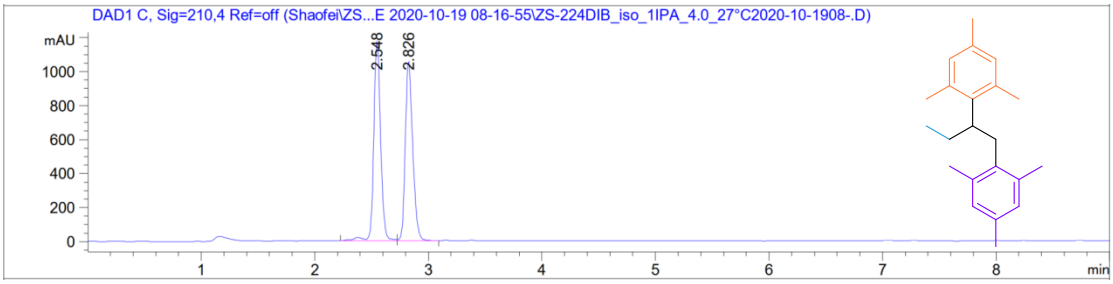

Signal 3: DAD1 C, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.361 | BV | 0.0819 | 1531.18201 | 288.44836 | 49.6537 |
| 2 | 4.603 | VV R | 0.0883 | 1552.54272 | 271.18124 | 50.3463 |
| Totals : | | | | 3083.72473 | 559.62961 | |



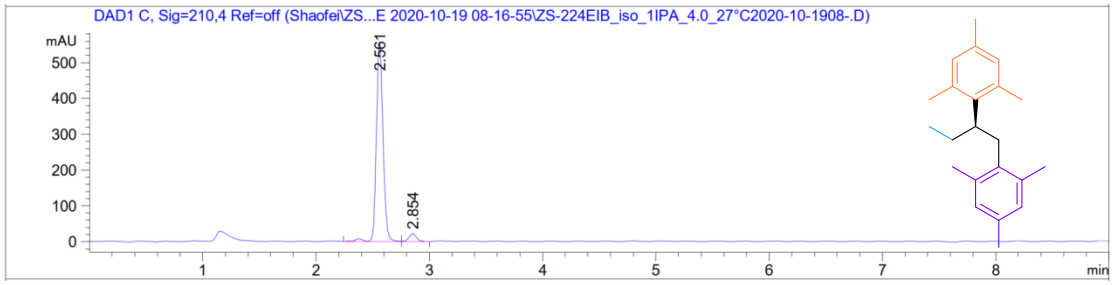

Signal 3: DAD1 C, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 4.373 | BV E | 0.0794 | 41.18303 | 8.09154 | 1.0408 |
| 2 | 4.606 | VV R | 0.0886 | 3915.56934 | 684.04169 | 98.9592 |
| Totals : | | | | 3956.75237 | 692.13323 | |




Signal 3: DAD1 C, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 2.548 | VV R | 0.0620 | 4927.90479 | 1168.73010 | 50.8481 |
| 2 | 2.826 | VB | 0.0687 | 4763.51807 | 1053.73572 | 49.1519 |
| Totals : | | | | 9691.42285 | 2222.46582 | |




Signal 3: DAD1 C, Sig=210,4 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 2.561 | VV R | 0.0609 | 2270.73267 | 555.32428 | 95.6957 |
| 2 | 2.854 | VB | 0.0720 | 102.13586 | 22.08240 | 4.3043 |
| Totals : | | | | 2372.86853 | 577.40668 | |

# Experimental section-Chapter 4

## General information

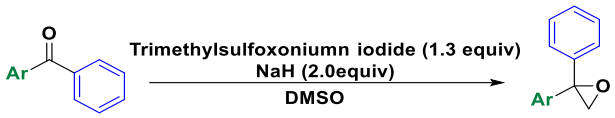
All reagents were used as received from commercial suppliers (*Alfa Aesar*, *Sigma Aldrich TCI* or *FluoroChem*) unless otherwise stated. HFIP (CAS: 920-66-1) was purchased from FluoroChem. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel $F_{254}$ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining using vanilin. Flash column chromatography (FC) was performed using silica gel 60 (230-400 mesh, Merck and co.). Yields refer to chromatographically and spectroscopically pure compounds. When stated, NMR yields were calculated by using hexamethyldisiloxane as an external standard.

$^{1}$H NMR, $^{13}$C NMR and $^{18}$F NMR spectra were recorded using a Bruker UltraShield 400, 500 or 600 at 300K. $^{1}$H NMR chemical shifts are reported in ppm using residual solvent peak as reference ($CDCl_3$: $\delta$ = 7.26 ppm or DMSO-$d_6$: $\delta$ = 2.50 ppm). Data for $^{1}$H NMR are presented as follows: chemical shift $\delta$ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant $J$ (Hz) and integration; $^{13}$C NMR spectra were recorded at 100, 125 or 150 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference ($CDCl_3$: $\delta$ = 77.16 ppm or DMSO-$d_6$: $\delta$ = 39.52 ppm). Multiplicity was defined by recorded a $^{13}$C NMR spectra using the attached proton test (APT). $^{18}$F NMR spectra were recorded at 376.5 or 471 MHz at ambient temperature. High-resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and IC), MicroTOF-Q Bruker (ESI) and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer).

**Materials:** All commercial materials were purchased from Sigma-Aldrich, TCI 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.

## Starting Material Preparation

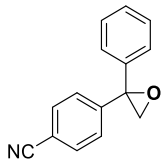
### General procedure A:




In a dry 50 mL round bottomed flask, a dry DMSO (10 mL) solution of trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) was stirred at rt for 1h under argon atmosphere. Then, corresponding ketone (5.0 mmol) was added and the resulting solution was stirred at rt for 16 h. The reaction was quenched with sat. solution of $NH_4Cl$ (20 mL), extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The desired products were obtained after purification by FC over silica gel (*n*-pentane/EtOAc 10:1).

## Characterization Data

***4-(2-Phenyloxiran-2-yl)benzonitrile***

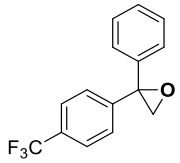



Chemical Formula: $C_{15}H_{11}NO$
Exact Mass: 221.0841

General Procedure **A** was followed with 4-benzoylbenzonitrile (1.04 g, 5.0 mmol), trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) in DMSO (10.0 mL). The reaction mixture was stirred at rt for 16 h. Purification by FC over silica gel (*n*-pentane/EtOAc, 10:1) afforded the desired product (326 mg, 59% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.63 (d, $J$ = 8.3 Hz, 2H), 7.45 (d, $J$ = 8.3 Hz, 2H), 7.40 – 7.32 (m, 5H), 3.40 (d, $J$ = 5.4 Hz, 1H), 3.20 (d, $J$ = 5.4 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.3, 138.0, 132.3, 128.8, 128.0, 127.9, 118.7, 112.0, 61.5, 57.0.

***2-Phenyl-2-(4-(trifluoromethyl)phenyl)oxirane***

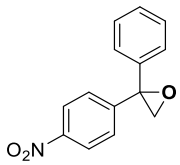


Chemical Formula: $C_{15}H_{11}F_3O$
Exact Mass: 264.0762

General Procedure **A** was followed with phenyl(4-(trifluoromethyl)phenyl)methanone (1.25 g, 5.0 mmol), trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) in DMSO (10.0 mL). The reaction mixture was stirred at rt for overnight. Purification by FC over silica gel (*n*-pentane/EtOAc, 10:1) afforded the desired product as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.34 (m, 5H), 3.38 (d, *J* = 5.4 Hz, 1H), 3.24 (d, *J* = 5.4 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 143.9 (d, *J* = 1.2 Hz), 138.6, 130.3 (q, *J* = 32.5 Hz), 128.7, 128.5, 127.8, 127.7, 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.1 Hz), 61.6, 56.9. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** *δ* -62.8.

***2-(4-Nitrophenyl)-2-phenyloxirane***

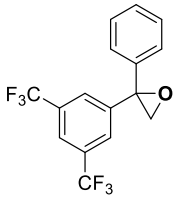


Chemical Formula: $C_{14}H_{11}NO_3$
Exact Mass: 241.0739

General Procedure **A** was followed with (4-nitrophenyl)(phenyl)methanone (1.14 g, 5.0 mmol), trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) in DMSO (10.0 mL). The reaction mixture was stirred at rt for overnight. Purification by FC over silica gel (*n*-pentane/EtOAc, 10:1) afforded the desired product (510 mg, 42% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** *δ* 8.19 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.44 – 7.31 (m, 5H), 3.43 (d, *J* = 5.4 Hz, 1H), 3.22 (d, *J* = 5.4 Hz, 1H).

***2-(3,5-Bis(trifluoromethyl)phenyl)-2-phenyloxirane***

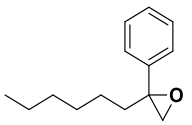



Chemical Formula: $C_{16}H_{10}F_6O$
Exact Mass: 332.0636

General Procedure **A** was followed with (3,5-bis(trifluoromethyl)phenyl) (phenyl)methanone (1.59 g, 5.0 mmol), trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) in DMSO (10.0 mL). The reaction mixture was stirred at rt for overnight. Purification by FC over silica gel (*n*-pentane/EtOAc, 10:1) afforded the desired product (199 mg, 12% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.75 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 1.7 Hz, 2H), 7.33 (dt, J = 4.7, 2.3 Hz, 3H), 7.28 (dt, J = 6.7, 2.2 Hz, 2H), 3.36 (d, J = 5.2 Hz, 1H), 3.14 (d, J = 5.3 Hz, 1H). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -62.8.

***2-Hexyl-2-phenyloxirane***

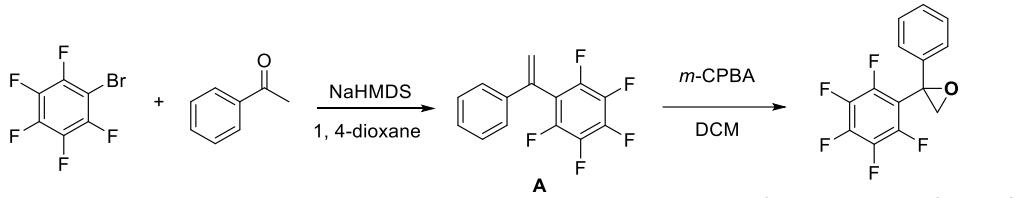



Chemical Formula: $C_{14}H_{20}O$
Exact Mass: 204.1514

General Procedure **A** was followed with 1-phenylheptan-1-one (0.95 g, 5.0 mmol), trimethylsulfoxoniumn iodide (1.45 g, 6.59 mmol) and sodium hydride (240 mg, 10 mmol) in DMSO (10.0 mL). The reaction mixture was stirred at rt for overnight. Purification by FC over silica gel (*n*-pentane/EtOAc, 10:1) afforded the desired product (405 mg, 40% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.31 (m, 4H), 7.29 – 7.24 (m, 1H), 2.95 (d, *J* = 5.4 Hz, 1H), 2.73 (d, *J* = 5.4 Hz, 1H), 2.17 (ddd, *J* = 15.1, 10.5, 4.8 Hz, 1H), 1.73 (ddd, *J* = 13.7, 10.0, 5.3 Hz, 1H), 1.45 – 1.18 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 140.4, 128.4, 127.5, 126.1, 60.6, 55.7, 35.7, 31.8, 29.5, 25.0, 22.7, 14.2.

***2-(Perfluorophenyl)-2-phenyloxirane***



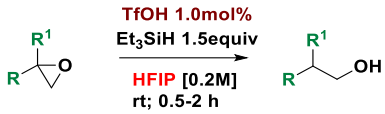

To a dry 50 mL round bottomed flask equipped with a magnetic stirring bar and under argon, a solution of α-bromostyrene (457.5 mg, 2.5 mmol), pentafluorobenzene (630 mg, 3.75 mmol, 1.5 equiv) and 1,10-phenanthroline (45 mg, 0.25 mmol, 10 mol%) in 15 mL dry DMF/xylenes (1/1) was added. Then, Copper(I) iodide (47.5 mg, 0.25 mmol) and $K_3PO_4$ (1.06 g, 5.0 mmol, 2.0 equiv.) was subsequently added and the mixture was stirred at 125 °C for 24 hours. Upon completion, the mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The resulting solution was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by FC over silica gel (*n*-pentane) to afford A (0.58 g, 2.15 mmol) as a colorless oil

The pure product A (0.58 g, 2.15 mmol) was dissolved in DCM (5 mL) and m-CPBA (0.8 g, >4.6 mmol) was added. The resulting mixture was stirred at rt for 16 h. Upon completion, the reaction mixture was quenched with a sat. solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel (*n*-pentane/EtOAc, 8:1) to furnish the desired products (153.7 mg, 25% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.34 – 7.15 (m, 5H), 3.30 (dt, *J* = 5.3, 1.1 Hz, 1H), 3.11 (d, *J* = 5.3 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 147.0 – 146.2 (m), 144.5, 142.8 – 142.3 (m), 140.6, 138.7 (dm, *J* = 14.1 Hz), 137.4 (dm, *J* = 8.0 Hz), 136.7 (q, *J* = 13.5, 12.7 Hz), 128.8, 128.7, 125.3, 113.7 (t, *J* = 16.8 Hz), 56.1, 54.2. **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** -144.52 to -144.52 to -144.66 (m), -154.58 (t, *J* = 20.2 Hz), -162.95 to -163.15 (m).

## Reductive Ring Opening of Epoxide

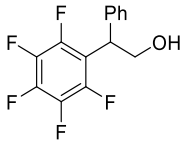
**General procedure B** for reductive ring opening of epoxide




Triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) and epoxide (0.2 mmol, 1.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.2 M) was added, and the solution was cool down to 0 °C for 5 min. Then, TfOH (1.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at rt for the indicated time (0.5-2 h). Upon completion, the reaction mixture was quenched with a sat. solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the desired products.

## Characterization Data

***2-(Perfluorophenyl)-2-phenylethan-1-ol 47***

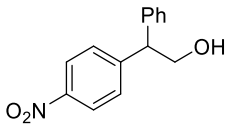



Chemical Formula: $C_{14}H_9F_5O$
Exact Mass: 288.0574

General Procedure **B** was followed with 2-(perfluorophenyl)-2-phenyloxirane (57.2 mg, 0.20 mmol) and triethylsilane (35.0 mg, 0.30 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min. Purification by FC over silica gel (*n*-pentane/EtOAc, 8:1) afforded **47** (53.0 mg, 92% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31–7.15 (m, 5H), 4.53 (t, $J$ = 8.0 Hz, 1H), 4.30–4.15 (m, 2H), 1.93 (t, $J$ = 5.4 Hz, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 145.4 (dm, $J$ = 244.4 Hz), 140.1 (dm, $J$ = 253.1 Hz), 138.2, 137.7 (dm, $J$ = 253.0 Hz), 129.0, 127.9 (t, $J$ = 1.4 Hz), 127.7, 115.3 (m), 63.6 (t, $J$ = 4.0 Hz), 44.4 (q, $J$ = 1.3 Hz). **$^{19}$F NMR (376.5 MHz, $CDCl_3$):** $\delta$ -141.6 (m), -156.08 (t, $J$ = 20.9 Hz), -161.9 (m). **HRMS (ESI):** *m/z* calcd. for $C_{14}H_9F_5ONa$ $[M+Na]^+$ 314.0466, found 314.0459.

*2-(4-Nitrophenyl)-2-phenylethan-1-ol 84*



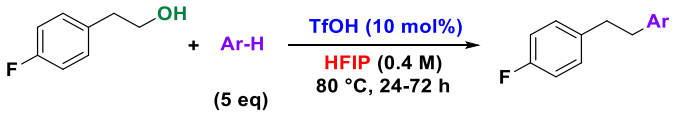

Chemical Formula: $C_{14}H_{13}NO_3$
Exact Mass: 243.0895

General Procedure **B** was followed with 2-(4-nitrophenyl)-2-phenyloxirane (48.2 mg, 0.20 mmol) and triethylsilane (35.0 mg, 0.30 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min. Purification by FC over silica gel (*n*-pentane/EtOAc, 8:1) afforded **84** (65.6 mg, 99% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 8.11 (d, $J$ = 8.8 Hz, 2H), 7.39 (d, $J$ = 8.8 Hz, 2H), 7.41–7.28 (m, 2H), 7.25–7.14 (m, 3H), 4.26 (t, $J$ = 7.0 Hz, 1H), 4.19–4.13 (m, 2H), 1.63–1.58 (m, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 149.4, 146.8, 140.0, 129.3, 129.1, 128.3, 127.5, 123.8, 65.6, 53.3. **HRMS (ESI):** *m/z* calcd. for $C_{14}H_{13}NO_3Na$ $[M+Na]^+$ 266.0788, found 266.0783.

**Monoarylation of Friedel-Crafts Arylation of Primary Aliphatic Alcohols**

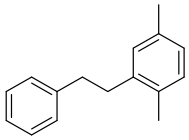
**General procedure C** to access (pentafluorophenyl)ethanol derivatives




Alcohol (1.0 eq) and nucleophile (5.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a teflon-coated magnetic stir. HFIP (1.0 mL, 0.4 M) and then TfOH (10 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at 80 °C for the indicated time. Upon completion, the reaction mixture was quenched with a sat. solution of $NaHCO_3$ and extracted with EtOAc (3 × 10mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the desired products. Regioisomeric ratios were calculated from $^1$H NMR spectra.

## Characterization Data of Monoalkylated Products

***1,4-Dimethyl-2-phenethylbenzene 208***

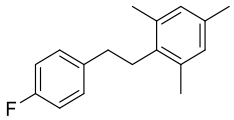


Chemical Formula: $C_{16}H_{18}$
Exact Mass: 210.1409

General procedure **C** was followed with 2-phenyl-1-ethanol (48.9 mg, 0.40 mmol) and *p*-xylene (0.25 mL, 2.0 mmol, 5.0 eq) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 48 h. Purification by FC over silica gel (*n*-pentane/EtOAc, 100:0 to 90:10, gradient) afforded **208** (78.4 mg, 94% yield) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.34–7.29 (m, 2H), 7.24–7.22 (m, 3H), 7.05 (d, $J$ = 7.6 Hz, 1H), 7.00 (s, 1H), 6.95 (dd, $J$ = 7.6, 1.9 Hz, 1H), 2.86 (s, 4H), 2.31 (s, 3H), 2.28 (s, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$):** $\delta$ 142.3, 140.0, 135.5, 132.9, 130.2, 129.7, 128.5 (2C), 126.9, 126.1, 37.0, 35.7, 21.1, 18.9. **HRMS (APPI):** *m/z* calcd. for $C_{16}H_{17}$ $[M-H]^+$ 209.1336, found 209.1327.

***2-(4-Fluorophenethyl)-1,3,5-trimethylbenzene 209***



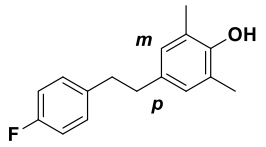
Chemical Formula: $C_{17}H_{19}F$
Exact Mass: 242,1471

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and mesitylene (279 µL, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **209** (82.0 mg, 85% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.20–7.16 (m, 2H), 7.02–6.97 (m, 2H), 6.87, (s, 2H), 2.86 (dd, $J$ = 10.4, 6.4 Hz, 2H), 2.72 (dd, $J$ = 10.4, 6.4 Hz, 2H), 2.31 (s, 6H), 2.28 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 161.5 (d, $J$ = 243.5 Hz), 138.0 (d, $J$ = 3.2 Hz), 136.1 (2C), 135.4, 135.3, 129.8 (d, $J$ = 7.6 Hz, 2CH), 129.1 (2CH), 115.3 (d, $J$ = 21.1 Hz, 2CH),

34.8, 32.0, 21.0, 19.8 ($2CH_3$). **$^{19}$F NMR (282 MHz, $CDCl_3$):** $\delta$ -117.6 (s, 1F). **HRMS (APPI):** *m/z* calcd. for $C_{17}H_{18}F$ $[M-H]^+$ 241.1387, found 241.1386.

***4-(4-Fluorophenethyl)-2,6-dimethylphenol 210***

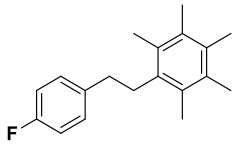



Chemical Formula: $C_{16}H_{17}FO$
Exact Mass: 244.1263

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 2,6-dimethylphenol (244.1 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **210** (91.8 mg, 94% yield, *m/p* 50:50) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.03 (ddd, *J* = 8.8, 5.5, 3.4 Hz, 2H, ***m***+***p***), 6.88 (ddd, *J* = 8.8, 5.6, 2.7 Hz, 2H, ***m***+***p***), 6.82 (d, *J* = 7.7 Hz, 0.5H, ***m***), 6.69 (s, 1H, ***p***), 6.56 (d, *J* = 7.6 Hz, 0.5H, ***m***), 4.53 (s, 0.5H, ***p***), 4.39 (s, 0.5H, ***m***), 2.72 (dddd, *J* = 26.6, 9.9, 7.0, 5.2 Hz, 4H, ***m***+***p***), 2.14 (s, 1.5H, ***m***), 2.13 (s, 3H, ***p***), 2.10 (s, 1.5H, ***m***).

***1-(4-Fluorophenethyl)-2,3,4,5,6-pentamethylbenzene 211***

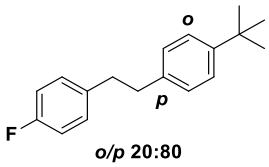



Chemical Formula: $C_{19}H_{23}F$
Exact Mass: 270.1784

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 2,6-dimethylphenol (296.3 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **211** (103.7 mg, 96% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.15 – 7.09 (m, 1H), 6.95 – 6.82 (m, 1H), 2.90 – 2.81 (m, 1H), 2.66– 2.57 (m, 1H), 2.20 (s, 3H), 2.16 (s, 2H), 2.15 (s, 4H).

***1-(Tert-butyl)-4-(4-fluorophenethyl)benzene 212***



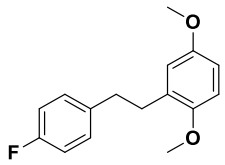

*o/p* 20:80

Chemical Formula: $C_{18}H_{21}F$
Exact Mass: 256.1627

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and *tert*-butylbenzene (268.2 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **212** (51.2 mg, 50% yield, *o/p* 20:80) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.23 (d, $J$ = 8.3 Hz, 2H), 7.18 (d, $J$ = 6.3 Hz, 2H), 7.04 – 6.98 (m, 2H), 6.88 – 6.84 (m, 2H), 2.80 (m, 4H), 1.20 (s, 9H).

***2-(4-Fluorophenethyl)-1,4-dimethoxybenzene 213***

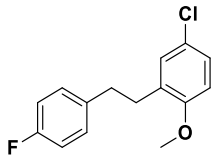



Chemical Formula: $C_{16}H_{17}FO_2$
Exact Mass: 260.1213

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 1,4-dimethoxybenzene (276.3 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **213** (57.2 mg, 55% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.06 (ddd, $J$ = 9.5, 5.8, 3.0 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.70 (s, 1H), 6.64 (d, $J$ = 3.1 Hz, 1H), 6.58 (d, $J$ = 3.0 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.77 (m, 4H).

***4-Chloro-2-(4-fluorophenethyl)-1-methoxybenzene 214***

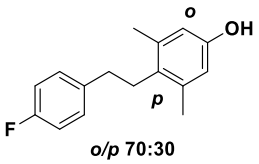



Chemical Formula: $C_{15}H_{14}ClFO$
Exact Mass: 264.0717

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 1-chloro-4-methoxybenzene (284.0 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **214** (38.1 mg, 36% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.05 (ddd, $J$ = 11.3, 5.6, 2.4 Hz, 2H), 6.96 (d, $J$ = 2.6 Hz, 1H), 6.93 – 6.83 (m, 3H), 6.68 (d, $J$ = 8.7 Hz, 1H), 3.71 (s, 3H), 2.76 (s, 4H).

***4-(4-Fluorophenethyl)-3,5-dimethylphenol 215***

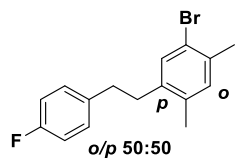



***o/p* 70:30**
Chemical Formula: $C_{16}H_{17}FO$
Exact Mass: 244.1263

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 1- 3,5-dimethylphenol (244.1 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **215** (88.9 mg, 91% yield, *o/p* 70:30) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer)**: $\delta$ 7.09 – 7.01 (m, 2H), 6.94 – 6.85 (m, 2H), 6.44 (s, 2H), 4.40 (s, 1H), 2.78 – 2.69 (m, 2H), 2.65 – 2.57 (m, 2H), 2.17 (s, 6H).

***1-Bromo-5-(4-fluorophenethyl)-2,4-dimethylbenzene 216***

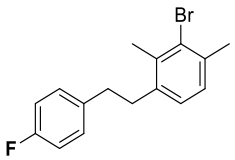



***o/p* 50:50**
Chemical Formula: $C_{16}H_{16}BrF$
Exact Mass: 306.0419

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 1- 1-bromo-2,4-dimethylbenzene (368.0 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **216** (61.2 mg, 50% yield, *o/p* 50:50) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 7.25 (d, $J$ = 8.1 Hz, 0.5H, ***o***), 7.19 (s, 0.5H, ***p***), 7.04 (dddd, $J$ = 14.7, 8.4, 5.4, 2.5 Hz, 2H, ***o***+***p***), 6.94 – 6.87 (m, 2.5H, ***o***+***p***), 6.79 (d, $J$ = 8.2 Hz, 0.5H, ***o***), 2.91 – 2.82 (m, 1H, ***o***), 2.71 (d, $J$ = 2.6 Hz, 2H, ***p***), 2.67 – 2.58 (m, 1H, ***o***), 2.34 (s, 1.5H), 2.25 (s, 1.5H), 2.16 (s, 1.5H), 2.09 (s, 1.5H).

***2-Bromo-5-(4-fluorophenethyl)-1,3-dimethylbenzene 217***

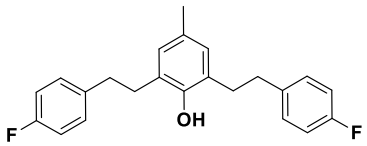



Chemical Formula: $C_{16}H_{16}BrF$
Exact Mass: 306.0419

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.40 mmol) and 1- 2-bromo-1,3-dimethylbenzene (368.0 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **217** (79.6 mg, 65% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.06 – 6.98 (m, 2H), 6.94 – 6.76 (m, 4H), 2.87 – 2.76 (m, 2H), 2.72 (dd, $J$ = 10.1, 6.2 Hz, 2H), 2.33 (s, 3H), 2.32 (s, 3H).

***2,6-Bis(4-fluorophenethyl)-4-methylphenol 219***



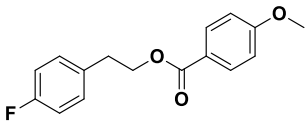

Chemical Formula: $C_{23}H_{22}F_2O$
Exact Mass: 352.1639

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.4 mmol) and *p*-cresol (216.1 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h.

Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **219** (28.2 mg, 20% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.10 – 7.00 (m, 4H), 6.96 – 6.84 (m, 4H), 6.69 (s, 2H), 3.99 (s, 1H), 2.84 – 2.64 (m, 8H), 2.15 (s, 3H).

***4-Fluorophenethyl 4-methoxybenzoate 220***



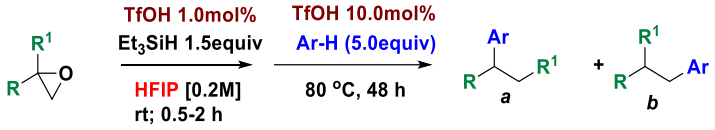

Chemical Formula: $C_{16}H_{15}FO_3$
Exact Mass: 274.1005

General procedure **C** was followed with 2-(4-fluorophenyl)-1-ethanol (50.1 µL, 0.4 mmol) and 1-methyl 4-methoxybenzoate (332.1 mg, 2.0 mmol, 5.0 equiv) or ethyl 4-methoxybenzoate (360.1 mg, 2.0 mmol, 5.0 equiv) in the presence of TfOH (3.6 µL, 0.040 mmol, 10 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at 80 °C for 24 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **220** (107.5 mg, 98% yield) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.92 – 7.84 (m, 2H), 7.20 – 7.11 (m, 2H), 6.99 – 6.89 (m, 2H), 6.88 – 6.79 (m, 2H), 4.40 (t, $J$ = 6.9 Hz, 2H), 3.78 (s, 3H), 2.96 (t, $J$ = 6.9 Hz, 2H).

## One-pot epoxide ring-opening and Friedel-Crafts alkylation

**General Procedures D** for one-pot epoxide ring-opening and Friedel-Crafts alkylation

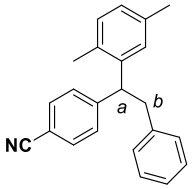



Triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) and epoxide (0.2 mmol, 1.0 eq) were charged (in air) in a 10 mL screw-cap vial equipped with a Teflon-coated magnetic stir. HFIP (1.0 mL, 0.2 M) was added, and the solution was cool down to 0 °C for 5 min. Then, TfOH (1.0 mol%) were added, and the glass tube was sealed. The reaction mixture was stirred at rt (22-26 °C) for the indicated time (0.5-2 h) until completion of first step. Then, the nucleophile (5.0 equiv) and TfOH (10.0 mol%) were added and the reaction mixture was heated at 80°C for 48 h. Upon completion, the reaction mixture was quenched with a sat.

solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the desired products. Regioisomeric ratios were calculated from $^1$H NMR spectra.

**Characterization Data**

***4-(1-(2,5-Dimethylphenyl)-2-phenylethyl)benzonitrile 221***

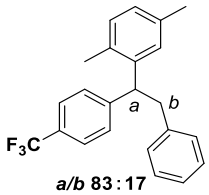



***a/b* 77:23**
Chemical Formula: $C_{23}H_{21}N$
Exact Mass: 311.1674

General procedure **D** was followed with 4-(2-phenyloxiran-2-yl)benzonitrile (44.2 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **221** (57.9 mg, 93% yield, *a/b* 77:23) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.54 – 7.46 (m, 2H), 7.25 – 7.19 (m, 4H), 7.17 – 7.13 (m, 2H), 7.02 – 6.92 (m, 4H), 4.42 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.49 – 3.33 (m, 1H), 3.27 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.39 (s, 3H), 2.08 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 149.5, 141.0, 139.5, 135.7, 133.1, 132.0, 130.6, 129.9, 129.2, 129.1, 128.3, 127.5, 126.3, 119.0, 109.9, 49.1, 42.2, 21.3, 19.3.

***1,4-Dimethyl-2-(2-phenyl-1-(4-(trifluoromethyl)phenyl)ethyl)benzene 222***

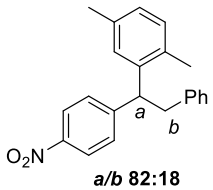



***a/b* 83 : 17**
Chemical Formula: $C_{23}H_{21}F_3$
Exact Mass: 354.1595

General procedure **D** was followed with 2-phenyl-2-(4-(trifluoromethyl)phenyl)oxirane (52.8 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **222** (46.1 mg, 65% yield, *a/b* 83:17) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer)**: $\delta$ 7.36 (d, $J$ = 8.3 Hz, 2H), 7.16 – 7.05 (m, 6H), 6.88 (td, $J$ = 5.7, 2.7 Hz, 4H), 4.34 (dd, $J$ = 8.9, 6.5 Hz, 1H), 3.29 (dd, $J$ = 13.4, 6.5 Hz, 1H), 3.19 (dd, $J$ = 13.4, 8.9 Hz, 1H), 2.27 (s, 3H), 1.98 (s, 3H). **$^{13}$C NMR (101 MHz, $CDCl_3$, major isomer):** $\delta$ 148.0 (d, $J$ = 1.5 Hz), 141.5, 139.8, 135.6, 133.1, 130.5(q, $J$ = 32.5 Hz), 129.3, 129.1, 128.7, 128.2, 127.5, 127.3, 126.2, 125.1 (q, $J$ = 3.8 Hz), 124.2 (q, $J$ = 272.1 Hz), 48.7, 42.3, 21.3, 19.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -62.8.

***1,4-Dimethyl-2-(2-(4-nitrophenyl)-2-phenylethyl)benzene 176***



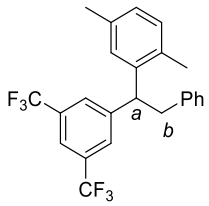

***a/b* 82:18**
Chemical Formula: $C_{22}H_{21}NO_2$
Exact Mass: 331.1572

General procedure **D** was followed with 2-(4-nitrophenyl)-2-phenyloxirane (48.2 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **176** (62.3 mg, 94% yield, *a/b* 82:18) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 8.05 (d, $J$ = 8.8 Hz, 2H), 7.26–7.15 (m, 5H), 7.11–7.07 (m, 1H), 7.02–6.90 (m, 4H), 4.46 (dd, $J$ = 9.4, 6.0 Hz, 1H), 3.45–3.38 (m, 1H), 3.28 (dd, $J$ = 13.4, 9.4 Hz, 1H), 2.37 (s, 3H), 2.07 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 151.7, 146.3, 140.9, 139.3, 135.8, 133.1, 130.7, 129.2, 129.0,

128.3, 127.6, 127.5, 126.4, 123.4, 49.0, 42.2, 21.3, 19.3. **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{21}NO_2Na$ $[M+Na]^+$ 354.1465, found 354.1460.

***2-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-phenylethyl)-1,4-dimethylbenzene 175***

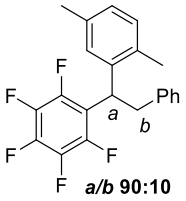



***a/b* 82:18**
Chemical Formula: $C_{24}H_{20}F_6$
Exact Mass: 422.1469

General procedure **D** was followed with 2-(3,5-bis(trifluoromethyl)phenyl)-2-phenyloxirane (66.4 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **175** (78.5 mg, 93% yield, *a/b* 82:18) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$, major isomer):** $\delta$ 7.69 (s, 1H), 7.45 (d, $J$ = 1.6 Hz, 2H), 7.26–7.19 (m, 5H), 7.11–7.00 (s, 1H), 6.97–6.92 (m, 2H), 4.49 (dd, $J$ = 9.2, 6.2 Hz, 1H), 3.44 (dd, $J$ = 13.4, 6.2 Hz, 1H), 3.26 (dd, $J$ = 13.4, 9.2 Hz, 1H), 2.41 (s, 3H), 2.08 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$, major isomer):** $\delta$ 146.5, 140.3, 139.0, 135.9, 133.0, 131.2 (q, $J$ = 33.0 Hz), 130.7, 129.0, 128.5 (m), 128.4, 127.7, 127.4, 126.5, 123.4 (q, $J$ = 272.8 Hz), 120.2 (p, $J$ = 3.9 Hz), 48.9, 42.3, 21.3, 19.3. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -62.8. **HRMS (ESI):** *m/z* calcd. for $C_{28}H_{28}F_6Na$ $[M+Na]^+$ 501.1987, found 501.1980.

***1-(2-(2,5-Dimethylphenyl)-1-phenylethyl)-2,3,4,5,6-pentafluorobenzene 169***

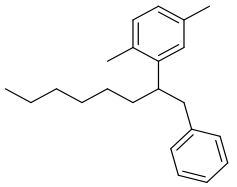



***a/b* 90:10**
Chemical Formula: $C_{22}H_{17}F_5$
Exact Mass: 376.1250

General procedure **D** was followed with 2-(perfluorophenyl)-2-phenyloxirane (57.2 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at 80 °C for 48 h. Purification by FC over silica gel (PE/EtOAc, 100:0 to 90:10, gradient) afforded **169** (62.4 mg, 83% yield, *a/b* 90:10) as a colorless oil.

**$^{1}$H NMR (500 MHz, $CDCl_3$, major isomer):** $\delta$ 7.37 (s, 1H), 7.27–7.16 (m, 3H), 7.09–7.05 (m, 2H), 7.04–6.98 (m, 2H), 4.74 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.48 (dd, *J* = 13.5, 10.2 Hz, 1H), 3.41 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 3H). **$^{13}$C NMR (125 MHz, $CDCl_3$, major isomer):** $\delta$ 145.3 (dm, *J* = 246.3 Hz), 139.7 (dm, *J* = 252.4 Hz), 137.4 (dm, *J* = 251.6 Hz), 139.1, 138.8, 135.8, 133.0, 130.5, 128.6, 128.4, 128.0 (t, *J* = 3.1 Hz), 127.9, 126.6, 116.6 (m), 39.7, 39.5, 21.3, 18.9. **$^{19}$F NMR (376.5 MHz, $CDCl_3$, major isomer):** $\delta$ -140.7 (dd, *J* = 22.6, 7.5 Hz), -156.7 (t, *J* = 21.0 Hz), -162.4 (td, *J* = 22.2, 7.5 Hz). **HRMS (ESI):** *m/z* calcd. for $C_{22}H_{17}F_5Na$ $[M+Na]^+$ 399.1143, found 399.1139.

***1,4-Dimethyl-2-(1-phenyloctan-2-yl)benzene 223***



Chemical Formula: $C_{22}H_{30}$
Exact Mass: 294.2348

General procedure **D** was followed with 2-hexyl-2-phenyloxirane (40.8 mg, 0.2 mmol) and triethylsilane (35.0 mg, 0.3 mmol, 1.5 eq) in the presence of TfOH (0.18 µL, 0.002 mmol, 1.0 mol%) in HFIP (1.0 mL). The reaction mixture was stirred at rt for 30 min and, then, *p*-xylene (0.12 mL, 1.0 mmol, 5.0 eq) and TfOH (1.8 µL, 0.020 mmol, 10.0 mol%) were added to the reaction mixture which was stirred at rt for 48 h. Purification by FC over silica gel (Petroleum Ether/EtOAc, 100:0 to 90:10, gradient) afforded **223** (34.7 mg, 83% yield) as a colorless oil.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.23 (t, J = 7.4 Hz, 2H), 7.18 (d, J = 7.1 Hz, 1H), 7.04 - 7.10 (m, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.91 (d, J = 7.8 Hz, 1H), 3.11 (p, J = 7.4 Hz, 1H), 2.83 (d, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 2.09 (s, 3H), 1.67 (p, *J* = 7.7, 7.0 Hz, 2H), 0.86 (t, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 143.52, 141.12, 135.25, 133.03, 129.85,

129.16, 128.01, 126.59, 125.70, 43.88, 42.29, 35.26, 31.77, 29.54, 27.49, 22.68, 21.32, 19.33, 14.12.

Université de Strasbourg

**Shaofei ZHANG**

EDSC École Doctorale des Sciences Chimiques

# Reactivity of Alcohols and Epoxides by Brønsted Acid Catalysis in Hexafluoroisopropanol (HFIP)

## Résumé

Les époxydes et les alcools primaires sont des briques moléculaires importantes pour la synthèse organique. Des stratégies efficaces pour l'ouverture de cycle régiosélective des époxydes et pour la substitution déshydratante directe des alcools primaires sont souhaitables car elles peuvent produire des composés précieux avec une économie d'atomes et d'étapes élevée. Cette thèse décrit une nouvelle stratégie pour la mono- et bis-arylation d'époxydes porteurs de groupes électroattracteurs puissants et pour l'arylation directe de Friedel-Crafts déshydratante d'alcools primaires avec le système TfOH/HFIP. Cette méthode ouvre un accès direct aux ions phénonium des phényléthanols sans étapes de pré-activation, qui devraient aller au-delà de la réaction de Friedel-Crafts, permettant de développer de nouvelles transformations ioniques. Divers alcools primaires précieux ont été préparés avec succès à partir d'époxyde, et il peut subir la réaction de Friedel-Crafts pour accéder aux composés arylés dans un pot en présence de TfOH avec l'aide de HFIP. HFIP joue un rôle important dans la synthèse organique en raison de ses propriétés uniques. La catalyse acide de Lewis ou Brønsted assistée par acide-Brønsted ou la catalyse acide cachée de Brønsted peuvent souvent être opérationnelles en présence de HFIP. Cette thèse a également réexaminé diverses réactions catalysées par un acide boronique, en particulier celles impliquant HFIP et l'activation d'alcools (réactions de Friedel-Crafts, transposition allylique, cyclisation déshydratante) ou d'oximes (réarrangement de Beckmann). Ces études ont révélé qu'une catalyse acide de Brønsted cachée est probablement impliqués dans la plupart des cas.

Mots clés : Epoxydes, alcools primaires, TfOH, HFIP, arylation de Friedel-Crafts, ions phénonium, catalyse acide boronique, catalyse acide de Brønsted cachée

## Abstract

Epoxides and primary alcohols are important building blocks for organic synthesis. Efficient strategies for the regioselective ring-opening of epoxides and for the direct dehydrative substitution of primary alcohols are desirable as they can produce valuable compounds with high atom- and step-economy. This thesis describes a new strategy for the mono- and bis-arylation of epoxides which bearing strong electron-withdrawing groups and to the direct dehydrative Friedel-Crafts arylation of primary alcohols with the TfOH/HFIP system. This method opens direct access to phenonium ions from phenyl ethanols without pre-activation steps, which should reach beyond the Friedel-Crafts reaction, allowing new ionic transformations to be developed. Various valuable primary alcohols were prepared from epoxide successfully, and it can undergo the Friedel-Crafts reaction to access the arylated compounds in one pot in the presence of TfOH with assistance from HFIP. HFIP play an important role in organic synthesis owing to the unique properties of its. Lewis- or Brønsted acid-assisted-Brønsted acid catalysis or hidden Brønsted acid catalysis may often be operative in the presence of HFIP. This thesis also re-examination of various published boronic acid catalyzed reactions, particularly those involving HFIP and the activation of alcohols (Friedel-Crafts reactions, allylic transposition, dehydrative cyclization) or oximes (Beckmann rearrangement), revealed that hidden Brønsted acid catalysis is likely involved in most cases.

Keywords: Epoxides, primary alcohols, TfOH, HFIP, Friedel-Crafts arylation, phenonium ions, boronic acid catalysis, hidden Brønsted acid catalysis