Fluorinated Aryl Boronates as Units in Organic Synthesis

Dissertation zur Erlangung des naturwissenschaftlichen Doktorgrades

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谨此献给我的家人

Für meine Familie

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List of Publications

The publications listed below are reproduced in this dissertation with permission from American Chemical Society and Wiley-VCH. The table itemizes at which position in this work the paper has been reproduced.

Publication	**Position**
Z. Liu, Y. P. Budiman, Y. M. Tian, A. Friedrich, M. Huang, S. A. Westcott, U. Radius, T. B. Marder, *Chem. Eur. J.* **2020**, *26*, 17267–17274.	Chapter 2
Z. Liu, G. K. Kole, Y. P. Budiman, Y. M. Tian, A. Friedrich, X. Luo, S. A. Westcott, U. Radius, T. B. Marder, *Angew. Chem. Int. Ed.* **2021**, *60*, 16529-16538.	Chapter 3
Z. Liu, Y.-M. Tian, G. K. Kole, Y. P. Budiman, A. Friedrich, S. A. Westcott, U. Radius, T. B. Marder, submitted	Chapter 4

List of Abbreviations

aq	Aqueous
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
B_2pin_2	Bis(pinacolato)diboron
bpy	2,2′-Bipyridine
cod	1,5-Cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
dan	1,8-Diaminonaphthalene
dba	Dibenzylideneacetone
DCM	Dichloromethane
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl

EtOAc	Ethyl acetate
equiv	Equivalents
GC-MS	Gas chromatography-mass spectrometry
HRMS	High-resolution mass spectrometry
ICy	1,3-Dicyclohexylimidazol-2-ylidene
IMes	1,3-Dimesitylimidazol-2-ylidene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
Phen	1,10-Phenanthroline
MeCN	Acetonitrile
MTBE	Methyl *tert*-butyl ether
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
rt	Room temperature
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Table of Contents

Chapter 1

Introduction

1 Introduction

Polyfluoroarenes exhibit significantly different properties compared to the parent nonfluorinated molecules and appear in numerous natural products, agrochemicals, pharmaceuticals, organic materials, etc.[1] and the number of such fluorinated compounds is rapidly growing.[2] For example, the oral diabetes drug Januvia, and extensively used pyrethroid insecticides,[3] all include polyfluoroaryl building blocks (Figure 1-1).

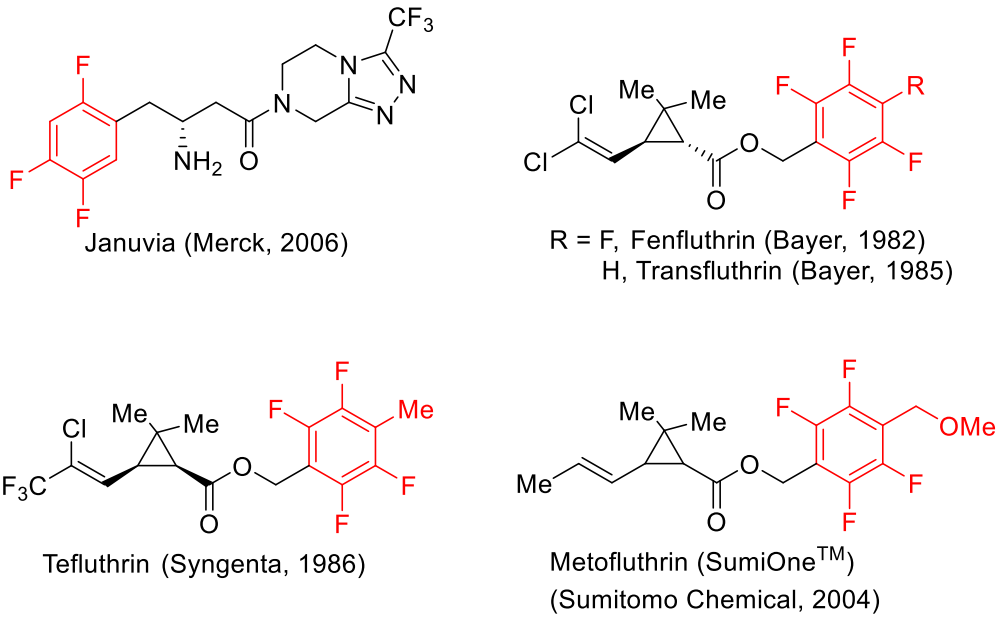


Figure 1-1. Januvia and pyrethroid insecticides including polyfluoroaryl units.

Ezetimibe (Figure 1-2) is the first class of new compounds that inhibit the absorption of bile in the small intestine and cholesterol in the diet. Basilea Pharmaceutica, which is a spin-off from Roche, discovered Isavuconazole (BAL-4815, RO-0094815, Figure 1-2), which can potentially be used to treat serious invasive and life-threatening fungal infections by disrupting the structure and function of fungal membranes. In 2002, Pfizer (Vfend) first developed Voriconazole (Figure 1-2), which was used for the therapy of fungal infections in patients unsuitable for other treatments and for the treatment of invasive aspergillosis.

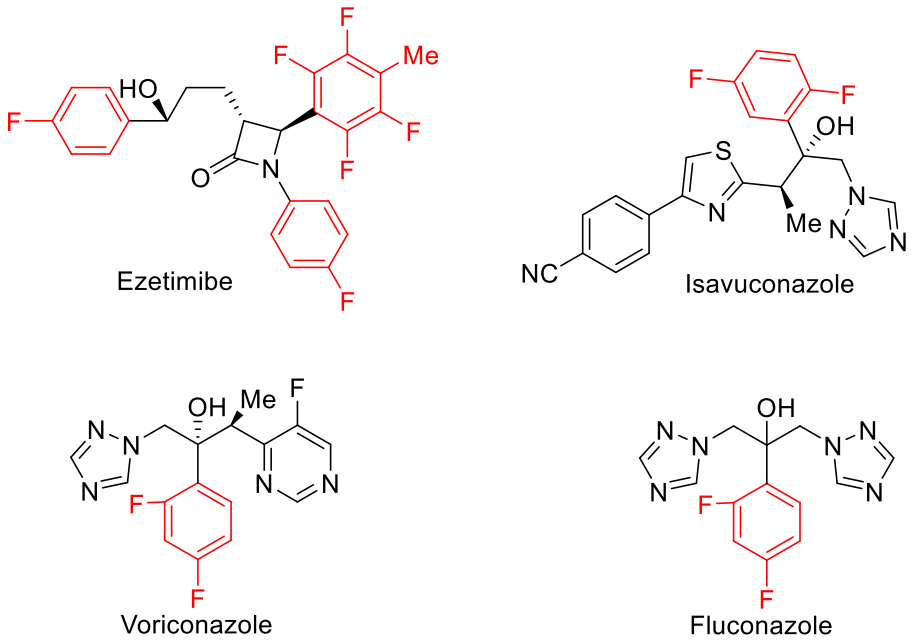


Figure 1-2. Fluoroarene-containing drugs: Ezetimibe, Isavuconazole, Voriconazole and Fluconazole.[2a]

Thus, exploring different methodologies for the introduction of fluorinated units into target compounds is highly desirable. One prospective method that has emerged recently is the generation of functionalized fluorine-containing boronate compounds, which can be coupled or added to substrates and the boryl group can be transformed into various functional groups (Figure 1-3). For example, fluorinated aryl boronates can be used in Suzuki-Miyaura cross-coupling reactions, which afford fluorinated biaryl compounds. Fluorinated aryl boronates are also used in other cross-coupling reactions such as Chan-Evans-Lam aminations, and Sonogashira alkynylation can also generate fluorinated organic compounds.[4]

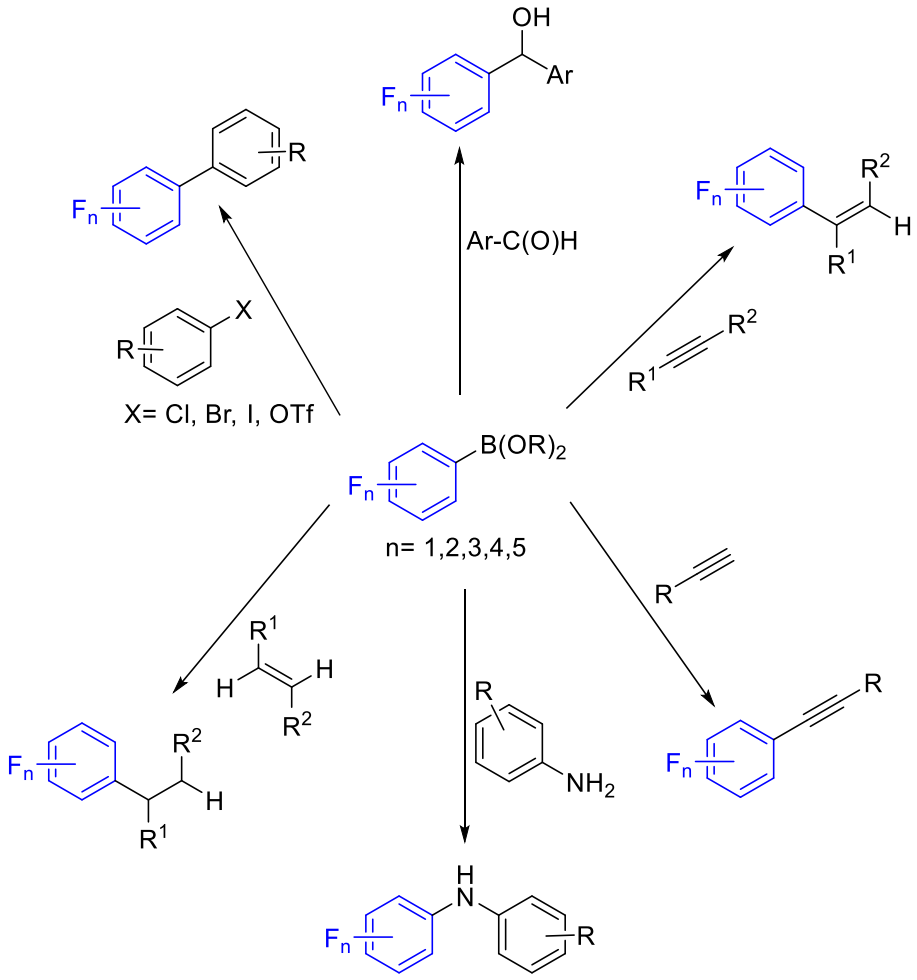
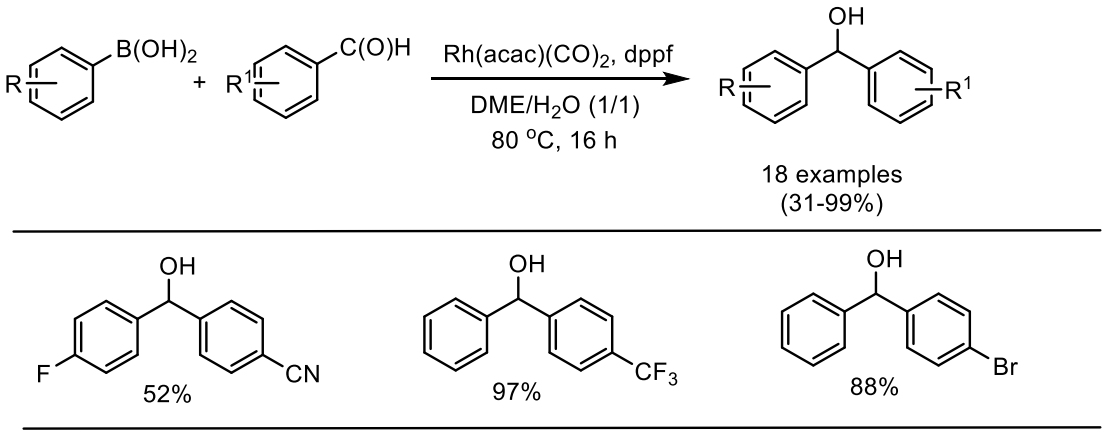


Figure 1-3. Applications of fluorinated aryl boronates.

1.1 Addition Reactions of Fluorinated Aryl Boronates

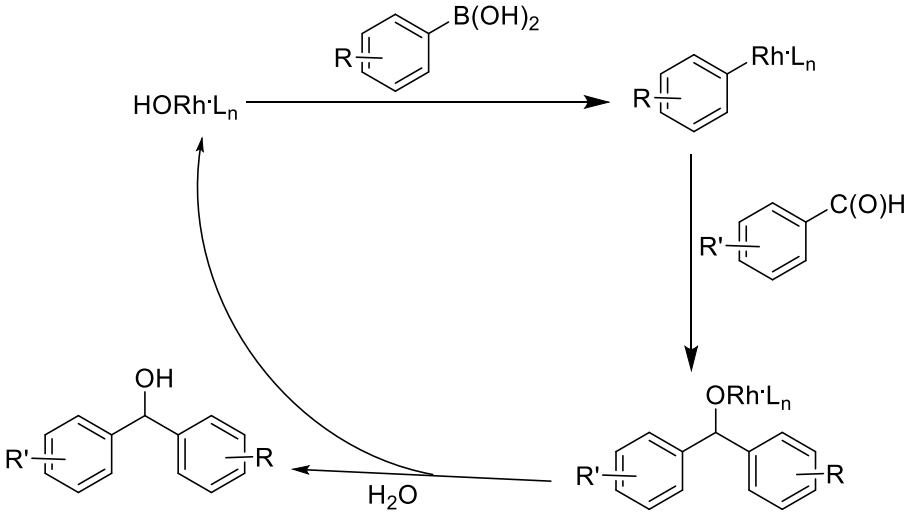
1.1.1 Addition of Fluorinated Aryl Boronates to Carbonyls

Efficient transition metal-catalyzed 1,2-additions of organometallic compounds to carbonyl groups for constructing alcohols have gained enormous attention in the past few decades.[5] Specifically, organoboronates have great advantages such as low toxicity, good functional group tolerance, and they are readily available.[6] In 1998, Miyaura *et al.*[7] first disclosed a Rh-catalyzed addition of arylboronic acids to aldehydes (Scheme 1-1). The reaction was tolerant to arylboronic acids containing electron-rich or electron-poor moieties, giving modest to excellent yields.



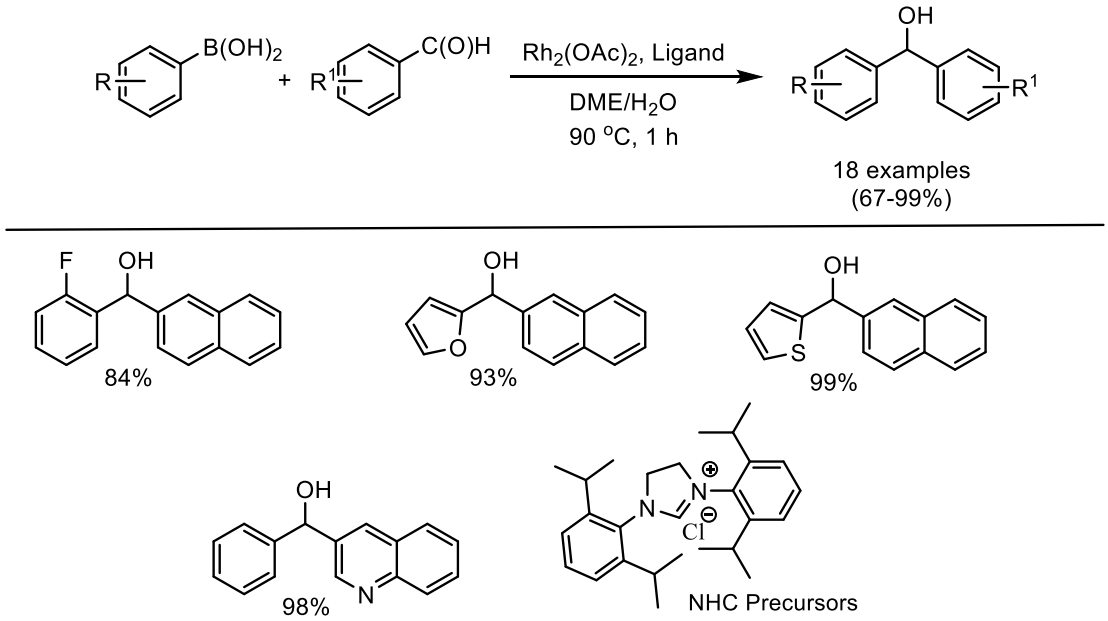
Scheme 1-1. Rh-catalyzed addition of boronic acids to aldehydes.

A proposed mechanism for this reaction is displayed in Scheme 1-2. First, the arylboronic acid and an RO-Rh complex undergo transmetalation to generate Ar-Rh intermediates and then insertion of aldehydes gives alcoholate intermediates, which are hydrolyzed giving the product.



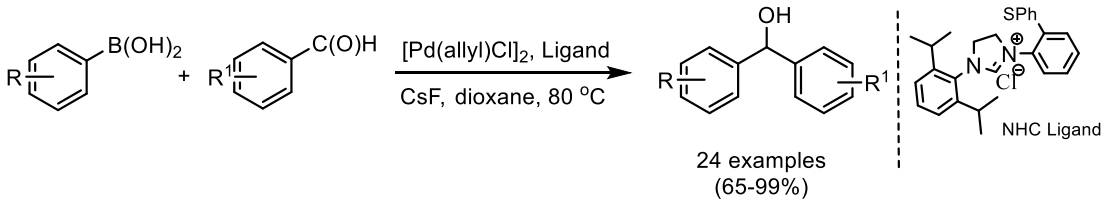
Scheme 1-2. Proposed mechanism for the Rh-catalyzed addition of boronic acids to aldehydes.

In subsequent studies, Gois *et al*.[8] disclosed a novel catalytic system for the addition of boronic acids to aldehydes, employing dirhodium(II) complexes as catalyst precursors and NHC as the ligand (Scheme 1-3). This reaction provided a new reaction mode using dirhodium(II) dimers, which may involve transmetalation between the aryl boronic acid and a dirhodium(II) complex.



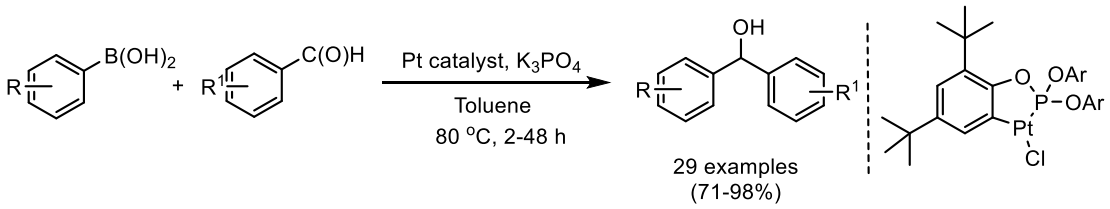
Scheme 1-3. Dirhodium(II)-catalyzed addition of boronic acids to aldehydes.

In 2008, Shirai *et al*.[9] reported an efficient Pd/thioether-imidazolinium chloride system, which promoted the addition of aryl-, heteroaryl-, alkenylboronic acids to aromatic, heteroaromatic, and aliphatic aldehydes (Scheme 1-4).



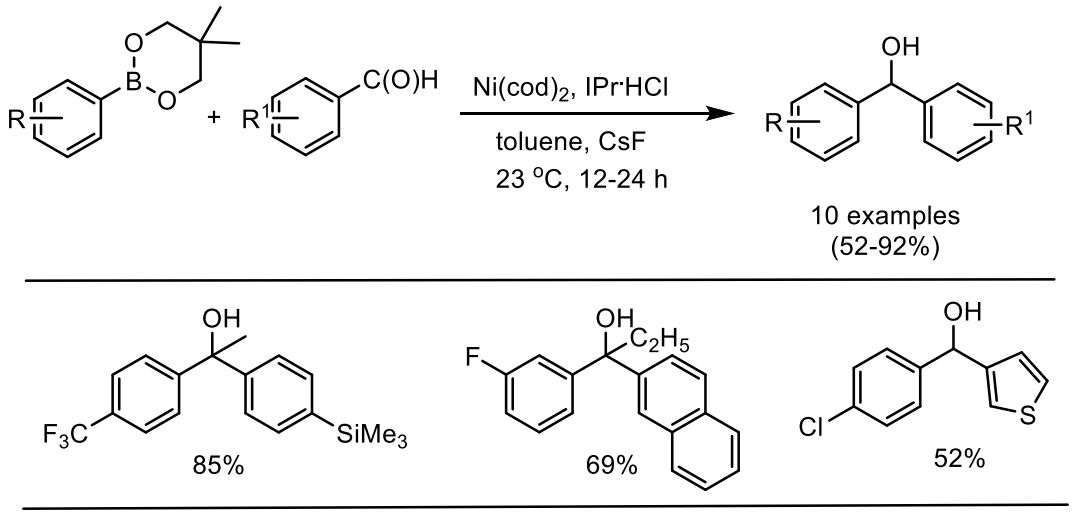
Scheme 1-4. Pd-catalyzed addition of boronic acids to aldehydes.

In 2008, Hu *et al*.[10] introduced an air and moisture-stable *ortho*-platinated triarylphosphite catalyst for the addition of arylboronic acids to aldehydes, with unprecedentedly low catalyst loading (Scheme 1-5). In addition, this catalyst is also efficient for a tandem sequence for the reaction of arylboronic acids and *α,β*-unsaturated aldehydes.



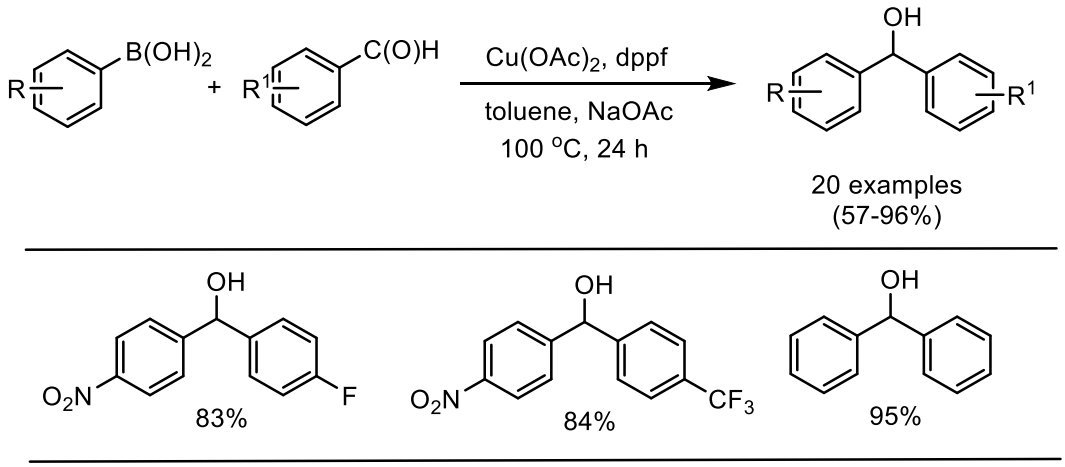
Scheme 1-5. Pt-catalyzed addition of boronic acids to aldehydes.

In 2009, Itami *et al.*[11] described an efficient $Ni(cod)_2$/IPr·HCl-catalyzed addition of neopentylboronate esters to ketones and aldehydes under remarkably mild conditions (Scheme 1-6).



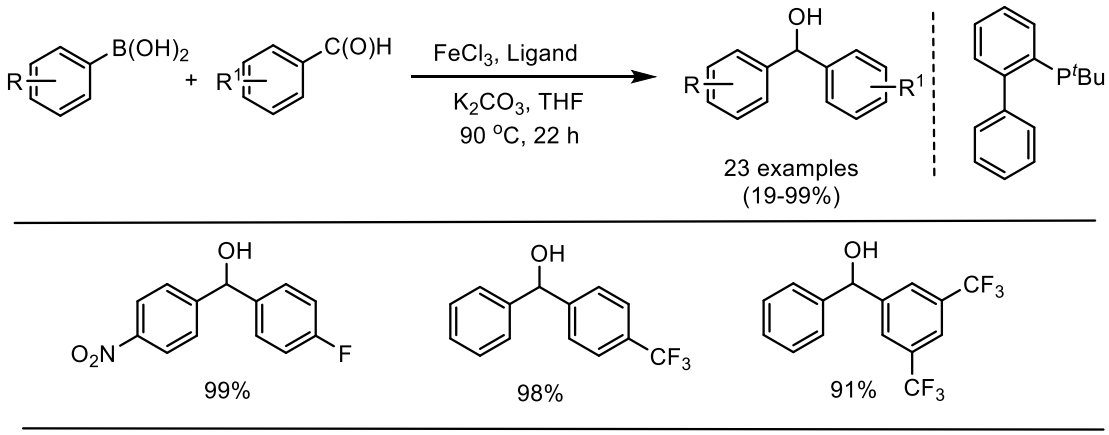
Scheme 1-6. Ni-catalyzed addition of Ar-Bneop to aldehydes.

In 2009, Wu *et al.*[12] reported a novel approach to generate alcohols, employing $Cu(OAc)_2$ and dppf as the ligand (dppf = 1,1'-bis(diphenylphosphino)ferrocene) in air (Scheme 1-7). Reactions of various aldehydes with arylboronic acids gave moderate to good yields.



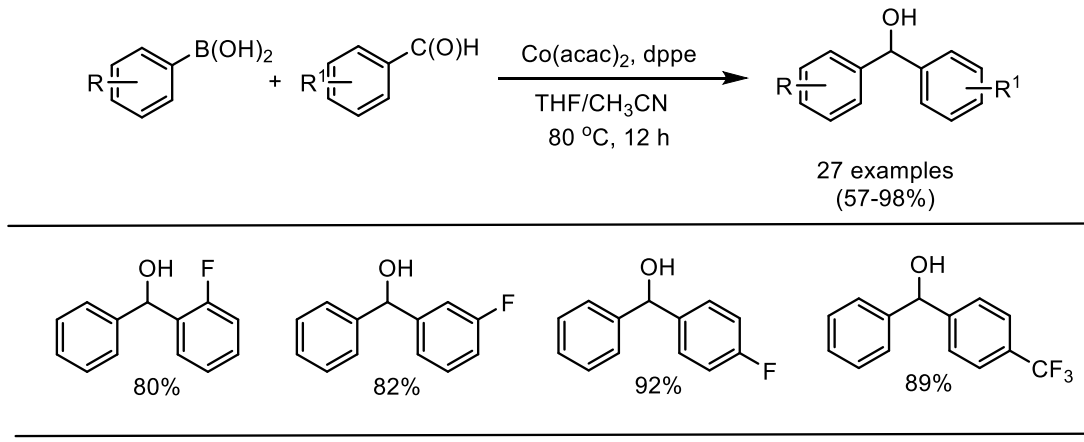
Scheme 1-7. Cu-catalyzed addition of boronic acids to aldehydes.

In 2009, Li *et al.*[13] described the $FeCl_3$ and 2-(di-tert-butylphosphino)biphenyl-promoted addition of arylboronic acids to aryl aldehydes (Scheme 1-8). Various electron-poor aryl aldehydes are suitable affording moderate to excellent yields. Electronic effects of the functional groups in both the arylaldehydes and arylboronic acids effect the yield of this reaction.



Scheme 1-8. Fe-catalyzed addition of boronic acids to aldehydes.

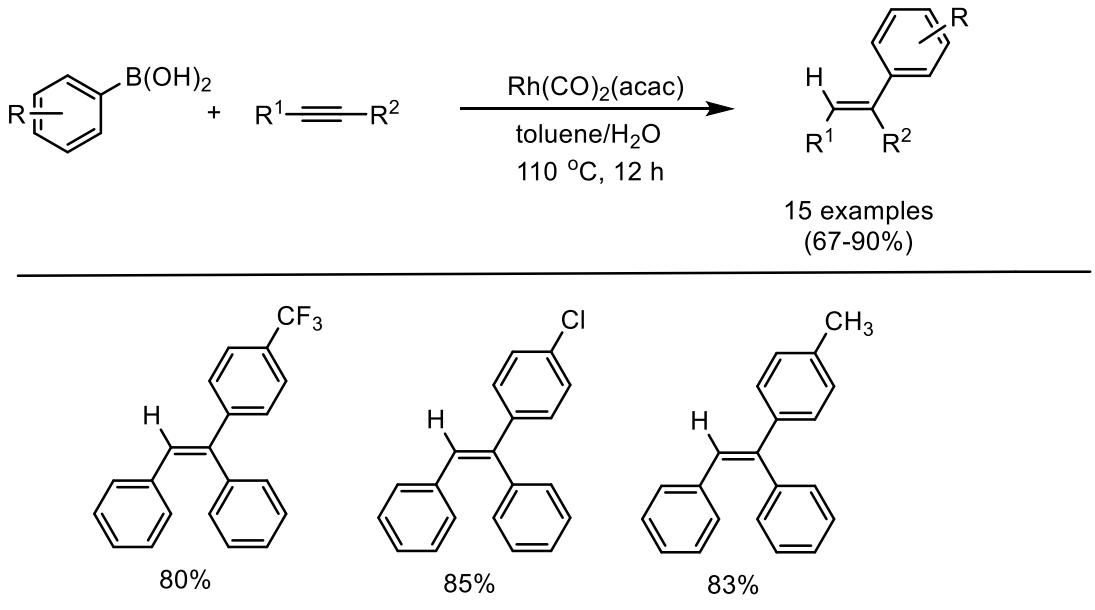
In 2010, Cheng *et al.*[14] demonstrated a Co-catalyzed addition of organoboronic acids to aldehydes, generating secondary alcohols in excellent yields (Scheme 1-9). Inexpensive CoI_2 and the commercially available chiral ligand (*R,R*)-BDPP generated chiral products, and numerous organoboronic acids and aldehydes are suitable substrates.



Scheme 1-9. Co-catalyzed addition of boronic acids to aldehydes.

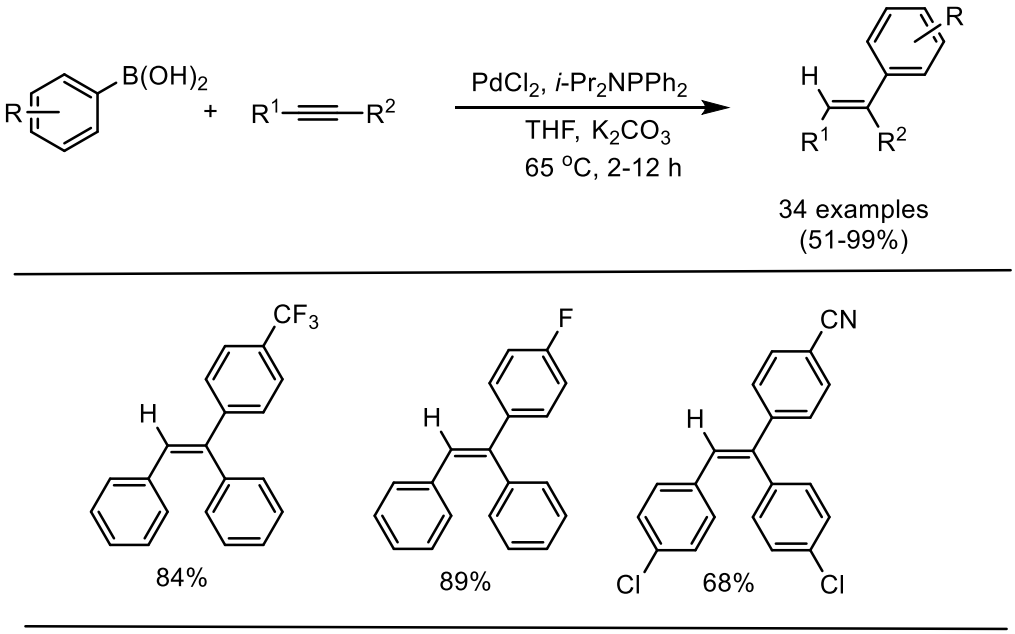
1.1.2 Addition of Fluorinated Aryl Boronates to Terminal Alkynes

Much effort has recently been spent on the catalytic hydroarylation of internal alkynes as to it provides quick access to highly functionalized alkenes.[15] In that regard, metal-catalyzed additions of arylboronic acids to alkynes has attracted attention.[16] In 2008, Cheng *et al.*[17] developed the hydroarylation of diaryl alkynes with boronic acids to synthesize triaryl-substituted ethene derivatives, using a rhodium catalyst (Scheme 1-10).



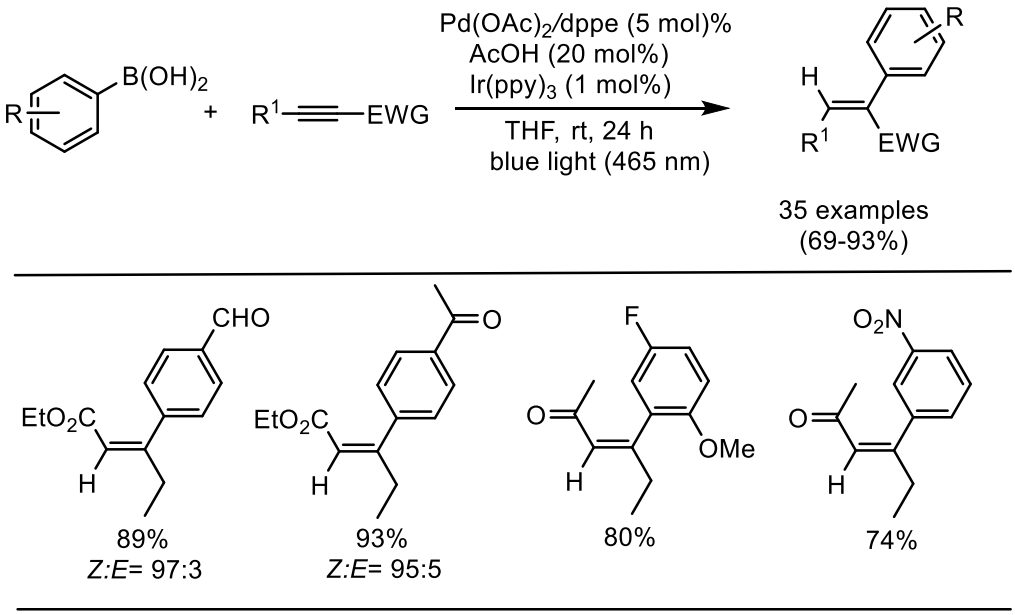
Scheme 1-10. Rh-catalyzed hydroarylation of diaryl alkynes with boronic acids.

In 2010, Chen and Wu *et al*.[18] reported a novel approach for the synthesis of trisubstituted arylalkenes via addition of arylboronic acids to alkynes catalyzed by $PdCl_2$ using *i*-Pr_2NPPh_2 as the ligand (Scheme 1-11).



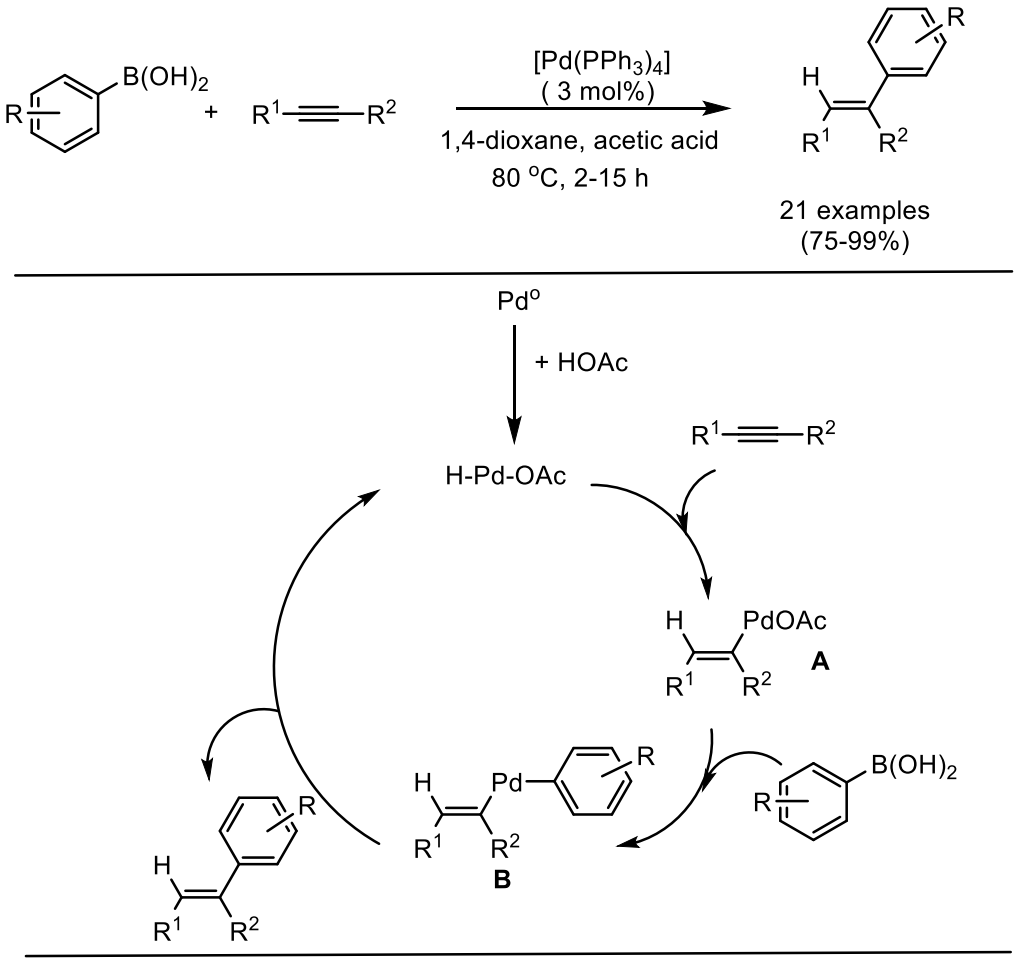
Scheme 1-11. Pd-catalyzed hydroarylation of diaryl acetylenes with boronic acids

In 2020, Carretero *et al*.[19] described the palladium and visible light photocatalyzed addition to electron-deficient internal alkynes of both electron-poor and electron-rich arylboronic acids, which gives good to excellent yields (Scheme 1-12). Mechanistic studies showed that $Pd(OAc)_2$ promoted the hydroarylation and $Ir(ppy)_3$-photocatalyzed the *E*-*Z* isomerization.



Scheme 1-12. Dual metal-catalyzed hydroarylation of internal alkynes with boronic acids.

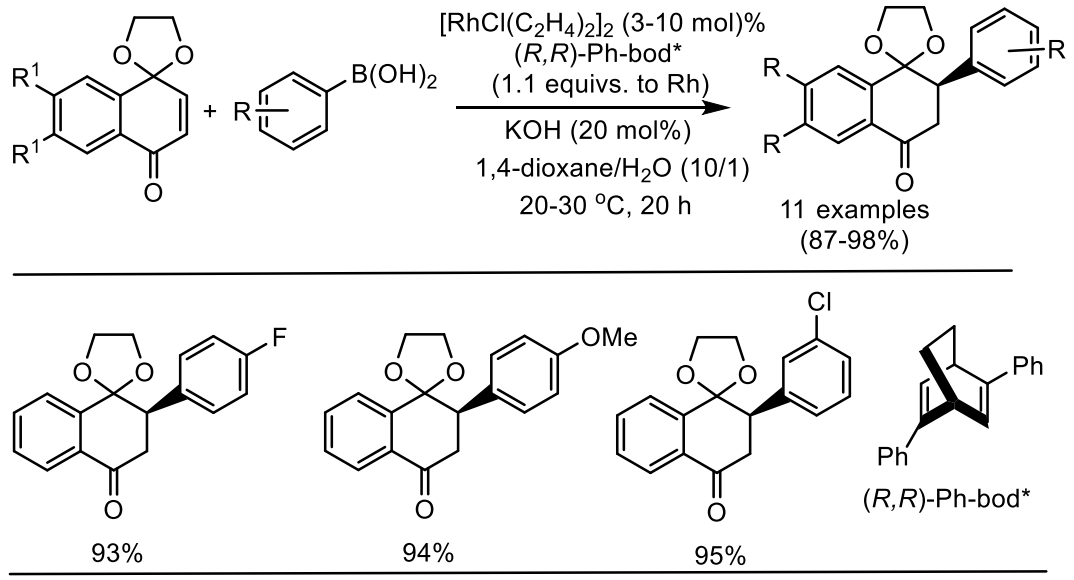
In 2004, Oh *et al*.[20] developed the Pd-catalyzed addition of aryl borates to alkynes, with readily available substrates and mild reaction conditions to afford excellent yields. The proposed mechanism is depicted in Scheme 1-13. Initially, $Pd(OAc)_2$ and HOAc generate a H-Pd-OAc complex and addition of H-Pd-OAc to the alkyne affords alkenyl palladium intermediate **A**. Then, the arylboronic acid and the alkenyl palladium intermediate generate intermediate **B** via transmetalation. Reductive elimination from **B** affords the desired product, regenerating the Pd^0 complex.



Scheme 1-13. Pd-catalyzed hydroarylation of internal alkynes with aryl boronic acids.

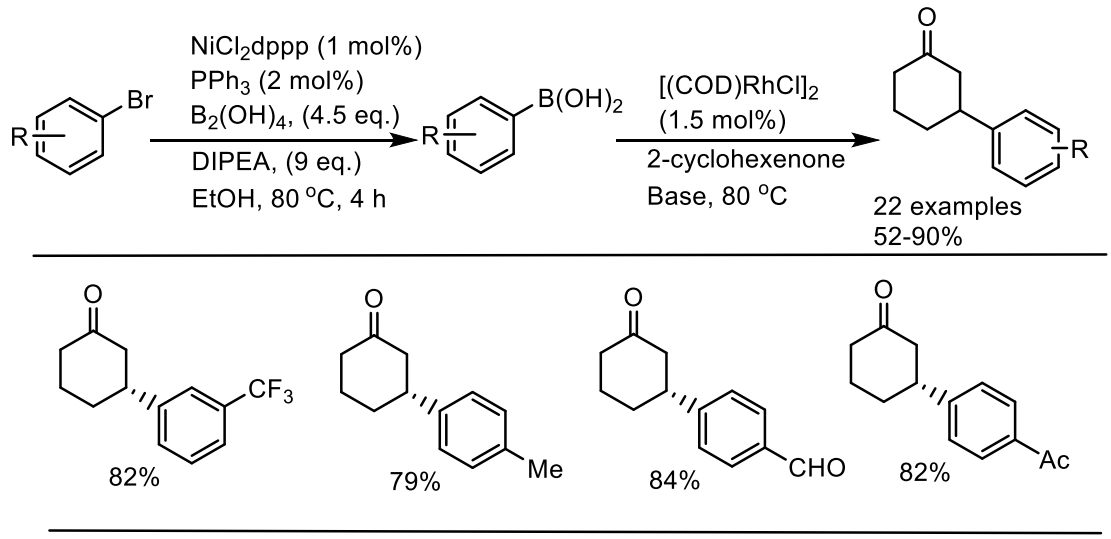
1.1.3 Addition Reaction of Fluorinated Aryl Boronates to Alkenes

Rh-catalyzed conjugate addition of arylboronic acids to alkenes represents a useful methodology for the asymmetric synthesis of carbon-carbon bonds.[21] In 2006, Hayashi *et al*.[22] developed an efficient system for the asymmetric 1,4-addition of arylboronic acids to quinone monoketals employing a chiral diene and a Rh complex, with high yields and excellent enantioselectivities (Scheme 1-14).



Scheme 1-14. Rh-catalyzed hydroarylation of alkenes with boronic acids.

In 2019, He *et al*.[23] disclosed a novel one-pot relay reaction, in which aryl halides and triflates initially afford aryl boronates *in situ*, which then add to olefins via a nickel/rhodium binary catalyst system (Scheme 1-15). This reaction employed aryl boronic acid substrates with electron-poor substituents to give products in excellent yields.

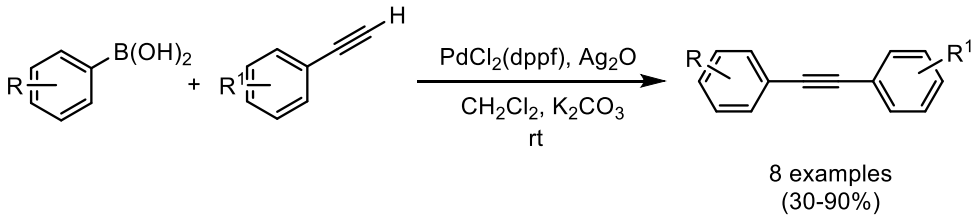


Scheme 1-15. Ni/Rh-catalyzed hydroarylation of alkenes with boronic acids.

1.2 Cross-coupling Reactions of Fluorinated Aryl Boronates

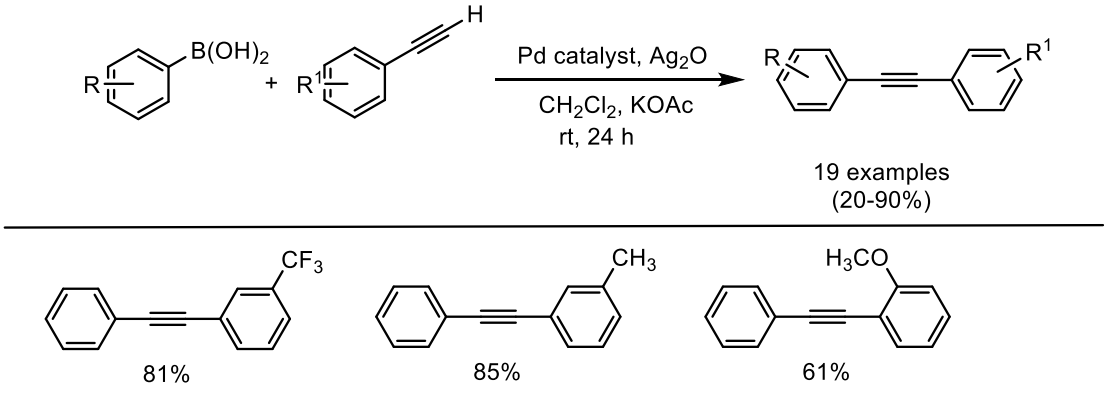
1.2.1 Cross-coupling of Fluorinated Aryl Boronates with Terminal Alkynes

Aryl and heteroaryl alkynes are useful in chemical synthesis due to their ability to be conveniently transformed into many compounds and they are widely used in the synthesis of pharmaceuticals, natural products, and materials.[24] Consequently, many methodologies to install alkynyl groups have been developed. In 2003, Zou *et al.* [25] reported a novel Pd-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids (Scheme 1-16).[25] The process is different from traditional Sonogashira cross-coupling and is suitable for both electron-rich and -deficient alkynes.



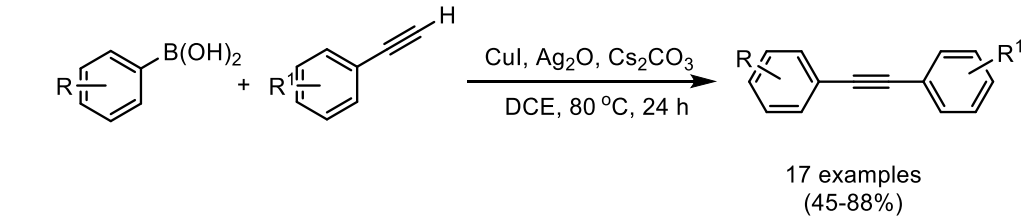
Scheme 1-16. Pd-catalyzed oxidative coupling of boronic acids with terminal alkynes.

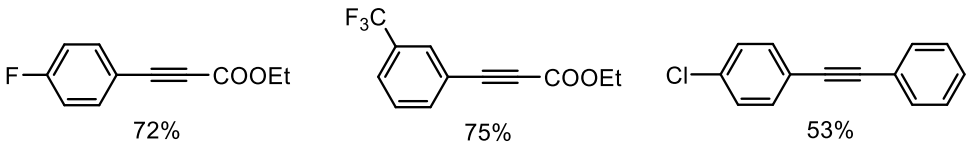
In 2007, Wu *et al.* [26] disclosed an efficient and convenient Pd-catalyzed cross-coupling of arylboronic acids/esters with terminal alkynes, using a cyclopalladated ferrocenylimine with Ag_2O as an additive (Scheme 1-17). Electron-deficient alkynes can be used as substrates.



Scheme 1-17. Pd-catalyzed oxidative coupling of boronic acids with terminal alkynes.

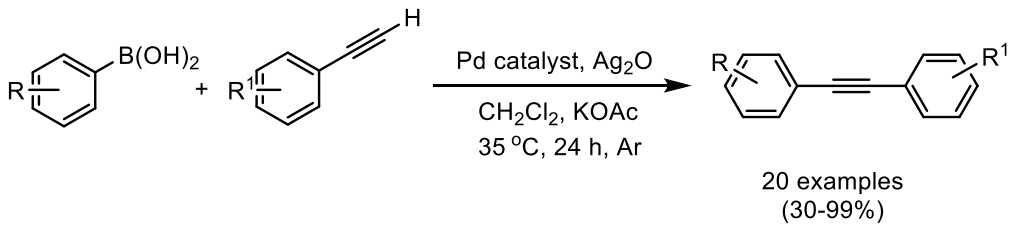
Cheng *et al*.[27] reported the oxidative coupling of arylboronic acids with terminal alkynes, in which copper was used as a catalyst (Scheme 1-18). This convenient methodology employs an inexpensive catalyst. However, this method also has some limitations, such as the requirement for high temperatures and long reaction times, giving only moderate yields.

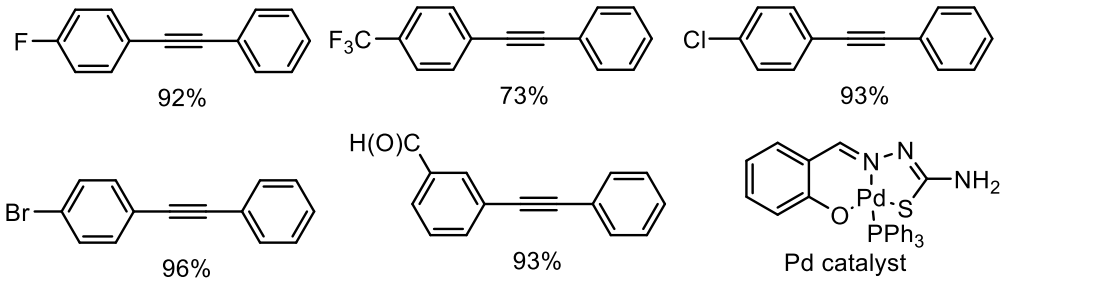




Scheme 1-18. Cu-catalyzed oxidative coupling of boronic acids with alkynes.

In 2014, Mao *et al*.[28] achieved Pd-catalyzed cross-coupling of arylboronic acids with alkynes or alkynyl carboxylic acids, as shown in Scheme 1-19.

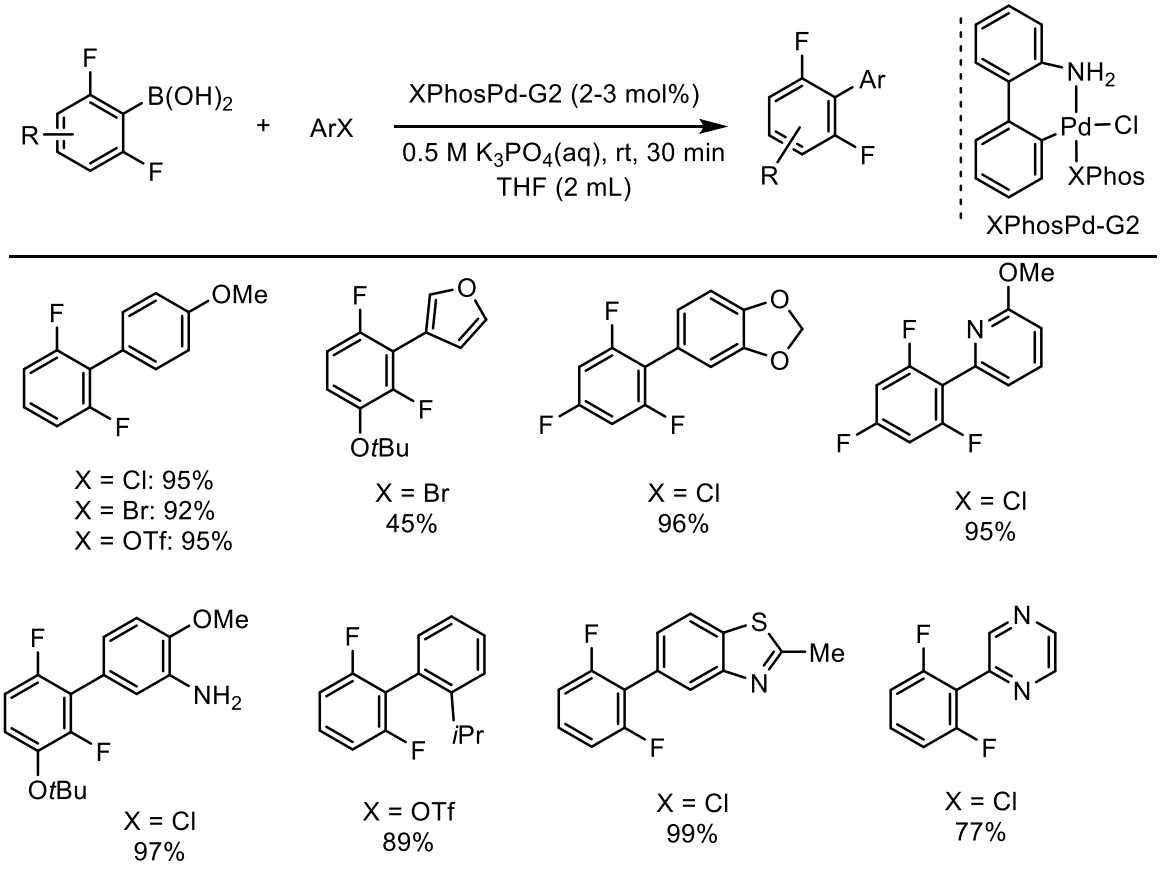




Scheme 1-19. Pd-catalyzed oxidative coupling of boronic acids with alkynes.

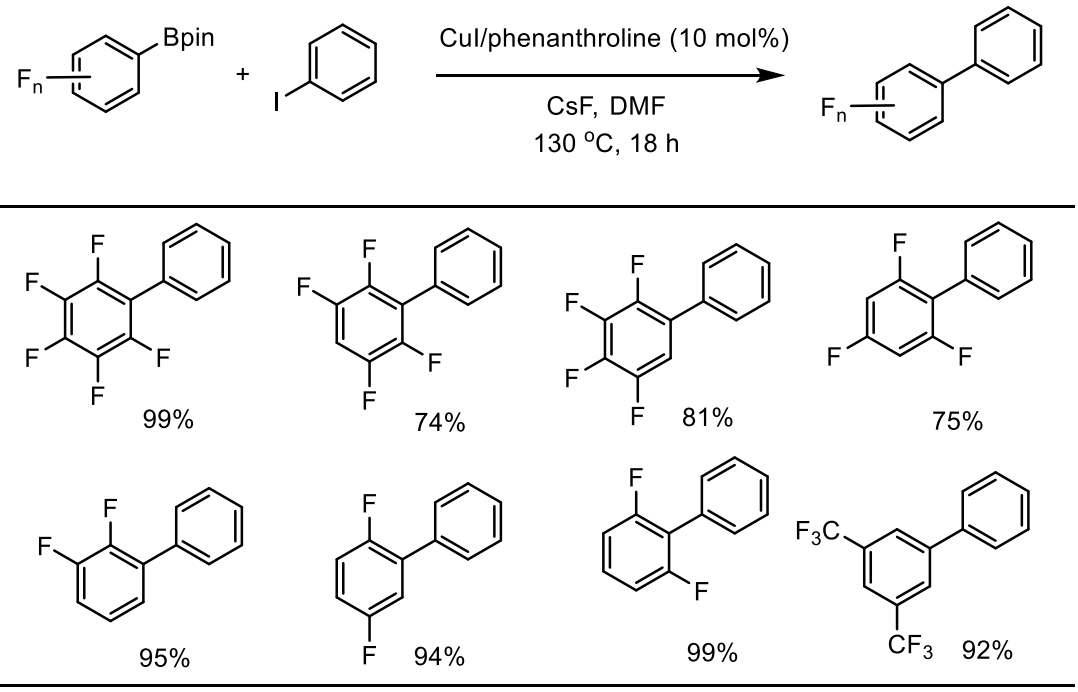
1.2.2 Suzuki-Miyaura Cross-coupling of Fluorinated Aryl Boronates

As among the most important building blocks in organic synthesis, biaryls have been used in medicinal, agrochemical, and material sciences.[29] Suzuki-Miyaura cross-coupling is a convenient and efficient method to build biphenyls, using organic halides as the electrophilic component. In 2010, Buchwald *et al.*[30] employed a Pd catalyst, and K_3PO_4 as the base, to cross-couple polyfluorophenylboronic acids with aryl halides (Scheme 1-20). The scope of the reaction included aryl bromides, chlorides, and triflates.

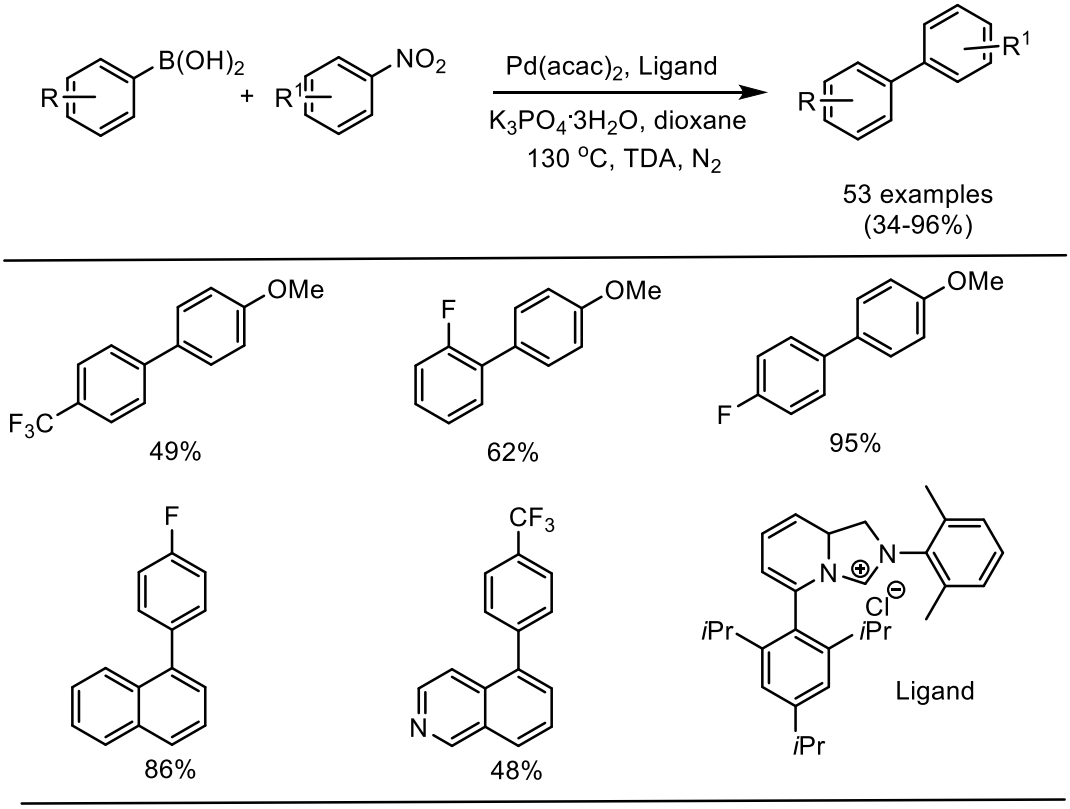


Scheme 1-20. Pd-catalyed cross-coupling of polyfluorophenylboronic acids with aryl halides.

In 2019, Radius and Marder *et al.*[31] reported the copper-catalyzed Suzuki-Miyaura cross-coupling of polyfluorophenyl-Bpin with aryl halides. Copper iodide and phenanthroline plus CsF were highly effective for the cross-coupling of polyfluorophenyl-Bpin with aryl iodides giving the desired products in good to excellent yields (Scheme 1-21).



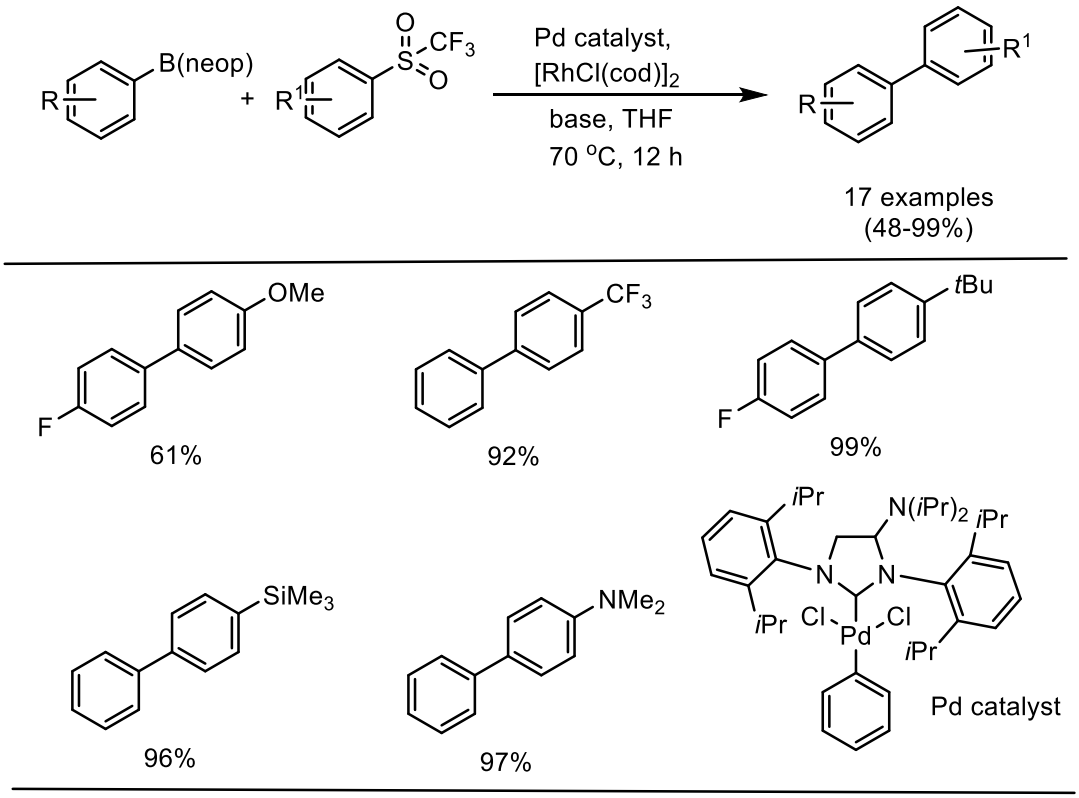
Scheme 1-21. Cross-coupling of polyfluorophenyl-Bpin compounds with phenyl iodide.



Scheme 1-22. Pd-catalyzed coupling of boronic acids with nitroarenes.

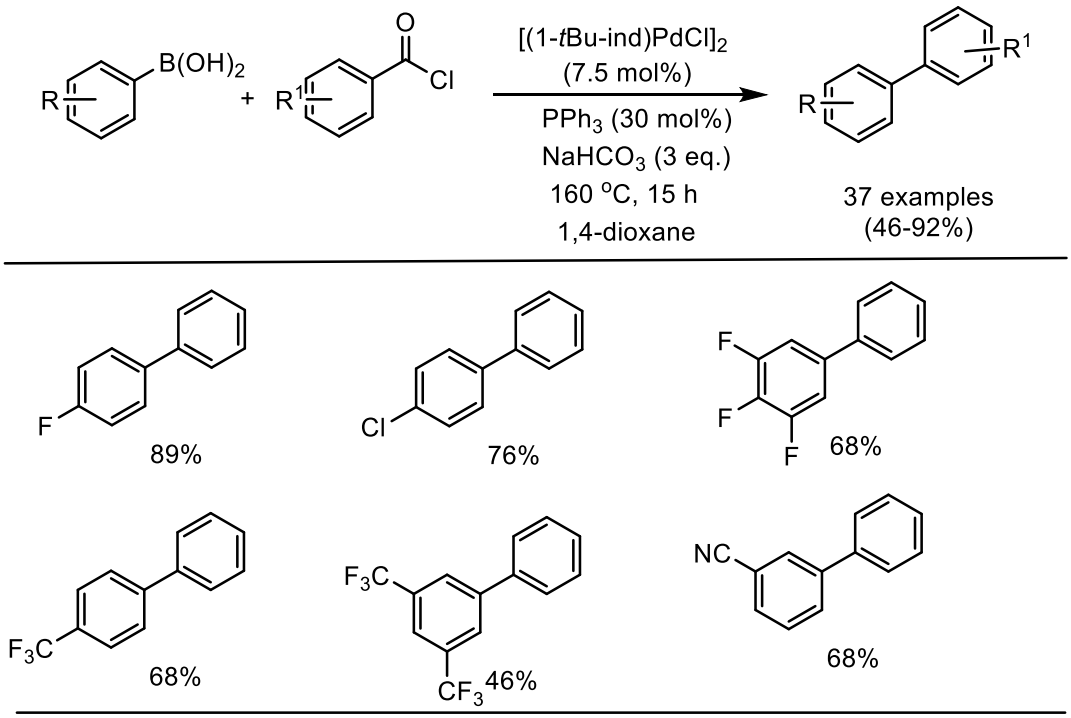
In 2019, Wu *et al*.[32] disclosed the Pd/NHC-catalyzed Suzuki-Miyaura coupling of nitroarenes with aromatic and aliphatic boronic acids, in which the ligand 2-aryl-5-(2,4,6-

triisopropylphenyl)-2,3-imidazolylidene[1,5-a]-pyridine and a small amount of TDA (tris(3,6-dioxaheptyl)amine) play crucial roles (Scheme 1-22). In 2019, Wu *et al*.[33] reported the cooperative Pd/Rh-catalyzed cross-coupling of aryl trifluoromethyl sulfones with Ar-Bneop (neop = neopentyl glycolato), generating biaryls in moderate to excellent yields (Scheme 1-23).

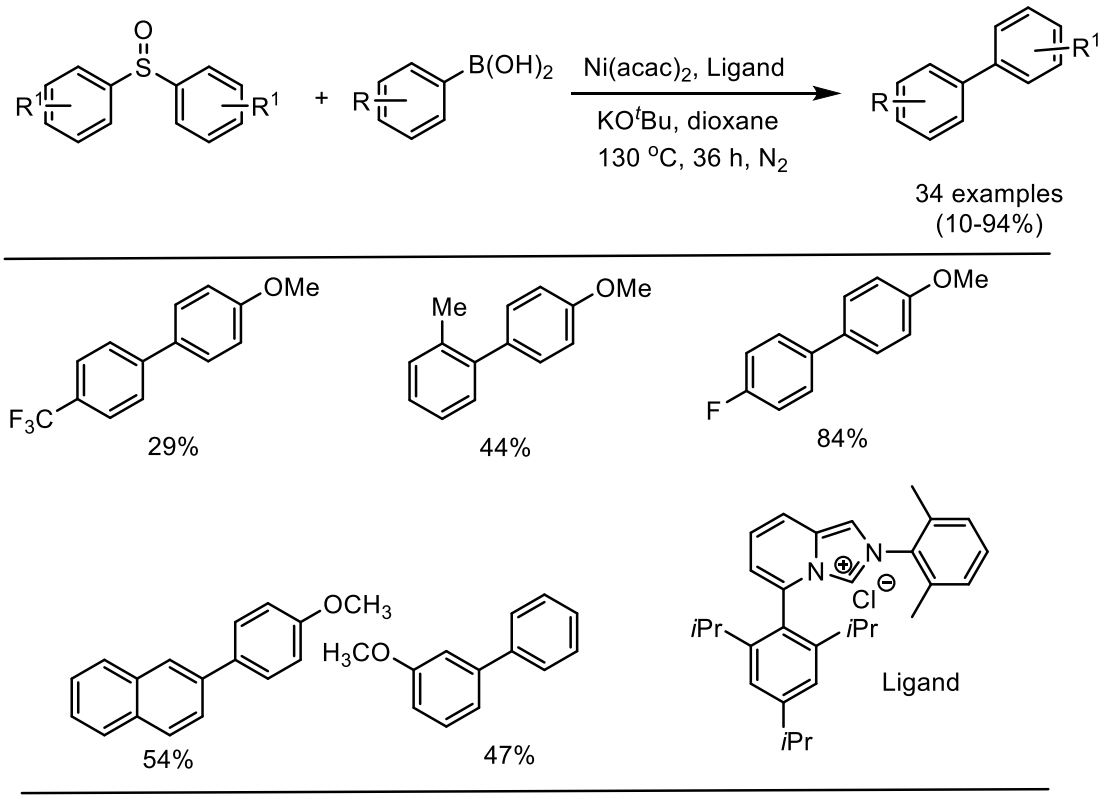


Scheme 1-23. Pd/Rh-catalyzed coupling of aryl trifluoromethyl sulfones and aryl boronates.

In 2020, Szostak *et al*.[34] reported the Pd-catalyzed cross-coupling of aroyl chlorides with boronic acids to give biaryls (Scheme 1-24) which is suitable for aryl boronic acids with electron-withdrawing substituents including Cl, F, and CF_3, giving good to excellent yields.



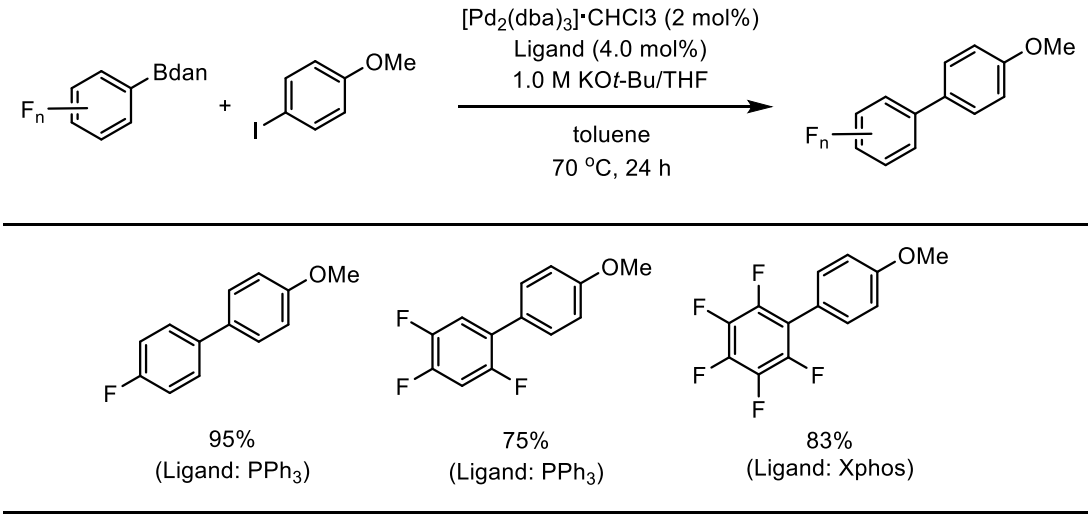
Scheme 1-24. Pd-catalyzed coupling of aroyl chlorides with aryl boronates.



Scheme 1-25. Ni-catalyzed coupling of aryl sulfoxides with aryl boronates.

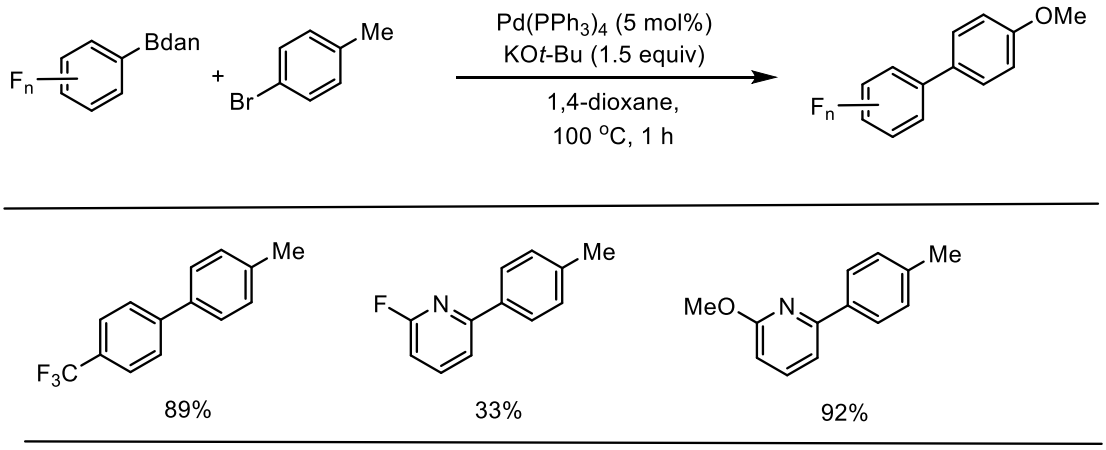
In 2020, Chen *et al*.[35] disclosed an effective cross-coupling of aryl sulfoxides with aryl boronates, using an easily prepared Ni/5-(2,4,6-triisopropylphenyl)imidazolylidene[1,5-a]pyridine catalyst system (Scheme 1-25), giving modest to excellent yields. Unfortunately, heterocyclic substrates were unsuitable for the reaction.

In the aryl boronate cross-coupling reactions, Lewis acidity also has an important impact on the reactivity. In 2007, Suginome *et al*.[36] developed aryl-Bdan (dan = naphthalene-1,8-diaminato) derivatives, in which the reduced Lewis acidity at boron led to lower C-B bond reactivity. In 2020, Saito *et al*.[37] described an highly effective Pd-catalyzed Suzuki-Miyaura cross-coupling of phenyl iodides with polyfluorophenyl-Bdan derivatives to afford biaryls. As shown in Scheme 1-26, a series of polyfluorophenyl-Bdan derivatives were used, with $[Pd_2(dba)_3]\cdot CHCl_3$ and different ligands such as Xphos and PPh_3 affording the products in good yield.



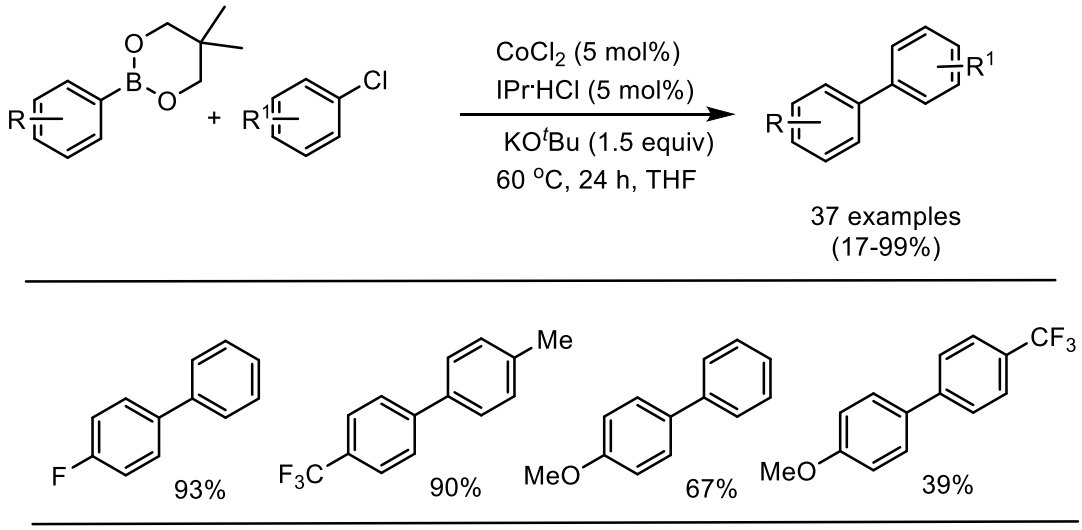
Scheme 1-26. Pd-catalyzed cross-coupling of polyfluoroaryl-Bdan with aryl iodide.

At the same time, Tsuchimoto *et al*.[38] disclosed an effecient Pd-catalyzed cross-coupling of 4-bromotoluene with fluorophenyl-Bdan derivatives to afford biaryls in modest to excellent yields (Scheme 1-27).



Scheme 1-27. Pd-catalyzed cross-coupling of fluoroaryl-Bdan with an aryl bromide.

In 2021, Bedford *et al*.[39] reported the Co-catalyzed cross-coupling of aryl chlorides with aryl-Bneop derivatives, promoted by commonly used alkoxide bases (Scheme 1-28). Under optimized reaction conditions, they found that the amount of base has an important impact. For example, KO^{t}Bu works well, but excess base poisons the catalyst. For, LiO^{t}Bu, even catalytic amounts kill the catalyst.

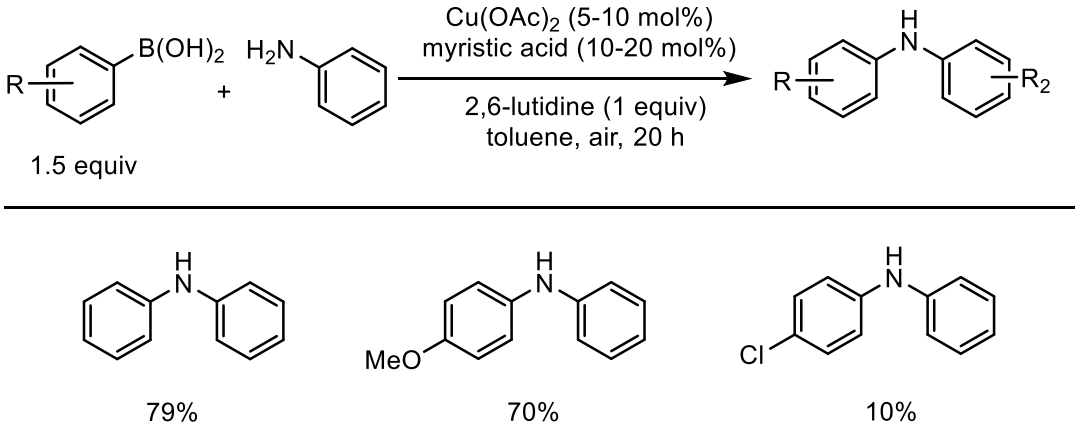


Scheme 1-28. Co-catalyzed cross-coupling of aryl chlorides with aryl boronates.

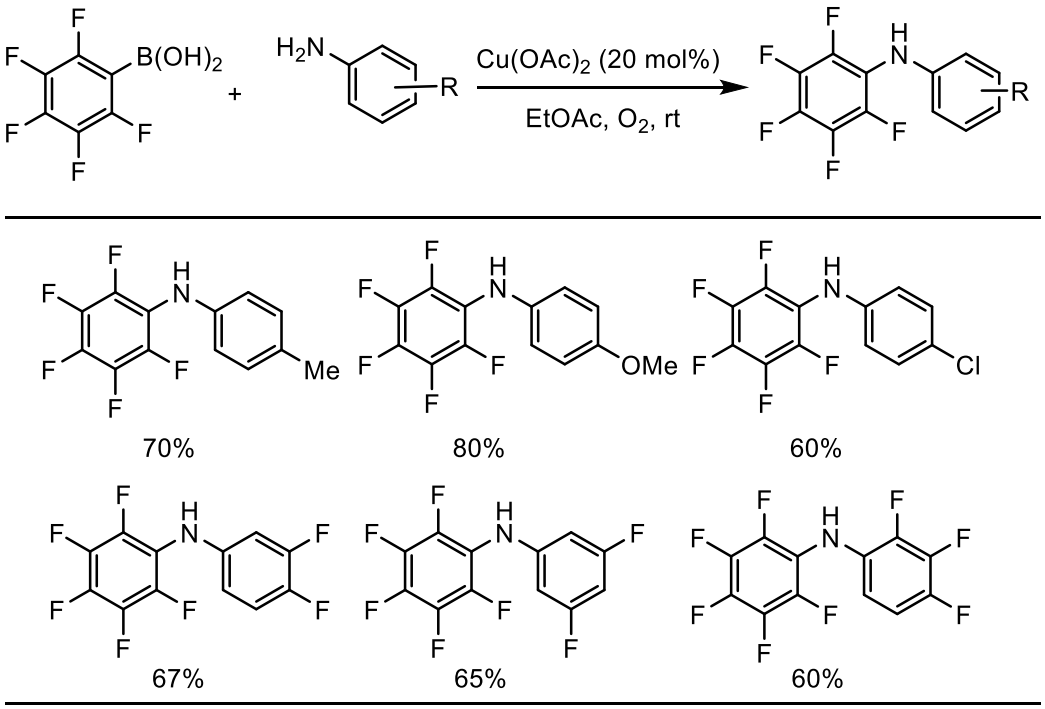
1.3 Amination of Fluorinated Aryl Boronates

1.3.1 Chan-Evans-Lam Cross-coupling

In the past few decades, amines have attracted much more attention, due to their ubiquitous appearance in agrochemicals, pharmaceuticals, natural products, and functional materials,[40] as has methodology for constructing amines. Cu-catalyzed N-arylations of aryl boronic acids play a key role,[41] which is known as the Chan-Evans-Lam cross-coupling reaction. Such reactions are conveniently conducted at room temperature, and avoid the use of expensive Pd catalysts.[42] In 2001, Buchwald *et al*.[43] reported the Cu-promoted cross-coupling of arylboronic acids with aryl amines, assisted by a small amount of myristic acid and a stoichiometric amount of 2,6-lutidine, but this system was not effective for aryl boronic acids with electron-withdrawing groups such as Cl (Scheme 1-29).



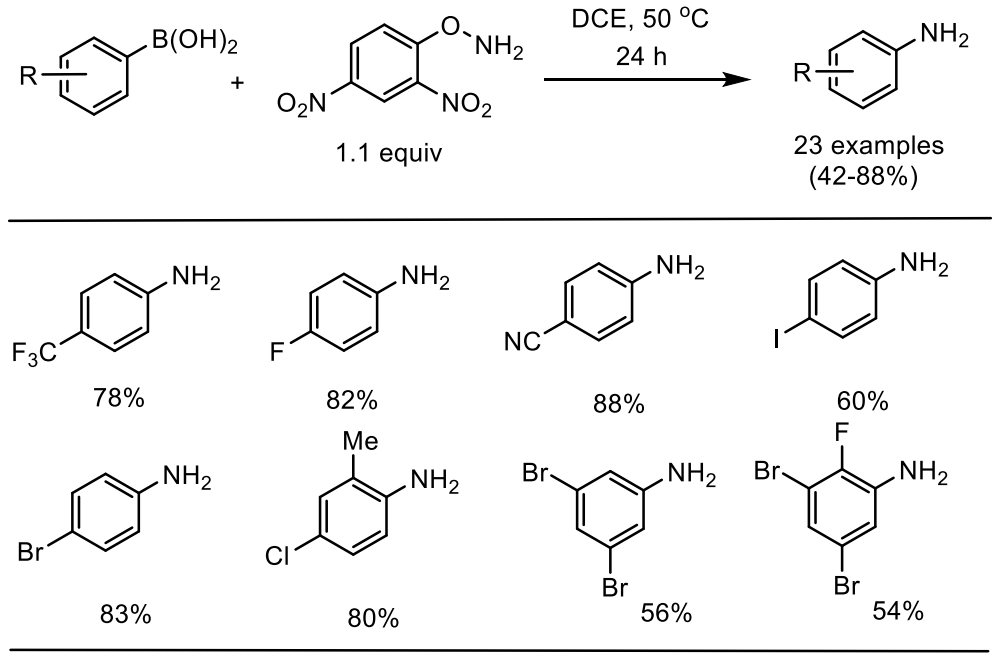
Scheme 1-29. Cu-catalyzed N-arylation of aryl boronic acids with anilines.



Scheme 1-30. Cu(II)-catalyzed N-arylation of $C_6F_5B(OH)_2$ with anilines.

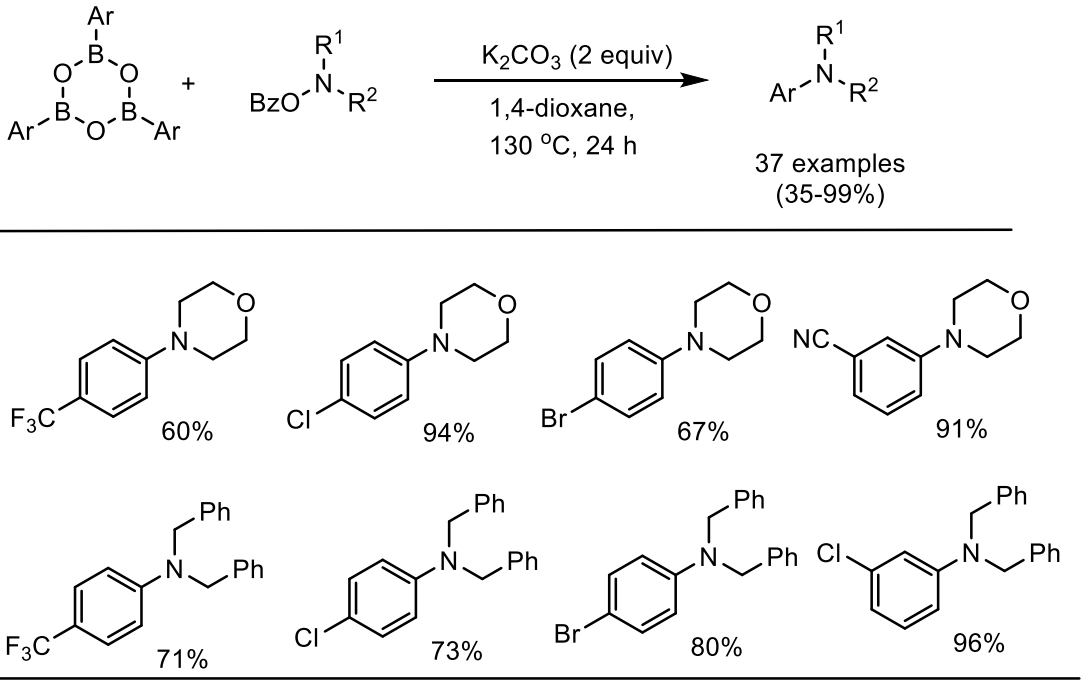
Recently, the reaction of pentafluorophenyl boronic acid with anilines to afford the corresponding N-pentafluorophenylanilines was reported by Su *et al*.[44] which is suitable for anilines containing electron-rich and electron-poor substituents, giving modest to excellent yields (Scheme 1-30).

In 2012, Kürti *et al*.[45] reported a novel metal-free system to synthesize primary aromatic amines from arylboronic acids, generating anilines in good to excellent yields under mild conditions (Scheme 1-31). Halogenated primary anilines also smoothly produced the desired products.



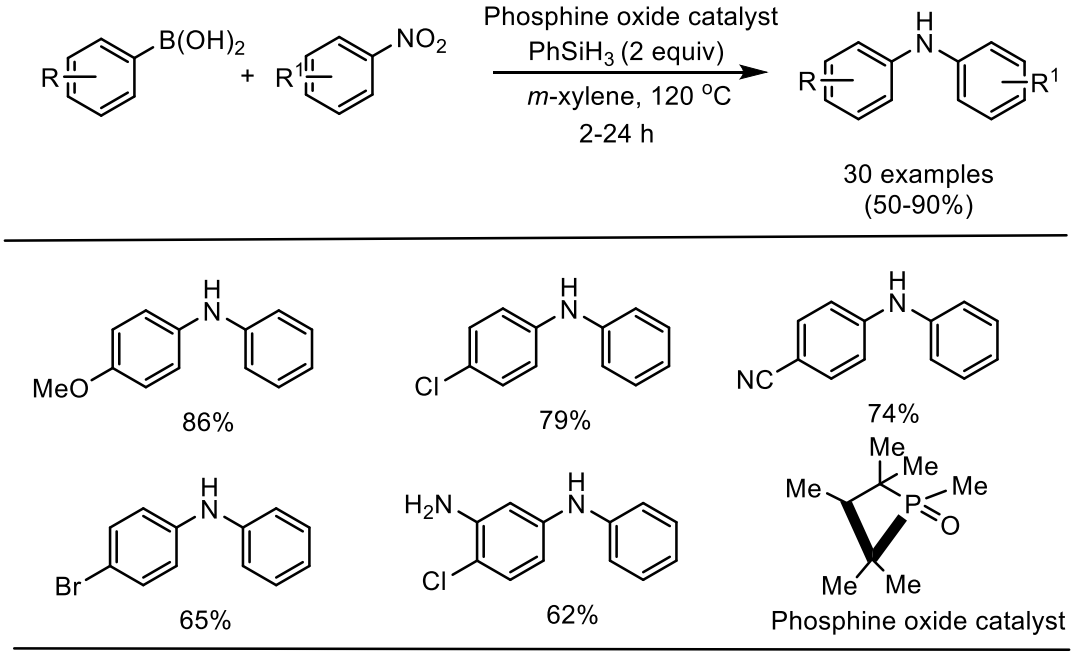
Scheme 1-31. Metal-free primary amination of arylboronic acids.

In 2012, Wang *et al.*[46] disclosed an efficient transition metal-free amination of arylboroxines with O-benzoyl hydroxylamines using K_2CO_3 as the base with moderate to good yields (Scheme 1-32).



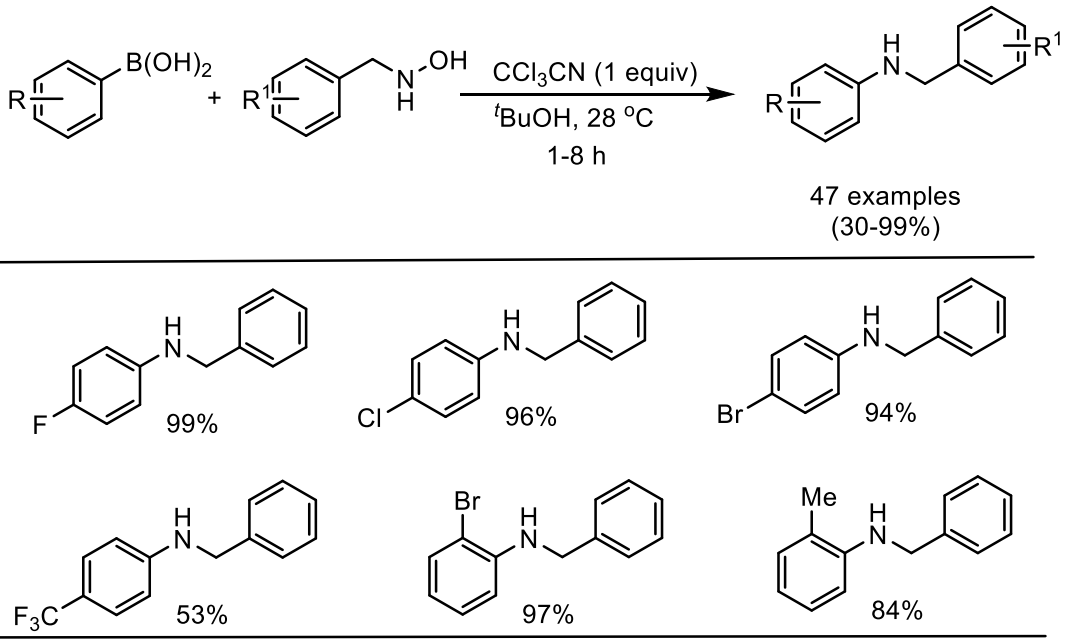
Scheme 1-32. Transition metal-free amination of arylboroxines.

In 2018, Radosevich *et al*.[47] developed a novel method to synthesize amines from nitroarenes and boronic acid derivatives using the phosphorus-based catalyst 1,2,2,3,4,4-hexamethylphosphetane and phenylsilane as the reducing agent, which is suitable for Ar-$B(OH)_2$ substrates including those with electron-rich and electron-poor substituents such as Cl and CN, giving good to excellent yields (Scheme 1-33).

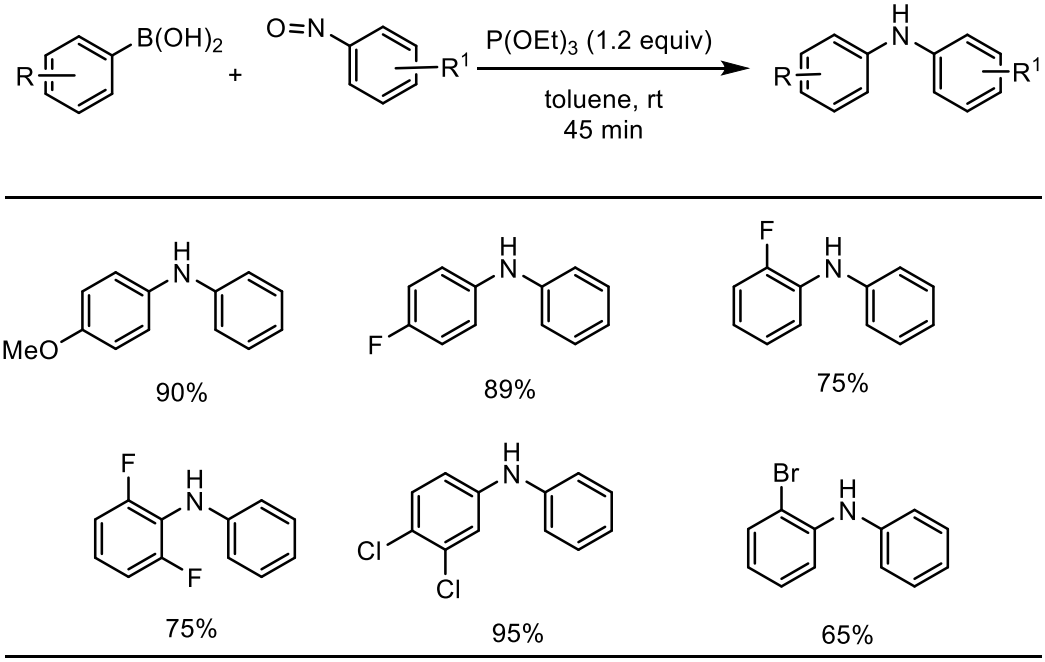


Scheme 1-33. Phosphine oxide-catalyzed coupling of nitroarenes and arylboronic acids.

In 2018, Niu *et al*.[48] demonstrated the amination of arylboronic acids with N-alkyl hydroxylamines under mild conditions, activated by trichloroacetonitrile in the absence of metal and base, with modest to excellent yields (Scheme 1-34).



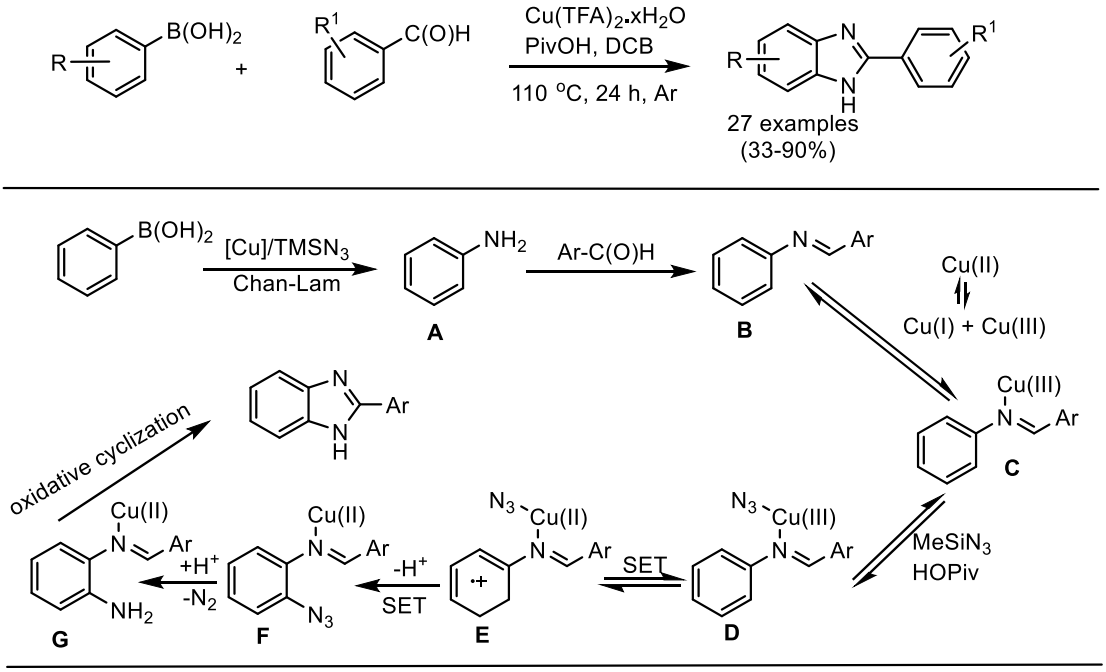
Scheme 1-34. Transition metal-free amination of organoboronic acids.



Scheme 1-35. C-N cross-coupling of aryl boronic acids with nitrosoarenes.

In 2018, Csákÿ *et al.*[49] developed an attractive transition metal- and base-free method for the C-N coupling of aryl boronic acids with nitrosoarenes. This room temperature reaction promoted by $P(OEt)_3$ gives unsymmetrical diarylamines in good to excellent yields (Scheme 1-35), but is not suitable for Ar-Bpin and Ar-$BF_3^-K^+$ substrates.

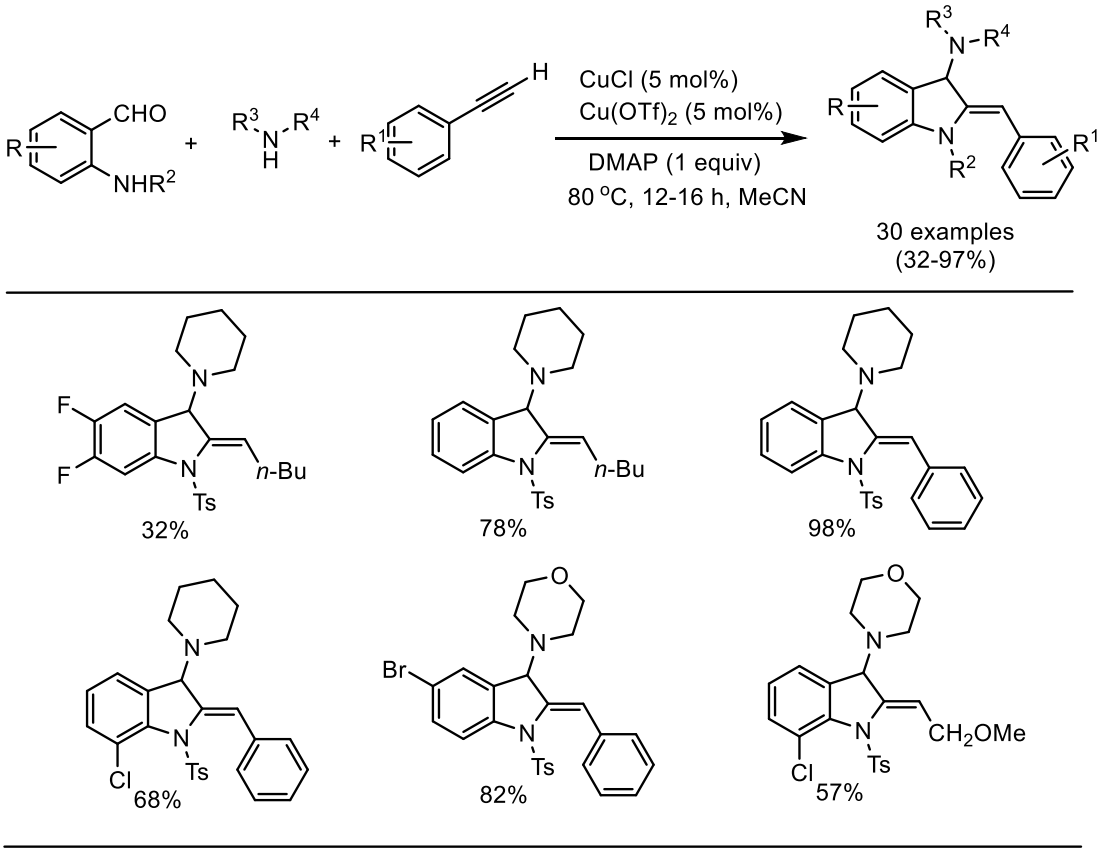
In 2020, Ding *et al.*[50] established a Cu-mediated protocol for the synthesis of benzimidazole, employing TMS-N_3 and aldehydes in DCB (*o*-dichlorobenzene), which is suitable for an extensive range of substituted Ar-CHO and Ar-$B(OH)_2$ substrates. The reaction was conducted under mild conditions furnishing the desired benzimidazoles in moderate to high yields. Scheme 1-36 shows the plausible mechanism which was proposed. First, Ph-$B(OH)_2$ underwent Chan-Evans-Lam coupling with TMS-N_3 affording aniline. Imine **B** would be furnished by condensation with the aldehyde. Intermediate **C** could be coordinated to Cu(III) which arises from disproportionation. Subsequently, intermediate **D** could be generated by the replacement of the ligand of **C** by HOPiv and $TMSN_3$. A single electron transfer (SET) between the aryl ring and the metal center formed **E**. Subsequently, N_3^- attacks the aryl ring resulting in the formation of intermediate **F**. Copper-assisted amination of intermediate **F** gives **G**, and oxidative cyclization formed the desired product.



Scheme 1-36. C-N cross-coupling of Ar-CHO with Ar-$B(OH)_2$.

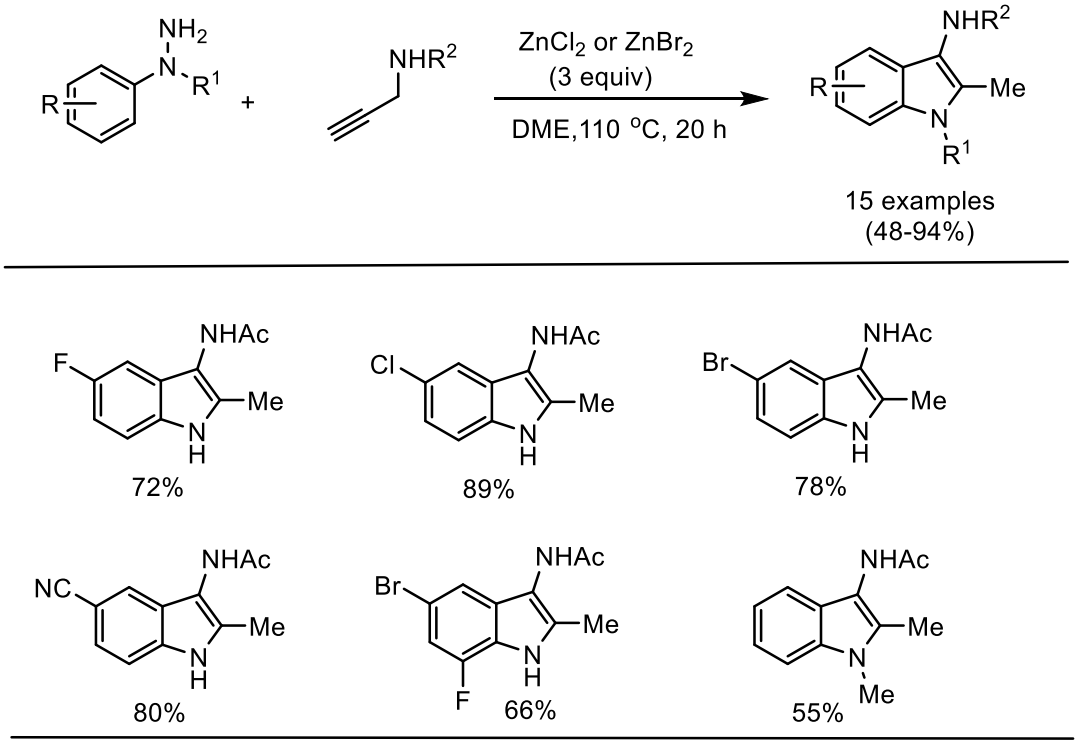
1.3.2 Synthes of 3-aminoindole Derivatives

Among numerous indole derivatives, 3-aminoindoles have found wide application in medicinal chemistry, e.g., as effective anticancer agents, potent inhibitors of tubulin polymerization, and for the prevention of type II diabetes.[51] In 2010, Gevorgyan *et al*.[52] reported a novel copper-catalyzed multicomponent coupling reaction to synthesize 3-aminoindole, using 2-aminobenzaldehyde, and an alkyne as precursors, affording good to excellent yields (Scheme 1-37).



Scheme 1-37. Three-component coupling to synthesize 3-aminoindolines.

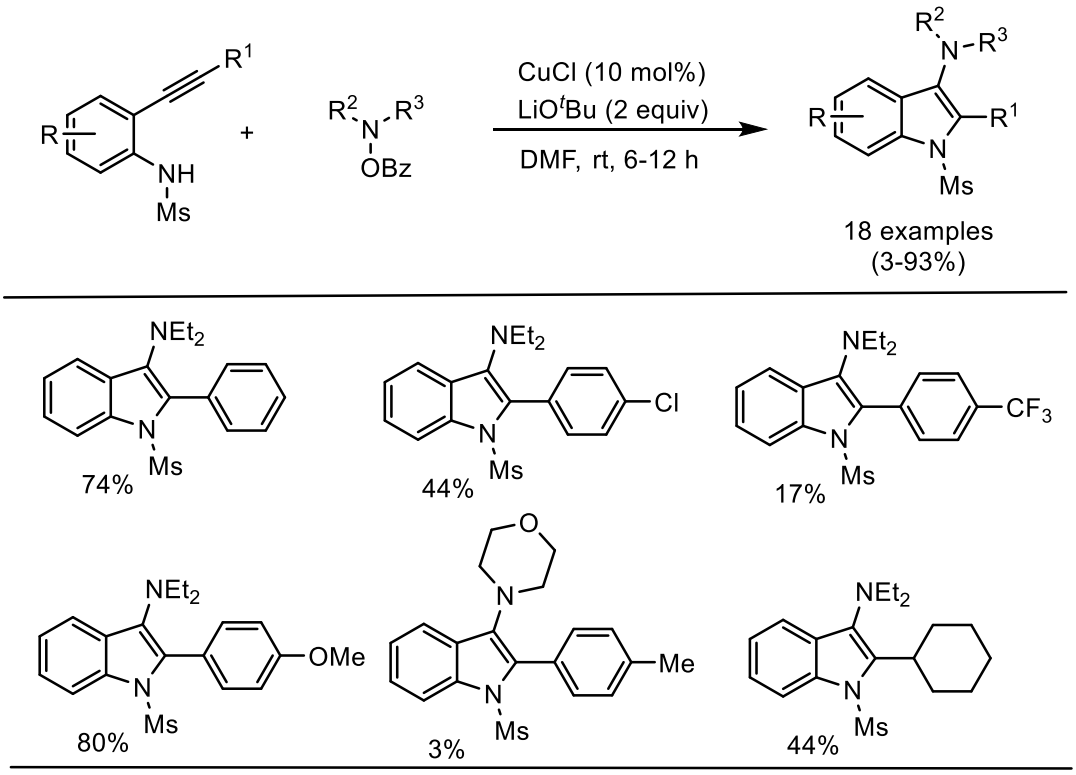
In 2010, Gevorgyan *et al*.[53] disclosed an efficient Zn-mediated cascade cyclization reaction between arylhydrazines and propargylic amides (Scheme 1-38), which tolerates a wide range of functional groups, giving good to excellent yields.



Scheme 1-38. Two-component cyclization reaction to synthesize 3-aminoindolines.

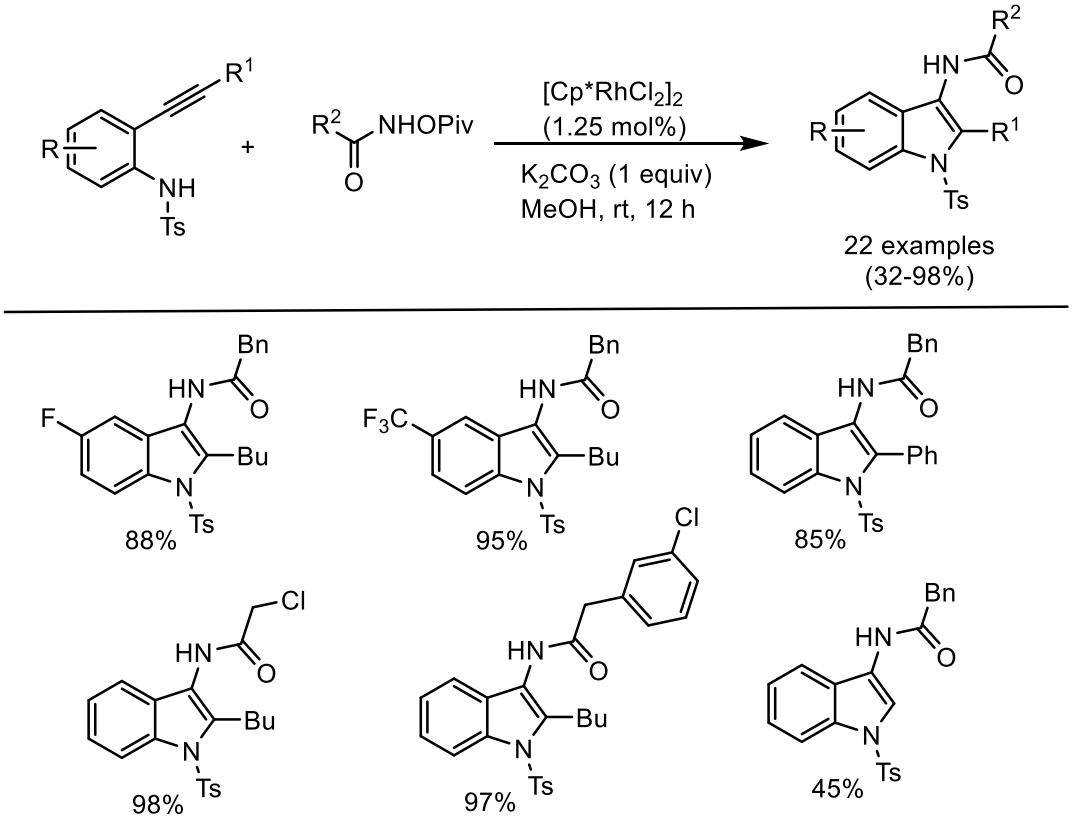
In 2012, Miura *et al*.[54] reported the Cu-catalyzed amination of *o*-alkynylphenols and -anilines with O-acylated hydroxylamines at room temperature to synthesize 3-aminobenzofurans and -indoles (Scheme 1-39). The optimized reaction employed Cu(II) as a catalyst and no ligand.

In 2016, Liu *et al*.[55] reported a novel and efficient Rh(III)-catalyzed cascade cyclization to furnish 3-amidoindoles and 3-amidobenzofurans, using N-pivaloyloxylamides as the electrophilic nitrogen reagents under mild conditions (Scheme 1-40). This process tolerated many functional groups and provided good to excellent yields.

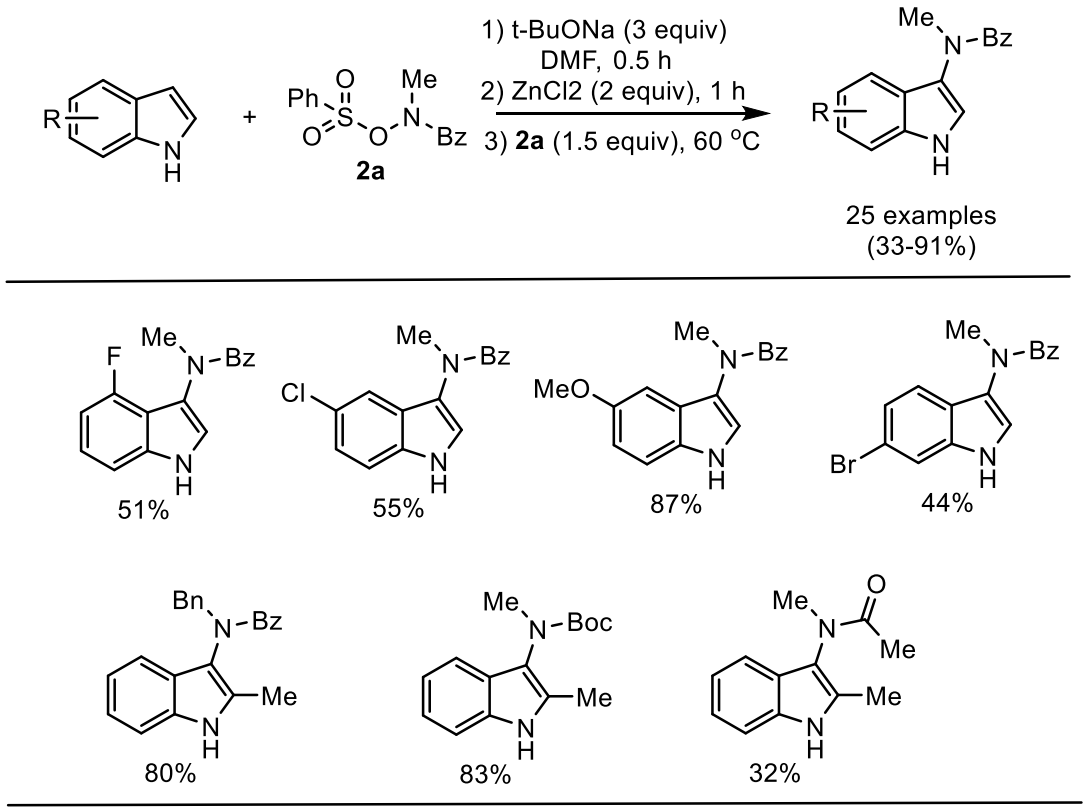


Scheme 1-39. Two-component annulation for the synthesis of 3-aminoindolines.

In 2017, Wang *et al.*[56] disclosed a novel $ZnCl_2$-mediated 3-amidation of indole skeletons using N-[(benzenesulfonyl)oxy]amides as the electrophilic nitrogen source (Scheme 1-41). Aminal products were furnished in the absence of $ZnCl_2$. The reaction gave moderate to excellent yields.



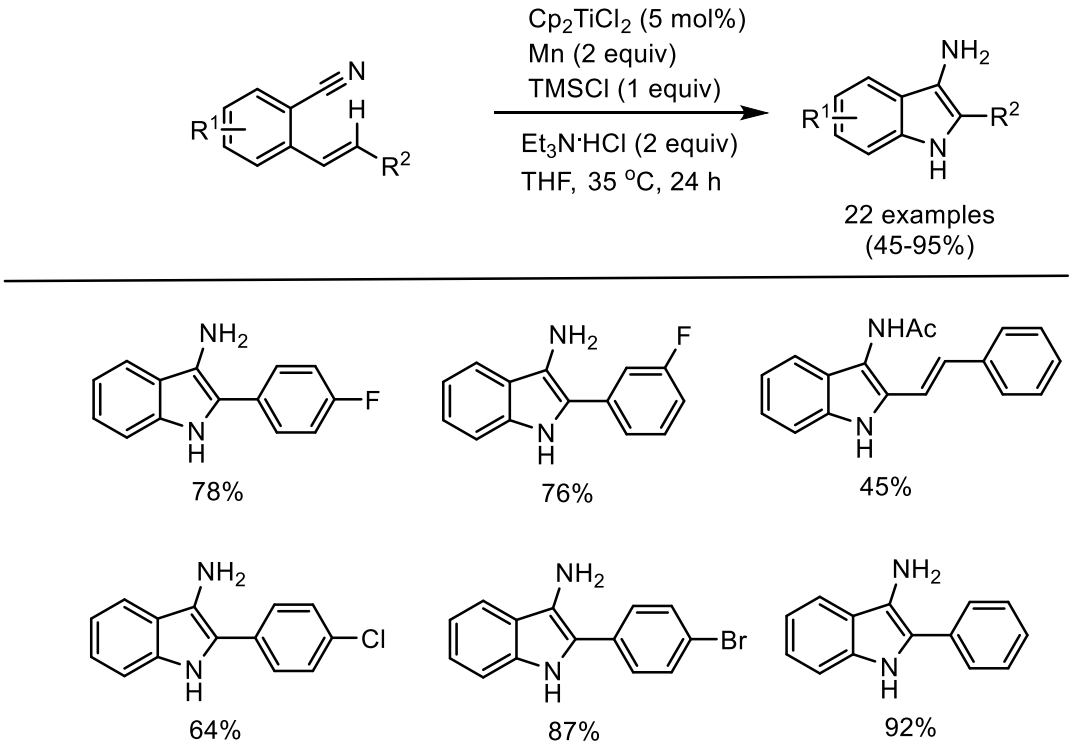
Scheme 1-40. Rh-catalyzed annulation for the synthesis of 3-aminoindolines.



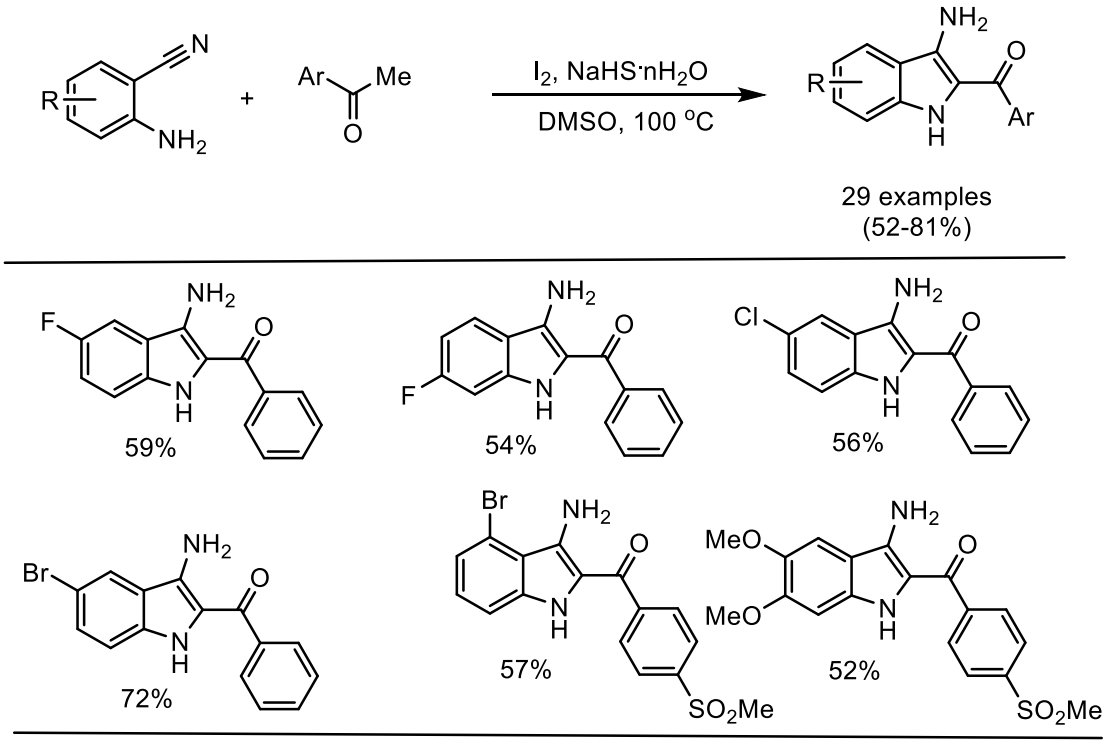
Scheme 1-41. Direct amidation of indoles at the C3 position.

In 2017, Streuff *et al.*[57] demonstrated an efficient Ti-catalyzed intramolecular cyclization to synthesize unprotected 3-aminoindoles, 3-aminopyrroles, and 3-iminoindolines (Scheme 1-42). The reaction tolerated a wide substrate scope, and easy to install diverse nitrogen protecting groups.

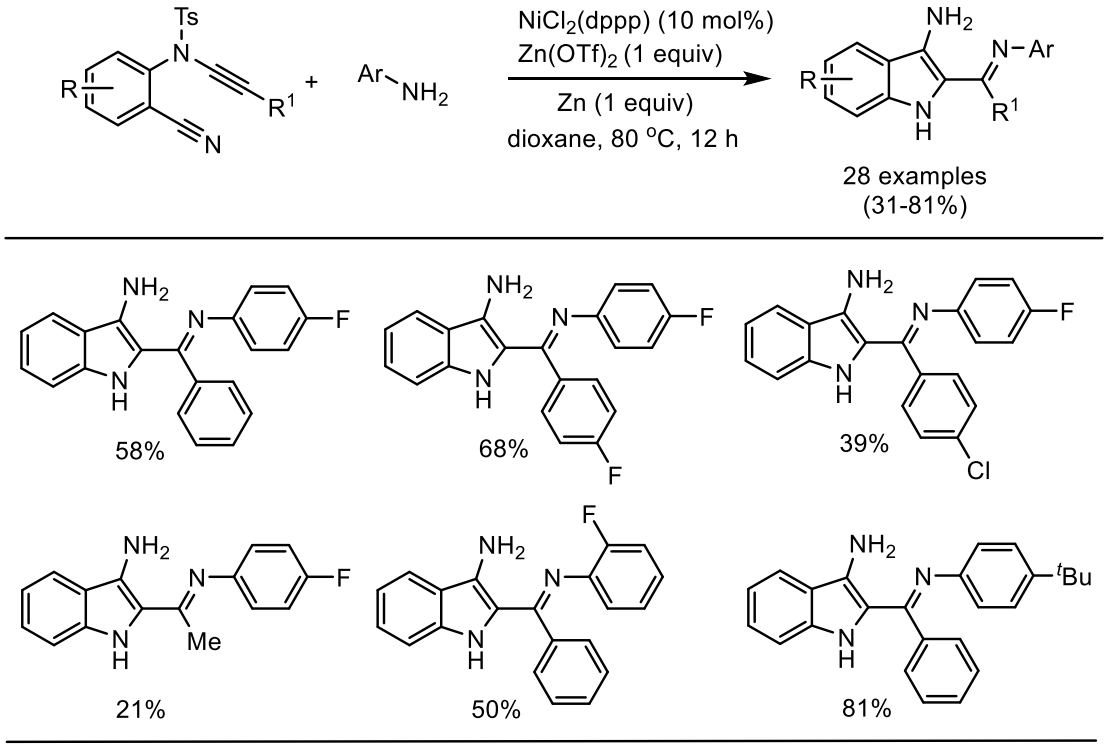
In 2018, Wu *et al.*[58] described a novel methodology to synthesize 2-acyl-3-aminoindoles from methyl ketones and 2-aminobenzonitriles, using $NaHS{\cdot}nH_2O$ as an umpolung reagent (Scheme 1-43). This process tolerated an extensive substrate scope and furnished good isolated yields.



Scheme 1-42. Ti-catalyzed intramolecular cyclization synthesis of 3-aminoindolines.



Scheme 1-43. $NaHS{\cdot}nH_2O$-induced synthesis of 2-acyl-3-aminoindoles.



Scheme 1-44. Ni/Zn-catalyzed annulation route to 3-aminoindolines.

In 2021, Liu *et al.*[59] reported an attractive and efficient methodology for the synthesis of 3-aminoindoles and 4-aminoisoquinoline derivatives, employing a Ni and Lewis acid dual catalyst (Scheme 1-44), with the help of a tosylate group on the ynamide to afford the alkenyl Ni complex with high regioselectivity. This protocol tolerated a wide substrate scope and provided good to excellent isolated yields.

1.4 Conclusion and Perspective

Polyfluoroarenes have attracted much attention because of their crucial role in pharmaceuticals, agrochemicals, and advanced materials. Exploring efficient methodologies to incorporate fluorine or fluorinated units into organic molecules is highly desirable. Among numerous methodologies, fluorine-containing boron compounds have gained much more attention, as the boron moiety is especially useful in many cross-couplings, such as the Suzuki-Miyaura and Chan-Evans-Lam reactions. It can be expected that many new and efficient methodologies to construct fluorinated organic molecules will be developed in the coming years.

1.5 References

[1] a) J. R. Nitschke, T. D. Tilley, *J. Am. Chem. Soc*. **2001**, *123*, 10183-10190; b) P. Zacharias, M. C. Gather, M. Rojahn, O. Nuyken, K. Meerholz, *Angew. Chem. Int. Ed*. **2007**, *46*, 4388-4392; *Angew. Chem*. **2007**, *119*, 4467-4471; c) F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.* **2007**, 1003-1022; d) Y.-Y. Lai, Y.-J. Cheng, C.-S. Hsu, *Energy Environ. Sci*. **2014**, *7*, 1866-1883; e) M. de Candia, F. Liantonio, A. Carotti, R. De Cristofaro, C. Altomare, *J. Med. Chem.* **2009**, *52*, 1018-1028; f) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem*. **2015**, *58*, 8315-8359; g) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev*. **2011**, *40*, 3496-3508; h) M. Hird, *Chem. Soc. Rev*. **2007**, *36*, 2070-2095; i) B. Wiegmann, P. G. Jones, G. Wagenblast, C. Lennartz, I. Münster, S. Metz, W. Kowalsky, H.-H. Johannes, *Organometallics* **2012**, *31*, 5223-5226; j) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev*. **2016**, *116*, 422-518; k) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330; l) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; m) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719-766.

[2] a) J. Wang, M. Sanchez-Rosello, J. Luis Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*. **2014**, *114*, 2432-2506; b) V. V. Grushin, *Acc. Chem. Res*. **2010**, *43*, 160-171.

[3] a) J. R. Lucas, Y. Shono, T. Iwasaki, T. Ishiwatari, N. Spero, G. Benzon, *J. Am. Mosq. Control Assoc*. **2007**, *23*, 47-54; b) Y. Shono, K. Ujihara, T. Iwasaki, M.; Mori, T. Sugano, T. Matsunaga, N. Matsuo, in Pesticide Chemistry (Eds.: H. Ohkawa, H. Miyagawa, P. W. Lee), Wiley-VCH, Weinheim, Germany, **2007**; p 149.

[4] Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder, *Adv. Synth. Catal.* **2021**. 363, 2224-2255.

[5] a) C. Bolm, J. P. Hildebrand, K. Muniz, N. Hermanns, *Angew. Chem. Int. Ed*. **2001**, *40*, 3284-3308; *Angew. Chem.* **2001**, *113*, 3382-3407; b) L. Pu, H. B. Yu, *Chem. Rev.* **2001**, *101*, 757-824; c) K. Fagnou, M. Lautens, *Chem. Rev*. **2003**, *103*, 169-196; d) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829-2844; e) P. Knochel, S. Perrone, N. Grenouillat, 9.04-Zinc and Cadmium. In Comprehensive Organometallic Chemistry III, Vol. 9 (Eds.: R. H. Crabtree, D. M. P. Mingos, P. Knochel), Elsevier, Oxford, **2007**, pp. 81-143.

[6] a) K. Yoshida, T. Hayashi, Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**; b) A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178-184; c) N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457-2483. For potassium organotrifluoroborates, see: d) S. Darses, J.-P. Genet, *Chem. Rev*. **2008**, *108*, 288-325; e) S. Darses, J.-P. Genet, *Eur. J. Org. Chem*. **2003**, 4313-4327; f) M. Pucheault, S. Darses, J.-P. Genet, *Chem. Commun.* **2005**, 4714-4716.

[7] M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem. Int. Ed.* **1998**, *37*, 3279-3280; *Angew. Chem.* **1998**, *110*, 3475-3477.

[8] P. M. P. Gois, A. F. Trindade, L. F. Veiros, V. André, M. T. Duarte, C. A. M. Afonso, S. Caddick, F. G. N. Cloke, *Angew. Chem. Int. Ed.* **2007**, *46*, 5750-5753; *Angew. Chem*. **2007**, *119*, 5852-5855

[9] M. Kuriyama, R. Shimazawa, R. Shirai, *J. Org. Chem*. **2008**, *73*, 1597-1600.

[10] Y. X. Liao, C. H. Xing, P. He, Q. S. Hu, *Org. Lett.* **2008**, *10*, 2509-2512.

[11] J. Bouffard, K. Itami, *Org Lett.* **2009**, *11*, 4410-4413.

[12] H. Zheng, Q. Zhang, J. Chen, M. Liu, S. Cheng, J. Ding, H. Wu, W. Su, *J. Org. Chem*. **2009**, *74*, 943-945.

[13] T. Zou, S. S. Pi, J. H. Li, *Org. Lett*. **2009**, *11*, 453-456.

[14] J. Karthikeyan, M. Jeganmohan, C. H. Cheng, *Chem. Eur. J.* **2010**, *16*, 8989-8992.

[15] a) E.-i. Negishi, G. Wang, H. Rao, Z. Xu, *J. Org. Chem*. **2010**, *75*, 3151-3182; b) R. Chinchilla, C. Nájera, *Chem. Rev*. **2014**, *114*, 1783-1826.

[16] a) N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457-2483; b) S. Darses, J. P. Genet, *Chem. Rev*. **2008**, *108*, 288-325.

[17] W. Zhang, M. Liu, H. Wu, J. Ding, J. Cheng, *Tetrahedron Lett*. **2008**, 5214-5216.

[18] X. Xu, J. Chen, W. Gao, H. Wu, J. Ding, W. Su, *Tetrahedron* **2010**, 2433-2438.

[19] J. Corpas, P. Mauleón, R. G. Arrayás, J. C. Carretero, *Org. Lett*. **2020**, *22*, 6473-6478.

[20] C. H. Oh, H. H. Jung, K. S. Kim, N. Kim, *Angew. Chem. Int. Ed.* **2003**, *42*, 805-808.

[21] a) P. Tian, H.-Q. Dong, G.-Q. Lin, *ACS Catal*. **2012**, *2*, 95119; g) M. Hayashi, R. Matsubara, *Tetrahedron Lett*. **2017**, *58*, 1793-1805; c) C.-G. Feng, M.-H. Xu, G.-Q. Lin, *Synlett* **2011**, *2011*, 1345-1356.

[22] N. Tokunaga, T. Hayashi, *Adv. Synth. Catal*. **2007**, *349*, 513-516.

[23] C. Fan, Q. Wu, C. Zhu, X. Wu, Y. Li, Y. Luo, J.-Bo. He, *Org. Lett*. **2019**, *21*, 8888-8892.

[24] a) *Acetylene Chemistry: Chemistry, Biology and Material Science*, (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, Germany, **2005**; b) S. Toyota, *Chem. Rev*. **2010**, *110*, 5398-5424; c) S. Diez-Gonzalez, *Catal. Sci. Technol.* **2011**, *1*, 166-178; d) A. Palisse, S. F. Kirsch, *Org. Biomol. Chem.* **2012**, *10*, 8041-8047; e) I. V. Alabugin, B. Gold, *J. Org. Chem*. **2013**, *78*, 7777-7784; f) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783-1826; g) P. Siemsen, P. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657; *Angew. Chem.* **2000**, *112*, 2740-2767; h) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979-2017; i) R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2003**, *42*, 1566-1568; *Angew. Chem.* **2003**, *115*, 1604-1606.

[25] G. Zou, J. Zhu, T. Tang, *Tetrahedron Lett.* **2003**, *44,* 8709-8711.

[26] F. Yang, Y. Wu, *Eur. J. Org. Chem.* **2007**, 3476-3479.

[27] C. D. Pan, F. Luo, J. Cheng, *Tetrahedron Lett.* **2009**, *50*, 5044-5046.

[28] L. Lu, P. Chellan, G. S. Smith, X. Zhang, H. Yan, J. Mao, *Tetrahedron* **2014**, 5980-5985.

[29] a) N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457-2483; b) D. G. Brown, J. Bostrom, *J. Med. Chem*. **2015**, *59*, 4443-4458; c) A. Biffis, P. Centomo, A. Del Zotto, M. Zecca, *Chem. Rev*. **2018**, *118*, 2249-2295.

[30] T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc*. **2010**, *132*, 14073-14075.

[31] Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem* **2019**, *11*, 5387-5396.

[32] K. Chen, W. Chen, X. Yi, W. Chen, M. Liu, H. Wu, *Chem. Commun*. **2019**, *55*, 9287-9290.

[33] J.-I. Fukuda, K. Nogi, H. Yorimitsu, *Org. Lett*. **2019**, *21*, 8987-8991.

[34] T. Zhou, P.-P. Xie, C.-L. Ji, X. Hong, M. Szostak, *Org. Lett*. **2020**, *22*, 6434-6440.

[35] X. Yi, K. Chen, J. Guo, W. Chen, W. Chen, *Adv. Synth. Catal*. **2020**, *362*, 4373-4377.

[36] H. Nogushi, K. Hojo, M. Suginome, *J. Am. Chem. Soc*. **2007**, *129*, 758-759.

[37] Y. Mutoh, K. Yamamoto, S. Saito, *ACS Catal*. **2020**, *10*, 352-357.

[38] H. Yoshida, M. Seki, S. Kamio, H. Tanaka, Y. Izumi, J. Li, I. Osaka, M. Abe, H. Andoh, T. Yajima, T. Tani, T. Tsuchimoto, *ACS Catal*. **2020**, *10*, 346-351.

[39] S. B. Tailor, M. Manzotti, G. J. Smith, S. A. Davis, R. B. Bedford, *ACS Catal*. **2021**, *11*, 3856-3866.

[40] *Amines: Synthesis, Properties and Applications* (Ed.: S. A. Lawrence), Cambridge University Press, Cambridge, **2004**.

[41] a) J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson, *J. Org. Chem*. **2016**, *81*, 3941-3950; b) M. J. West, J. W. B. Fyfe, J. C. Vantourout, A. J. B. Watson, *Chem. Rev*. **2019**, *119*, 12491-12523.

[42] a) B. P. Fors, D. A. Watson, M. K. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc*. **2008**, *130*, 13552-13554; b) Q. Sheng, J. F. Hartwig, *Org. Lett*. **2008**, *10*, 4109-4112.

[43] J. C. Antilla, S. L. Buchwald, *Org. Lett*. **2001**, *3*, 2077-2079.

[44] W. Zhong, Z. Liu, C. Yu, W. Su, *Synlett* **2008**, *18*, 2888-2892.

[45] C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti, *J. Am. Chem. Soc*. **2012**, *134*, 18253-18256.

[46] Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang, *Org. Lett*. **2012**, *14*, 4230-4233.

[47] T. V. Nykaza, J. C. Cooper, G. Li, N. Mahieu, A. Ramirez, M. R. Luzung, A. T. Radosevich, *J. Am. Chem. Soc*. **2018**, *140*, 15200-15205.

[48] H.-B. Sun, L. Gong, Y.-B. Tian, J.-G. Wu, X. Zhang, J. Liu, Z. Fu, D. Niu, *Angew. Chem. Int. Ed*. **2018**, *57*, 9456-9460; *Angew. Chem*. **2018**, *130*, 9600-9604.

[49] S. Roscales, A. G. Csákÿ *Org. Lett*. **2018**, *20*, 1667-1671.

[50] Z. Xie, F. Zhou, K. Ding, *Adv. Synth. Catal*. **2020**, *362*, 3442-3446.

[51] a) R. H. Bahekar, M. R. Jain, A. Goel, D. N. Patel, V. M. Prajapati, A. A. Gupta, P. A. Jadav, P. R. Patel, *Bioorg. Med. Chem*. **2007**, *15*, 3248-3265; b) R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, N. Zonta, J. Balzarini, A. Brancale, H.-P. Hsieh, E. Hamel, *J. Med. Chem.* **2008**, *51*, 1464-1468; c) A. Kumar, S. Sharma, Archana, K. Bajaj, S. Sharma, H. Panwar, T. Singh, V. K. Srivastava, *Bioorg. Med. Chem*. **2003**, *11*, 5293-5299; d) E. Arzel, P. Rocca, P. Grellier, M. Labaeïd, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard, G. Quéguiner, *J. Med. Chem.* **2001**, *44*, 949-960.

[52] D. Chernyak, N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal*. **2010**, *352*, 961-966.

[53] A. Pews-Davtyan, A. Tillack, A. C. Schmole, S. Ortinau, M. J. Frech, A. Rolfs, M. A. Beller, *Org. Biomol. Chem.* **2010**, *8*, 1149-1153.

[54] N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem*. **2012**, *77*, 617-625.

[55] Z. Hu, X. Tong, G. Liu, *Org. Lett*. **2016**, *18*, 2058-2061.

[56] G. X. Ortiz, Jr., B. N. Hemric, Q. Wang, *Org. Lett*. **2017**, *19*, 1314-1317.

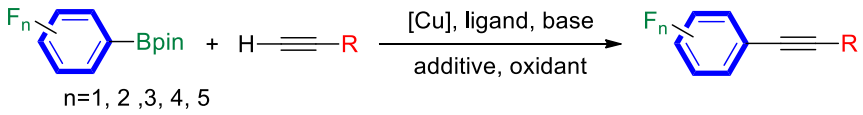
[57] L. H. Leijendekker, J. Weweler, T. M. Leuther, J. Streuff, *Angew. Chem. Int. Ed*. **2017**, *56*, 6103-6106; *Angew.Chem*. **2017**, *129*, 6199-6202.

[58] X. Geng, X. Wu, C. Wang, P. Zhao, Y. Zhou, X. Sun, L.-Jiao Wang, W.-Juan Guan, Y.-Dong Wu, A.-X. Wu, *Chem. Commun*. **2018**, *54*, 12730-12733.

[59] X. Hu, X. Xie, Y. Gan, G. Wang, Y. Liu, *Org. Lett*. **2021**, *23*, 1296-1301.

Chapter 2

Copper-Catalyzed Oxidative Cross-Coupling of Electron-Deficient Polyfluorophenylboronate Esters with Terminal Alkynes



2 Copper-Catalyzed Oxidative Cross-Coupling of Electron-Deficient Polyfluorophenylboronate Esters with Terminal Alkynes

2.1 Abstract

We report herein a mild procedure for the copper-catalyzed oxidative cross-coupling of electron-deficient polyfluorophenylboronate esters with terminal alkynes. This method displays good functional group tolerance and broad substrate scope, generating cross-coupled alkynyl(fluoro)arene products in moderate to excellent yields. Thus, it represents a simple and alternative to the conventional Sonogashira reaction.

2.2 Introduction

Functionalized aryl and heteroaryl alkynes are powerful building blocks in chemical synthesis because of their versatility to be transformed into various useful molecules and also their ubiquity in natural product synthesis, pharmaceuticals, and advanced materials.[1] Consequently, much effort has been expended to develop efficient methods to install various alkynyl groups. Some of the strategies which have been established include: (1) Sonogashira palladium/copper-catalyzed sp^2-sp cross-coupling of aryl halides with terminal alkynes;[2] (2) direct alkynylation of unreactive alkyl and aryl C-H bonds with prefunctionalized alkynating reagents such as alkynyl halides[3] and hypervalent iodine reagents;[4] (3) alkynylation of tetra- and penta-fluoroarenes and heteroarenes via C-H bond activation;[5,6] and (4) cross-coupling of copper(I) acetylides with aryl halides, known as the Castro–Stephens reaction.[7,8,9] However, some drawbacks remain, such as the use of precious metal catalysts including those of Pd,[2] Rh,[4a,b,h] and Au,[4c,d] strategies that depend on the use of alkynyl halides or hypervalent iodine reagents, which are less readily available than the corresponding terminal alkynes, and the fact that copper(I) acetylides can be heat and shock sensitive when isolated.

It is generally acknowledged that polyfluoroarenes are important fluorinated aromatic cores and key structural units for various organic molecules, such as pharmaceuticals, agrochemicals and organic materials.[10] The development of efficient methods to

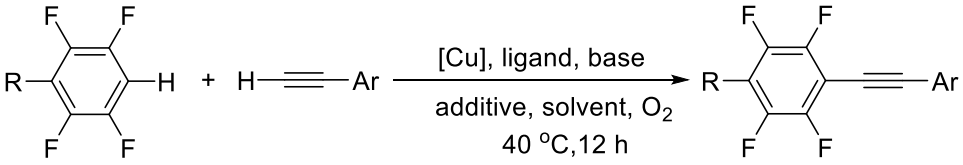
introduce fluorine or fluorinated building blocks into organic molecules has been the subject of intense research. Under certain conditions, Sonogashira cross-couplings involving highly fluorinated aryl halides can be problematic, giving low yields[11a] and side reactions, i.e., hydrodehalogenation accompanied by homocoupling of the terminal alkyne.[11b] The latter problem seems to arise from the slow reductive elimination of the fluoroaryl alkyne from Pd(II), which leads to competing reverse transmetallation processes, i.e., transfer of aryl groups from Pd to Cu in exchange for a second alkynyl moiety being transferred from Cu to Pd. Thus, an alternative approach would be useful. In 2010, Su and co-workers demonstrated the direct functionalization of polyfluoroarene C-H bonds with terminal alkynes, which has proven to be a viable method to generate the corresponding alkynylated products (Scheme 2-1a),[12] but this reaction is limited to C_6F_5H or 4-RC_6F_4H substrates. Soon after, the oxidative alkynylation of azoles containing acidic C-H bonds with terminal alkynes was reported by the groups of Miura,[13] Chang,[14] and others.[15] Recently, Su and co-workers reported a palladium-catalyzed alkynylation of heterocyclic substrates such as thiophenes and furans.[16] Although these achievements were promising, they were restricted by elevated temperatures (>90 °C) and limited substrate scope. In 2003, the palladium-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids was first disclosed by Zou and co-workers (Scheme 2-1b).[17] In the past few years, various modifications of this Pd-catalyzed reaction have been developed.[18] However, palladium is costly and only a few electron-withdrawing substituents on the aromatic ring of arylboronic acids were employed. Recently, Cheng *et al*. disclosed a copper-catalyzed oxidative coupling of arylboronic acids with terminal alkynes.[19] However, the reported method suffers from some disadvantages including high reaction temperature, long reaction time (36 h), and only moderate yields. From a synthetic point of view, the development of an improved procedure, employing an inexpensive catalyst for widespread application, has remained a highly desirable goal.

We reported the C-F borylation of fluoroarenes using a NHC (N-heterocyclic carbene)-ligated Ni complex as a catalyst to generate fluorinated arylboronic acid pinacol esters (Ar_FBpin) in good to excellent yields.[20a,b] Very recently, we reported optimized conditions for the Suzuki-Miyaura cross-coupling of Ar_FBpin with aryl iodides and bromides using a combination of CuI and phenanthroline as a catalyst precursor to generate cross-coupled products in moderate to excellent yields.[20c] We have recently

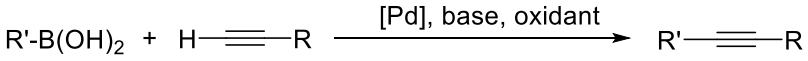
reported the palladium-catalyzed homocoupling of fluorinated arylboronates,[20d] and the borylation of aryl chlorides, using NHC-stabilized nickel(0) complexes[20e] or a readily prepared NHC-stabilized Cu catalyst.[20f] Inspired by these results, we attempted to develop a Cu-catalyst system for the oxidative cross-coupling of Ar_FBpin compounds with terminal alkynes.

Scheme 2-1. Selected Oxidative Cross-Coupling Reactions of Alkynes

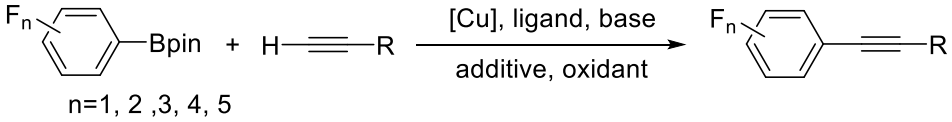
a) Polyfluoroarenes with terminal alkynes[12]



b) Arylboronic acids with terminal alkynes[17,18]



c) This work: Polyfluorophenylboronate esters with terminal alkynes



moderate to excellent yields
mild reaction conditions
high functionality tolerance
wide substrate scope
simple terminal alkyne as coupling partner
inexpensive reaction system

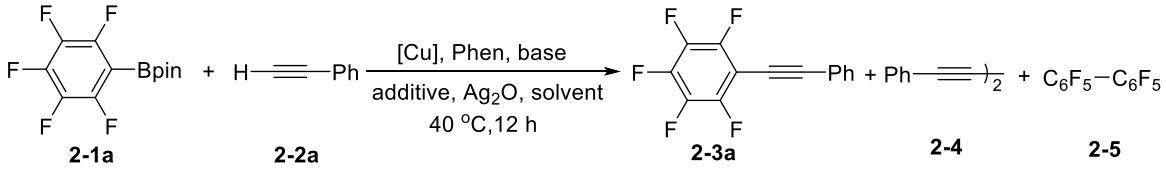
2.3 Result and Discussion

2.3.1 Optimization of Reaction Conditions

We initially investigated the cross-coupling reaction with model substrates pentafluorophenyl-Bpin (**2-1a**) and phenylacetylene (**2-2a**), using Ag_2O as the oxidant and

phenanthroline (Phen) as the ligand. During our initial experiments, no reaction occurred when $CuBr_2$ was employed as the metal source, with *t*BuOLi as the base in DMF solution (Table 2-1, entry 1). However, employing CuCl as catalyst precursor gave rise to compound **2-3a** in 10% yield (Table 2-1, entry 2). The introduction of $Cu(OAc)_2$ as the catalyst precursor improved the yield to 18% (Table 2-1, entry 3). However, large amounts of diyne byproduct **2-4** and perfluorobiphenyl compound **2-5** were produced. We speculated that strong bases, such as *t*BuOLi, might accelerate the formation of **2-5**. Under otherwise identical conditions, replacing the strong base with K_3PO_4 effectively inhibited the homocoupling of pentafluorophenylBpin (Table 2-1, entry 4). To our surprise, the addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) significantly improved the yield to 58% and suppressed the formation of **2-4** (Table 2-1, entry 5). It is possible that DDQ serves as an electron-transfer mediator.[12,21] To optimize the reaction performance, we screened the reaction parameters, including the base and the solvent. Of the bases examined, K_2CO_3 proved to be the most effective (entry 7). Both KF and Cs_2CO_3 gave significantly lower yields (entries 6 and 8). In addition, reaction optimization also revealed that the solvent had a significant impact on this reaction. Lower yields were observed when reactions were performed in other solvents such as 1,2-dichloroethane (DCE), CH_3CN, THF, DMSO, MTBE, and toluene (entries 9-14). Notably, the replacement of Ag_2O with O_2 failed to give any desired product (entry 17), indicating the unique roles of Ag_2O in promoting this reaction. Attempts to run the reaction in air resulted in a very low yield of the desired product (entry 15). Reducing the amount of K_2CO_3 and Ag_2O also diminished the yield (Table 2-1, entries 18 and 19).

Table 2-1. Optimization of Reaction Conditions[a]



Entry	[Cu] (15 mol%)	Base (2 equiv)	Additive (40 mol%)	Solvent	Yield(%)[b]		
					2-3a	**2-4**	**2-5**
1	$CuBr_2$	*t*BuOLi	-	DMF	0	65	36
2	CuCl	*t*BuOLi	-	DMF	10	55	35
3	$Cu(OAc)_2$	*t*BuOLi	-	DMF	18	60	35
4	$Cu(OAc)_2$	K_3PO_4	-	DMF	35	52	8
5	$Cu(OAc)_2$	K_3PO_4	DDQ	DMF	58	5	8
6	$Cu(OAc)_2$	Cs_2CO_3	DDQ	DMF	11	25	25
7	**$Cu(OAc)_2$**	**K_2CO_3**	**DDQ**	**DMF**	**82**	**3**	**4**
8	$Cu(OAc)_2$	KF	DDQ	DMF	15	10	45
9	$Cu(OAc)_2$	K_2CO_3	DDQ	MTBE	0	5	35
10	$Cu(OAc)_2$	K_2CO_3	DDQ	DCE	0	5	0
11	$Cu(OAc)_2$	K_2CO_3	DDQ	toluene	0	10	10
12	$Cu(OAc)_2$	K_2CO_3	DDQ	DMSO	25	15	20
13	$Cu(OAc)_2$	K_2CO_3	DDQ	CH_3CN	10	15	10
14	$Cu(OAc)_2$	K_2CO_3	DDQ	THF	5	10	15
15[c],	$Cu(OAc)_2$	K_2CO_3	DDQ	DMF	5	5	40
16[d]	$Cu(OAc)_2$	K_2CO_3	DDQ	DMF	5	10	35
17[e,f]	$Cu(OAc)_2$	K_2CO_3	DDQ	DMF	0	6	10
18[g]	$Cu(OAc)_2$	K_2CO_3	DDQ	DMF	35	5	30
19[h]	$Cu(OAc)_2$	K_2CO_3	DDQ	DMF	25	28	30

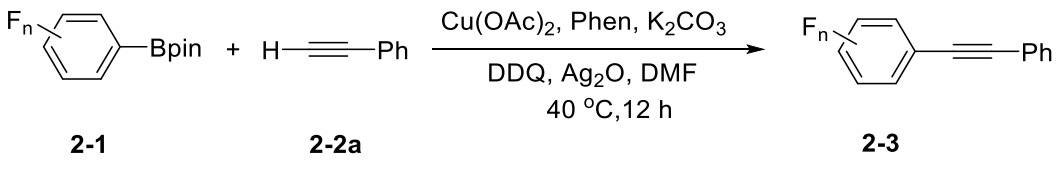
[a] Reaction conditions: **2-1a** (0.4 mmol), **2-2a** (0.45 mmol), $Cu(OAc)_2$ (15 mol%), phenanthroline (Phen, 15 mol%), Ag_2O (1.8 equiv), DDQ (40 mol%), base (2.0 equiv),

anhydrous and degassed solvent (5 mL). The mixture was stirred at 40 °C under argon, in a sealed tube for 12 h. [b] 2-**3a**: isolated yield, **2-4**: isolated yield, **2-5**: the yields were determined by GC-MS analysis *vs*. a calibrated internal standard (*n*-dodecane) and are averages of two runs; [c] The reaction was performed in air. [d] Room temperature. [e] In the absence of Ag_2O. [f] Under O_2. [g] Ag_2O (1.2 equiv.). [h] Base (1.0 equiv.).

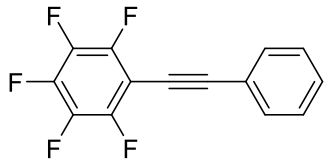
2.3.2 Investigation of Reaction Scope

With the optimized conditions in hand, we focused our attention on investigating the scope and limitations of the oxidative cross-coupling reaction. As shown in Scheme 2-2, various fluorophenylboronate esters **2-1** containing 1-4 fluorine atoms were tested. Under the standard conditions (Table 2-1, entry 7), different tetrafluorophenylboronate esters and trifluorophenylboronate esters smoothly underwent alkynylation, giving good to excellent yields (Scheme 2-2, **2-3b-3f**). However, these reaction conditions were not suitable for Ar_FBpin substrates containing di- or mono-fluorinated arylboronates, such as 2,5- or 2,3-difluorophenyl-Bpin (**2-1g** and **2-1i**) and 3-fluorophenyl-Bpin (**2-1h**), perhaps due to the lower Lewis acidity of the boronates, which is impacted by the number fluorine and, especially, *ortho*-fluorine substituents. We speculated that increasing the temperature might be crucial for overcoming the barrier to C-B bond activation and thus to obtain efficient catalysis. When reactions were performed at 80 °C, the corresponding products **2-3g** and **2-3i** were formed in good yields. It also noteworthy that replacement of the weak base with a stronger base afforded the corresponding product in good yield (**2-3h**).

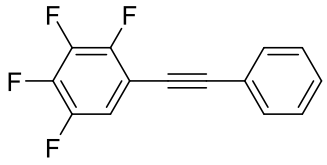
Scheme 2-2. Scope of the Reaction with Respect to the Different Polyfluorophenyl Boronate Substrates 2-1 [a]



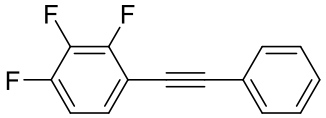
2-1 **2-2a** **2-3**



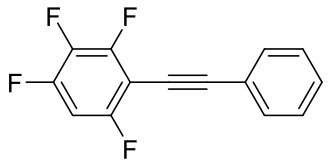
2-3a: 82%[c]



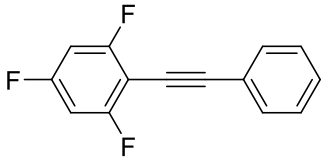
2-3b: 92%



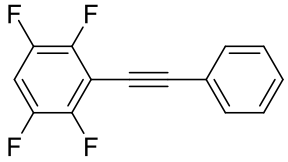
2-3c: 83%



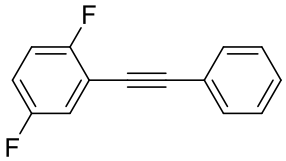
2-3d: 70%



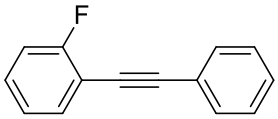
2-3e: 72%



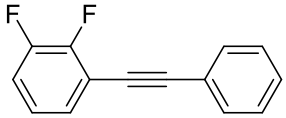
2-3f: 86%



2-3g: 80%[d]



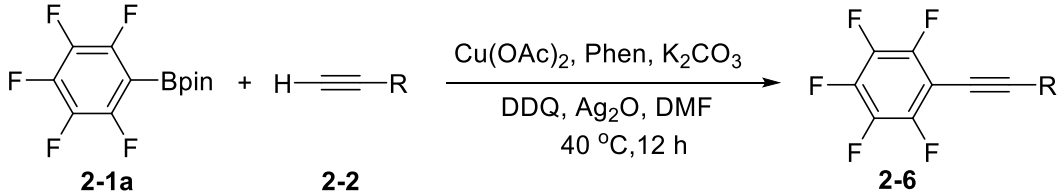
2-3h: 85%[d,e]



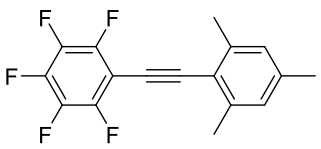
2-3i:65%[d]

[a] Reaction conditions: **2-1** (0.4 mmol), **2-2a** (0.45 mmol), $Cu(OAc)_2$ (15 mol %), Phen (15 mol %), Ag_2O (1.2 equiv.), DDQ (40 mol %), K_2CO_3 (2.0 equiv.), DMF (4 mL), 40 °C, 12 h, Argon. [b] **2-3**: isolated yield. [c] Ag_2O (1.8 equiv.). [d] 80 °C. [e] *t*BuOLi.

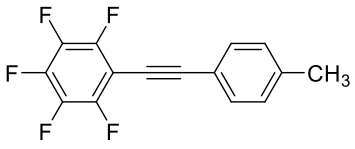
Scheme 2-3. Scope of the Reaction with Respect to the Different Terminal Alkyne Substrates 2-2[a]



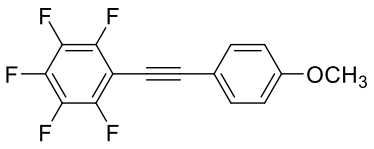
2-1a **2-2** **2-6**



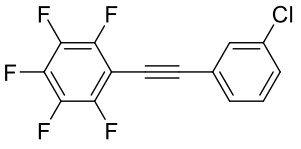
2-6a: 86%



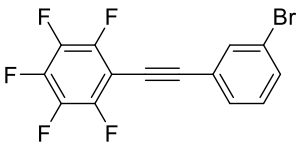
2-6b:81%



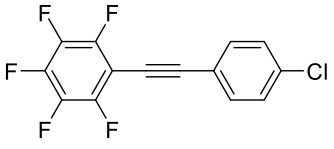
2-6c: 78%



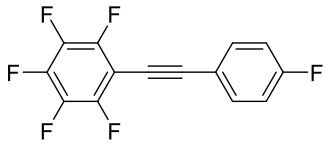
2-6d: 76%



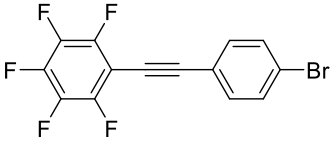
2-6e: 68%



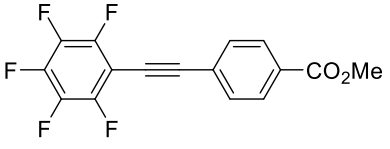
2-6f: 60%



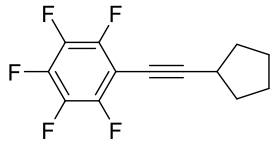
2-6g: 65%



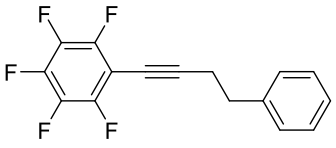
2-6h: 85%



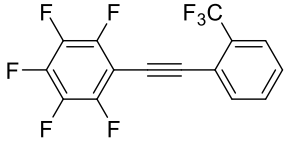
2-6i: 77%



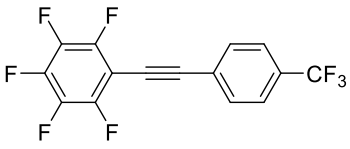
2-6j: 45%[c]



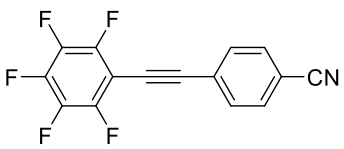
2-6k: 80%



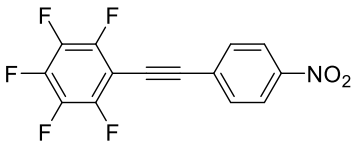
2-6l: 48%



2-6m: 50%



ND



ND

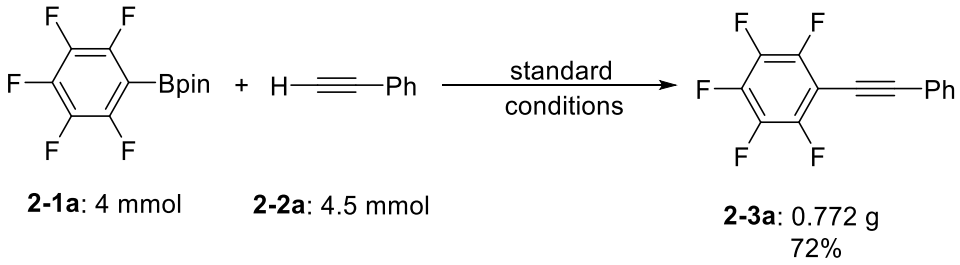
[a] Reaction conditions: **2-1a** (0.4 mmol), **2-2** (0.45 mmol), $Cu(OAc)_2$ (15 mol %), Phen (15 mol %), Ag_2O (1.8 equiv), DDQ (40 mol %), K_2CO_3 (2.0 equiv.), DMF (4 mL), 40 °C, 12 h, Argon. [b] **2-6**: isolated yield. [c] 24 h.

The substituents of alkynes **2-2** were then varied, in order to further explore the scope of the reaction. As shown in Scheme 2-3, a series of alkynes **2-2** with different electron-withdrawing and electron-donating substituents on the aromatic ring were subjected to the optimal conditions. The experimental results showed that a broad range of substituents on

the arylalkynes **2-2**, including methyl, methoxy, chloro, bromo, and fluoro groups at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring were well tolerated, providing the desired compounds in moderate to excellent yields (Scheme 2-3, **2-6a-6h**). Furthermore, the structures of compounds **2-6a** and **2-6g** were unambiguously confirmed *via* single crystal X-ray diffraction (*vide infra*). An ester group, which may not be tolerated in reactions employing organozinc reagents, is also compatible with this reaction (**2-6i**). Importantly, aliphatic alkynes proceeded to give the desired products in moderate to good yields (**2-6j** and **2-6k**). With a highly electron-withdrawing CF_3-substituent, only moderate yields were observed (**2-6l** and **2-6m**). Unfortunately, less reactive 4-nitro-phenyl and 4-cyano-phenyl alkynes were not suitable for the reaction under the standard conditions.

2.3.3 Gram Scale Reaction

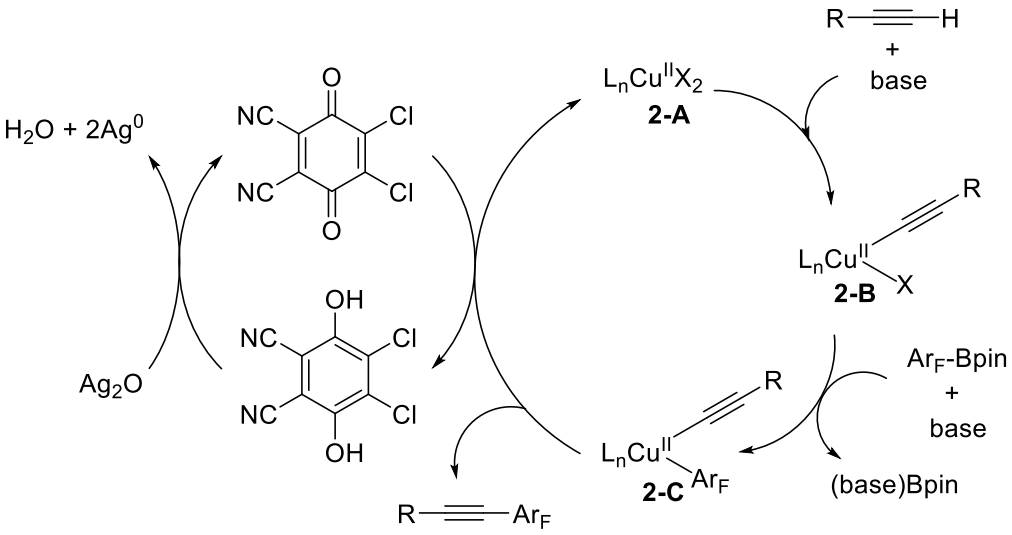
To examine the feasibility of scaling up the reaction, a gram-scale coupling of C_6F_5-Bpin with phenylacetylene was employed (Scheme 2-4). The desired coupling product was obtained with minimal loss of yield (72%).



Scheme 2-4. Gram scale reaction.

2.3.4 Plausible mechanism

Based on previous reports,[22] and the aforementioned observations, a plausible catalytic cycle for our oxidative cross-coupling reaction is shown in Scheme 2-5. The first step would involve the addition of alkynyl anion leading to the formation of alkynylcopper(II) species **2-B**. Subsequent transmetalation between Ar_FBpin and intermediate **2-B** occurs to form intermediate **2-C**. The desired product **2-3a** would be generated by C-C reductive elimination. Finally, the oxidation of Cu(0) species with DDQ and Ag_2O regenerates **2-A** to complete the catalytic cycle.



Scheme 2-5: Proposed Mechanism

2.3.5 Molecular and Crystal Structures: Intermolecular π···π Stacking Interactions

The crystal structures of the cross-coupling products **2-6a** and **2-6g** were analyzed using single-crystal X-ray diffraction. The molecular geometries of these compounds in their crystal structures are shown in Figure 2-1. The central C≡C bond lengths are 1.195(2) and 1.1996(6) Å (Table 2-2) and, hence, typical of C≡C triple bonds (1.192 Å).[23] The sp-sp^2 C–C single bonds between the alkyne and the fully fluorinated phenyl rings are slightly shorter (1.4265(7) and 1.427(2) Å) than the corresponding bonds to the mesityl ring of **2-6a** (1.4350(7) Å) or the *para* mono-fluorinated phenyl ring of **2-6g** (1.437(2) Å). The sp-sp^2 C–C bonds to tetra- or penta-fluorinated phenyl rings are also shorter than those to the fully or mostly hydrogen-containing phenyl rings of mixed compounds in other partially fluorinated tolans,[24] rod-like 1,4-bis(phenylethynyl)benzenes,[25] and phenyl and perfluorophenyl end-capped polyynes.[26] The shortening is due to the strong electron-withdrawing nature of the fluorine atoms, and the length difference is also observed in the co-crystals of fully hydrogen-containing and fully fluorinated tolans,[24] rod-like 1,4-bis(phenylethynyl)benzenes,[27] and phenyl end-capped polyynes.[26] The molecules of **2-6a** and **2-6g** are nearly planar with a very small twist between the aryl moieties (2.959(3) and 3.04(5)°, Table 2-2). A small twist angle of between 0 and 6° is also typical of the hydrogenated and fluorinated tolans, rod-like 1,4-bis(phenylethynyl)benzenes, and phenyl endcapped polyynes.[24-27] Larger twist angles

were reported for compounds related to **2-6g** in which the fluorine atom at the *para*-position of the phenyl ring is substituted by iodine (9.4(2)°), bromine (15.69(8)°), and NO_2 (9.90(7)°).[28] This may be related to the prevalence of different intermolecular interactions in these compounds (see below).

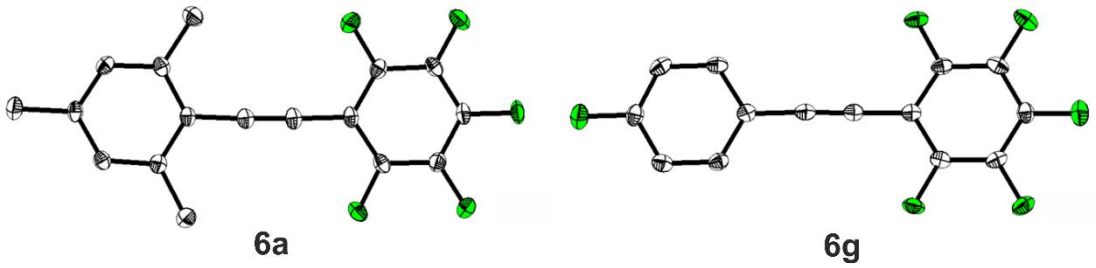


Figure 2-1. Solid-state molecular structures of **2-6a** and **2-6g** determined by single-crystal X-ray diffraction at 100 K. Ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colors: white (carbon), green (fluorine).

Table 2-2. Selected bond lengths (Å) and angles (°) of 2-**6a** and **2-6g**, and π···π stacking distances (Å).

	2-6a	**2-6g**
C≡C triple bond	1.1996(6)	1.195(2)
$C_{Aryl(H/F)}$–C_{triple}	1.4350(7)	1.437(2)
$C_{Aryl(F)}$–C_{triple}	1.4265(7)	1.427(2)
∠ Aryl(F)-Aryl(H/F)	2.959(3)	3.04(5)
centroid-centroid distance	3.586(3) 3.629(3)	3.705(3) 3.913(3)
interplanar separation	3.361(3) / 3.424(3) 3.325(3) / 3.376(3)	3.349(2) / 3.415(2) 3.379(2) / 3.438(2)
offset shift[a]	1.248(3) / 1.064(2) 1.455(2) / 1.332(2)	1.586(3) / 1.439(3) 1.975(3) / 1.868(3)

[a] The offset shift, also called inter-centroid shift, is the distance within a plane of an aryl ring between the centroid of the respective aryl ring and the intersection point with the normal to the plane through the centroid of the other aryl ring.

In compounds **2-6a** and **2-6g**, the nearly planar molecules are related by inversion symmetry and are oriented offset face-to-face in a head-to-tail fashion forming infinite π-stacks (Figure 2-2). The interplanar separations between the aromatic rings (3.325(3) – 3.438(2) Å, Table 2-2) are in the normal range of π-π stacking interactions, which are typical of molecules for which the packing is dominated by arene-perfluoroarene interactions. The differences in electronegativity of hydrogen and fluorine atoms with respect to the carbon atoms leads to the formation of opposite multipoles for fully fluorinated and nonfluorinated aryl groups and, hence, to attractive multipole forces between these groups.[29] Head-to-tail stacking *via* arene-perfluoroarene interactions, analogously to that observed in **2-6a** and **2-6g**, is commonly found in self-complementary compounds that contain both fluorinated and nonfluorinated aryl groups. Examples are partially fluorinated tolans[24] and phenyl-endcapped polyynes,[26] but also co-crystals of

bis(phenylethynyl)benzenes with inversely alternating fluorinated and nonfluorinated phenyl rings.[25] We conclude that methylation at the 2-, 4-, and 6-positions of the phenyl ring in **2-6a** does not alter this common stacking motif and, hence, the influence of arene-perfluoroarene interaction on the molecular packing. Arene-perfluoroarene π-stacking was also observed in the 1:1 co-crystal of mesitylene and hexafluorobenzene.[30] Weak intermolecular C–H···F, C···F, and F···F interactions exist between adjacent stacks in **2-6a** and **2-6g** (Figure 2-2, Table 2-4). Mono-fluorination at the *para*-position of the phenyl ring in **2-6g** does not have a significant influence on the arene-perfluoroarene packing, which is very similar to that of 1-pentafluorophenyl-2-phenylacetylene.[24] This was expected as the mono-chlorination of partially fluorinated tolan at the same *para* position did not alter the packing motif.[28a] The effect of halogenation with chlorine, bromine, and iodine atoms at the *para*-positions of partially fluorinated tolans on the presence of arene-perfluoroarene interaction, studied earlier by Marder and co-workers,[28a] revealed the absence of arene-perfluoroarene stacking only for the compounds substituted with the heavier halogens (Br, I). This was explained by the prevalence of Br···Br and I···I interactions determining the packing of the molecules.[28a] Also note the larger twist angle between the phenyl rings in these compounds (15.69(8) and 9.4(2)°) when compared to those in arene-perfluoroarene π-stacked tolans (see discussion above). Similarly, the substitution of other strong electron-withdrawing groups such as NO_2 and CN at the *para*-position of the phenyl ring in partially fluorinated tolans showed the prevalence of O···O and C–H···N interactions and the absence of arene-perfluoroarene interactions in their crystal structures.[28b]

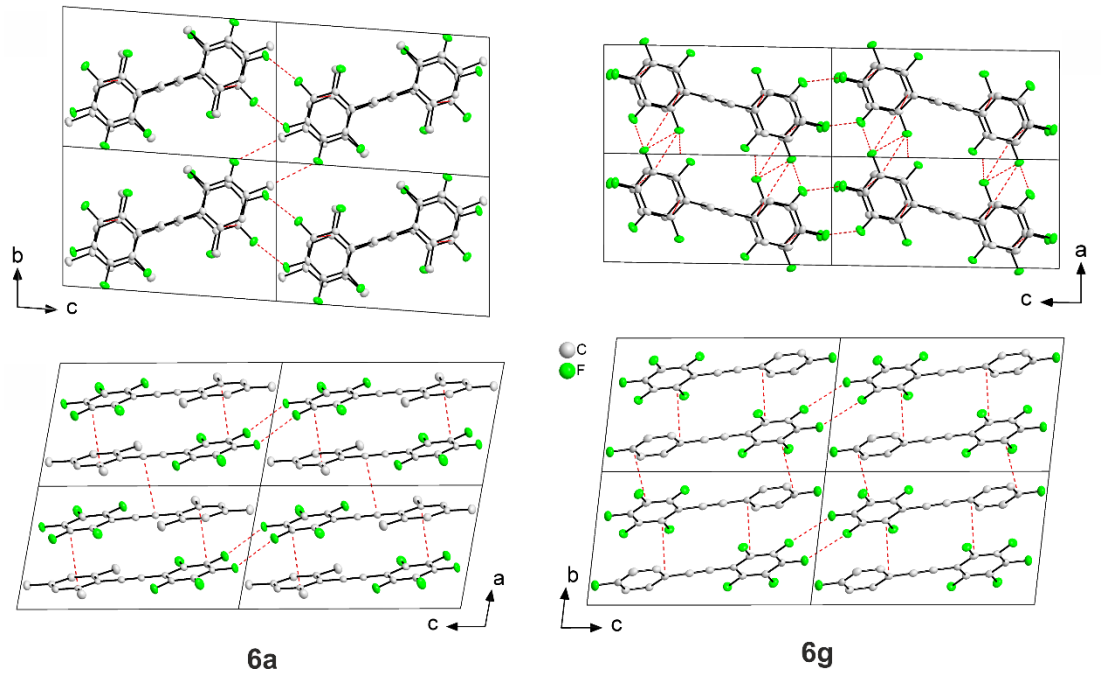


Figure 2-2. Crystal structures of (left) **2-6a** and (right) **2-6g** projected along (top) the stacking direction of the molecules, and (bottom) the *b* and *a* axis, respectively, at 100 K. Molecules are π-stacked along the *a* axis (2-**6a**) and the *b* axis (2-**6g**), respectively, in alternating orientations. Four unit cells are shown in each projection. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colors: white (carbon), green (fluorine). Red dotted lines represent intermolecular contacts which are shorter than the sum of the Van der Waals radii.

2.4 Conclusions

In conclusion, we have developed a copper-catalyzed method for the direct alkynylation of electron-deficient polyfluorophenylboronate esters with terminal alkynes. This reaction features broad functional group tolerance, mild reaction conditions, and simple operation. From a synthetic point of view, the present reaction has the potential to be applied widely in organic synthesis, because many shelf-stable aryl and alkyl boronate esters are commercially available. The partially fluorinated tolans also display interesting fluoroarene-arene π-stacking interactions in the solid-state, as demonstrated by single-crystal X-ray diffraction in two cases.

2.5 Detailed Experiments and Characterization Data

2.5.1 General Information

NMR spectra were recorded on a Bruker AC–500 spectrometer (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR, and 470 MHz for ^{19}F NMR) with $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm and ^{1}H NMR spectra were referenced via residual proton resonances of $CDCl_3$ (7.26 ppm), $^{13}C\{^{1}H\}$ spectra were referenced to $CDCl_3$ (77.16 ppm) and ^{19}F spectra are referenced to external $CFCl_3$. The following abbreviations are used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. GCMS analyses were performed on an Agilent Technologies GCMS system (GC 7890A, EI-MS 5975C). HRMS were recorded using a Thermo Scientific Exactive Plus Orbitrap MS system with either an HESI source with an aux-gas temperature of 50 ℃ or an APCI source with a corona needle with an aux-gas temperature of 400 ℃. Chemical yields refer to pure, isolated products. Automated flash chromatography was performed on silica gel (Biotage SNAP catridge KP-Sil), obtained from Biotage, using a Biotage® Isolera Four Flash system. Solvents were generally removed using a rotary evaporator *in vacuo* at a maximum temperature of 55 ℃. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. B_2pin_2 was kindly provided by AllyChem Co. Ltd. (Dalian, China). Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer as solids, using an ATR unit, and are reported in cm^{-1}. Elemental analyses were performed on a LECO CHNS-932 Elemental Analyzer in our institute.

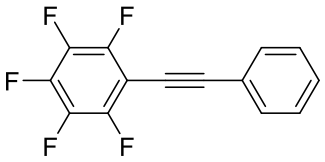
2.5.2 Borylation of Polyfluoroarenes

In an argon filled glovebox, a solution of $[Ir(COD)(OMe)]_2$ (0.5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2 mol%), bis(pinacolato)diboron (B_2pin_2) (0.5 eq) and polyfluoroarene (1 eq) in hexane (dry and degassed) was stirred at room temperature in a sealed reaction vessel for 48 h.[31] The volatile materials were removed *in vacuo* to give the crude product, together with unreacted starting material. The residue was then purified by flash chromatography on silica gel, to provide the corresponding fluoroarylboronate ester product.

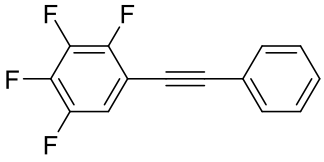
2.5.3 General Procedure

In an argon filled glovebox, a microwave reaction tube with a sealable crimp-cap and equipped with a magnetic stir bar was charged with a polyfluorophenylboronate ester **2-1** (0.4 mmol), terminal alkynes **2-2** (0.45 mmol), $Cu(OAc)_2$ (11 mg, 15 mol %), Phen (11 mg, 15 mol %), DDQ (50 mg, 40 mol %), K_2CO_3 (138 mg, 0.8 mmol), in DMF (3.0 mL, dried and degassed) and Ag_2O (1.8/1.2 eq, 167 mg/111 mg) was added at room temperature. The sealed reaction vessel was removed from the glovebox and placed in an oil bath at 40 °C for 12 h. After the reaction was completed, it was cooled to room temperature and monitored for completion by TLC. The resulting solution was poured into saturated brine (5 mL) and then extracted with EtOAc (two times). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: n-pentane) to give the desired product.

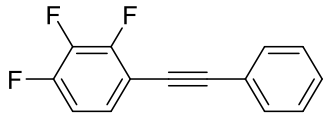
2.5.4 Characterization Data



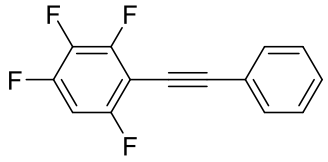
(**2-3a**):[32] 87.9 mg, 82% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.59-7.57 (dm, J = 7 Hz, 2H), 7.43-7.37 (m, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.1 (dm, $J_{F\text{-}C}$ = 250 Hz), 141.4 (dm, $J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $J_{F\text{-}C}$ = 250 Hz), 131.9, 129.6, 128.5, 121.6, 101.5 (m), 100.3 (tm, $J_{F\text{-}C}$ = 18 Hz), 73.1 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.1 – -136.2 (m, 2F), -152.8 – -152.9 (m, 1F), -161.9 – -162.0 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_5F_5$: 268.0306, found: 268.0295.



(**2-3b**): 92 mg, 92% yield, white solid. IR (ATR[cm^{-1}]) 2223 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56-7.54 (m, 2H), 7.41-7.36 (m, 3H), 7.16-7.10 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 148.2 (dm, J_{F-C} = 250 Hz), 146.9 (dm, J_{F-C} = 250 Hz), 141.9 (dm, J_{F-C} = 248 Hz), 141.8 (dm, J_{F-C} = 250 Hz), 131.8, 129.3, 128.5, 121.8, 114.2 (dd, J_{F-C} = 21 Hz, 4 Hz), 108.5 (m), 96.5 (m), 79.6 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.2 – -135.3 (m, 1F), -139.3 – -139.4 (m, 1F), -153.7 – -153.8 (m, 1F), -154.9 – -155.1 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_6F_4$: 250.0400, found: 250.0396. Elemental analysis calcd for $C_{14}H_6F_4$: C 67.21, H 2.24; found: C 67.47, H 2.49.

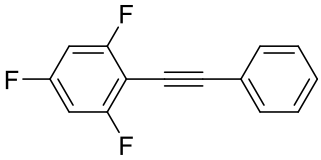


(**2-3c**):[33] 77 mg, 83% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.57-7.55 (m, 2H), 7.38-7.37 (m, 3H), 7.27-7.22 (m, 1H), 6.98-6.93 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 151.9 (ddd, J_{F-C} = 250 Hz, 12 Hz, 4 Hz), 151.3 (ddd, J_{F-C} = 250 Hz, 10 Hz, 3 Hz), 140.2 (dt, J_{F-C} = 250 Hz, 15 Hz), 131.7, 129.0, 128.5, 127.0 (m), 122.3, 112.3 (dd, J_{F-C} = 19 Hz, 4 Hz), 109.8 (dd, J_{F-C} = 13 Hz, 4 Hz), 95.3 (m), 80.5 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -130.2 – -130.3 (m, 1F), -131.9 – -132.0 (m, 1F), -159.5 – -159.6 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_7F_3$ $[M+H]^+$ 233.0573, found: 233.0562.

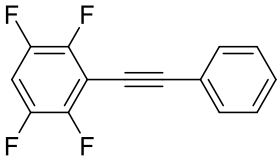


(**2-3d**): 70 mg, 70% yield, white solid. IR (ATR[cm^{-1}]) 2225 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.59-7.57 (m, 2H), 7.40-7.36 (m, 3H), 6.85-6.80 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 157.4 (dm, J_{F-C} = 250 Hz), 151.7 (dm, J_{F-C} = 248 Hz), 150.6 (dm, J_{F-C} = 250 Hz), 137.3 (dm, J_{F-C} = 249 Hz), 131.8, 129.3, 128.5, 121.9, 100.9 (td, J_{F-C} = 25 Hz, 4 Hz), 100.2 (m), 74.2 (t, J_{F-C} = 3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -110.9 – -111.0 (m, 1F), -128.4 – -128.5 (m, 1F), -130.0 – -130.1 (m,

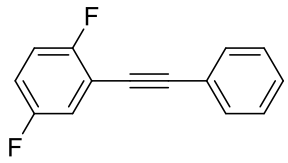
1F), -164.3 – -164.4 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_6F_4$: 250.0400, found: 250.0396. Elemental analysis calcd for $C_{14}H_6F_4$: C 67.21, H 2.24; found: C 67.55, H 2.41.



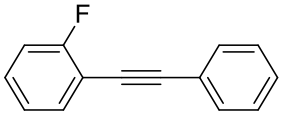
(**2-3e**): 66.8 mg, 72% yield, white solid. IR (ATR[cm^{-1}]) 2223 ($\nu_{C\equiv C}$). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.58-7.56 (m, 2H), 7.38-7.32 (m, 3H), 6.74-6.71 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 163.2 (dm, J_{F-C} = 250 Hz), 162.2 (dm, J_{F-C} = 250 Hz), 131.7, 128.9, 128.4, 122.4, 100.5 (m), 98.8, 75.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -104.3 – -104.4 (m, 2F), -105.2 – -105.3 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_7F_3$: 232.0494, found: 232.0490. Elemental analysis calcd for $C_{14}H_7F_3$: C 72.42, H 3.04; found: C 72.71, H 3.24.



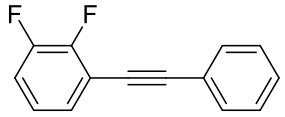
(**2-3f**): 86 mg, 86% yield, white solid. IR (ATR[cm^{-1}]) 2227 ($\nu_{C\equiv C}$). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.61-7.59 (m, 2H), 7.42-7.37 (m, 3H), 7.08-7.02 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 146.6 (dm, J_{F-C} = 250 Hz), 145.8 (dm, J_{F-C} = 250 Hz), 131.9, 129.6, 128.5, 121.7, 106.1 (t, J_{F-C} = 23 Hz), 105.5 (m), 101.8 (t, J_{F-C} = 4 Hz), 74.4 (t, J_{F-C} = 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.6 – -136.7 (m, 2F), -138.9 – -139.1 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_6F_4$: 250.0400, found: 250.0396. Elemental analysis calcd for $C_{14}H_6F_4$: C 67.21, H 2.24; found: C 67.45, H 2.48.



(**2-3g**): 68.6 mg, 80% yield, oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.57-7.54 (m, 2H), 7.38-7.35 (m, 3H), 7.22-7.19 (m, 1H), 7.08-6.98 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 158.8 (dd, J_{F-C} = 248 Hz, 3 Hz), 158.1 (dd, J_{F-C} =250 Hz, 3 Hz), 132.5, 131.8, 129.2, 128.9, 128.5, 122.4, 119.4 (dd, J_{F-C} = 25 Hz, 2 Hz) , 116.5 (m), 113.1 (m), 95.3 (d, J_{F-C} = 4 Hz), 81.6 (d, J_{F-C} = 3 Hz), 73.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -115.9 – -116.0 (m, 1F), -118.9 – -119.0 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_8F_2$ $[M+H]^+$ 215.0667, found: 215.0662.

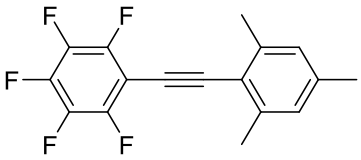


(**2-3h**):[34] 66.7 mg, 85% yield, oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56-7.54 (m, 2H), 7.37-7.36 (m, 3H), 7.32-7.30 (m, 2H), 7.25-7.23 (m, 1H), 7.07-7.03 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 162.4 (d, J_{F-C} = 250 Hz), 131.7, 129.9 (d, J_{F-C} = 9 Hz), 128.6, 128.4, 127.5 (d, J_{F-C} = 3 Hz), 125.2 (d, J_{F-C} = 10 Hz), 122.8, 118.4 (d, J_{F-C} = 22 Hz), 115.6 (d, J_{F-C} = 21 Hz), 90.3, 88.1 (d, J_{F-C} = 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -112.9 – -113.0 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_9F$ 196.0688, found: 196.0673.

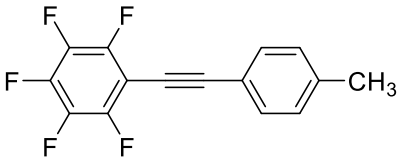


(**2-3i**): 55.6 mg, 65% yield, oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.58-7.56 (m, 2H), 7.38-7.35 (m, 3H), 7.29-7.26 (m, 1H), 7.17-7.12 (m, 1H), 7.08-7.03 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 150.9 (dd, J_{F-C} = 249 Hz, 14 Hz), 150.6 (dd, J_{F-C} = 250 Hz, 12 Hz), 132.5, 131.8, 128.9, 128.4, 128.2 (d, J_{F-C} = 3 Hz), 123.9 (dd, J_{F-C} = 12 Hz, 3 Hz), 117.4 (d, J_{F-C} = 17 Hz), 114.2 (dd, J_{F-C} = 13 Hz, 2 Hz), 95.6 (d, J_{F-C} = 4 Hz), 81.6.

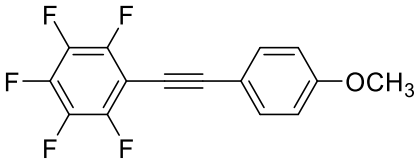
^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -134.9 – -135.0 (m, 1F), -137.5 – -137.6 (m, 1F). HRMS (ESI): calcd. for $C_{14}H_8F_2$ $[M+H]^+$ 215.0667, found: 215.0662.



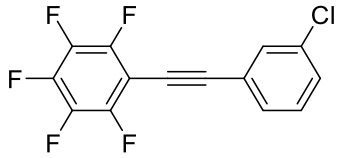
(**2-6a**): 106.6 mg, 86% yield, white solid. IR (ATR[cm^{-1}]) 2223 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.92-6.91 (m, 2H), 2.47 (s, 6H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 146.7 (dm, J_{F-C} = 250 Hz), 141.1 (dm, J_{F-C} = 251 Hz), 140.8, 139.5, 137.6 (dm, J_{F-C} = 252 Hz), 127.8, 118.5, 100.9 (tm, J_{F-C} = 18 Hz), 100.1 (m), 80.6 (m), 21.4, 20.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.6 – -136.7 (m, 2F), -150.4 (t, J_F = 21 Hz, 1F), -162.3 – -162.4 (m, 2F). HRMS (ESI): calcd. for $C_{17}H_{11}F_5$ $[M+H]^+$ 311.0854, found: 311.0842. Elemental analysis calcd for $C_{17}H_{11}F_5$: C 65.81, H 3.57; found: C 65.98, H 3.72.



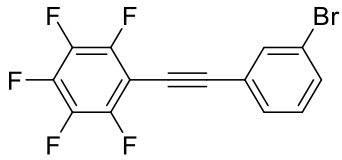
(**2-6b**):[35] 91.4 mg, 81% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.48-7.46 (m, 2H), 7.21-7.19 (m, 2H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.1 (dm, J_{F-C} = 250 Hz), 141.3 (dm, J_{F-C} = 250 Hz), 140.1, 137.7 (dm, J_{F-C} = 250 Hz), 131.8, 129.3, 118.5, 101.9 (m), 100.6 (tm, J_{F-C} = 18 Hz), 72.5 (m), 21.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.2 – -136.3 (m, 2F), -153.3 (t, J_F = 21 Hz, 1F), -162.0 – -162.1 (m, 2F). HRMS (ESI): calcd. for $C_{15}H_7F_5$ $[M+H]^+$ 283.0541, found: 283.0526.



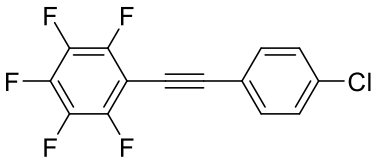
(**2-6c**):[35] 92.9 mg, 78% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.53-7.50 (m, 2H), 6.92-6.89 (m, 2H), 3.85 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 160.7, 147.1 (dm, J_{F-C} = 252 Hz), 141.1 (dm, J_{F-C} = 250 Hz), 137.7 (dm, J_{F-C} = 250 Hz), 133.5, 114.2, 113.6, 101.9 (m), 100.7 (tm, J_{F-C} = 18 Hz), 72.0 (m), 55.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.5 – -136.6 (m, 2F), -153.7 (t, J_F = 21 Hz, 1F), -162.1 – -162.2 (m, 2F). HRMS (ESI): calcd. for $C_{15}H_7F_5O$ $[M+H]^+$ 299.0490, found: 299.0475.



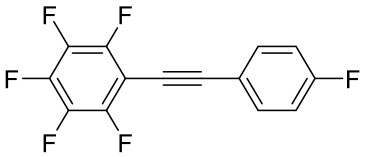
(**2-6d**):[35] 91.8 mg, 76% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.57-7.56 (m, 1H), 7.47-7.45 (td, J = 8 Hz, 2 Hz, 1H), 7.41-7.39 (m, 1H), 7.34-7.31(m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.2 (dm, J_{F-C} = 250 Hz), 141.7 (dm, J_{F-C} = 250 Hz), 137.7 (dm, J_{F-C} = 250 Hz), 134.5, 131.7, 130.0, 129.9, 129.8, 123.2, 99.8 (m), 74.1 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.6 – -135.7 (m, 2F), -151.8 – -151.9 (m, 1F), -161.5 – -161.6 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_4F_5Cl$ 301.9926, found: 301.9905.



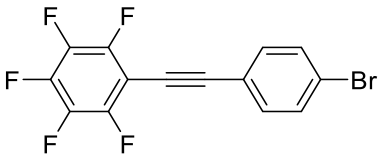
(**2-6e**): 96.8 mg, 68% yield, white solid. IR (ATR[cm^{-1}]) 2234 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.73 (t, J = 2 Hz, 1H), 7.56-7.54 (m, 1H), 7.52-7.50 (td, J = 8 Hz, 2 Hz, 1H), 7.27 (t, J = 8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.2 (dm, J_{F-C} = 249 Hz), 141.7 (dm, J_{F-C} = 251 Hz), 137.7 (dm, J_{F-C} = 251 Hz), 134.5, 132.8, 130.5, 129.5, 123.5, 122.4, 99.9 (m), 99.7 (m), 74.2 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.6 – -135.7 (m, 2F), -151.8 – -151.9 (m, 1F), -161.4 – -161.5 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_4BrF_5$: 345.9411, found: 345.9407. Elemental analysis calcd for $C_{14}H_4BrF_5$: C 48.45, H 1.16; found: C 48.62, H 1.36.



(**2-6f**): 72.5 mg, 60% yield, white solid. IR (ATR[cm^{-1}]) 2232 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.52-7.50 (dm, J = 8 Hz, 2H), 7.38-7.36 (dm, J = 8 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.2 (d, $J_{F\text{-}C}$ = 250 Hz), 141.5 (d, $J_{F\text{-}C}$ = 252 Hz), 137.6 (dm, $J_{F\text{-}C}$ = 250 Hz), 135.9, 133.1, 128.9, 120.0, 100.3 (m), 100.0 (m), 74.1 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.8 – -135.9 (m, 2F), -152.1 – -152.2 (m, 1F), -161.6 – -161.7 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_4ClF_5$: 301.9916, found: 301.9907. Elemental analysis calcd for $C_{14}H_4ClF_5$: C 55.56, H 1.33; found: C 55.72, H 1.49.

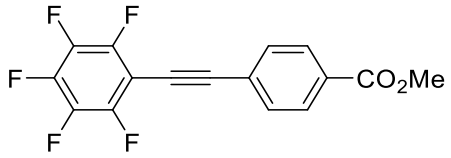


(**2-6g**):[35] 74.4 mg, 65% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.59-7.55 (m, 2H), 7.11-7.07 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 163.3 (d, $J_{F\text{-}C}$ = 250 Hz), 147.1 (dm, $J_{F\text{-}C}$ = 250 Hz), 141.5 (dm, $J_{F\text{-}C}$ = 252 Hz), 137.7 (dm, $J_{F\text{-}C}$ = 251 Hz), 133.9 (d, $J_{F\text{-}C}$ = 9 Hz), 117.6 (d, $J_{F\text{-}C}$ = 7 Hz), 116.0 (d, $J_{F\text{-}C}$ = 15 Hz), 100.3 (m), 72.9 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -108.3 – -108.4 (m, 1F), -136.0 – -136.1 (m, 2F), -152.6 (t, J_F = 21 Hz, 1F), -161.7 – -161.8 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_4F_6$ $[M+H]^+$ 287.0290, found: 287.0273.

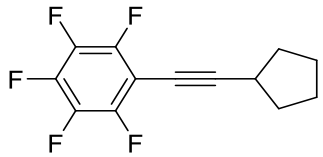


(**2-6h**):[35] 117.6 mg, 85% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.55-7.52 (dm, J = 8 Hz, 2H), 7.45-7.43 (dm, J = 9 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.1 (dm, $J_{F\text{-}C}$ = 250 Hz), 141.6 (dm, $J_{F\text{-}C}$ = 251 Hz), 137.7 (dm, $J_{F\text{-}C}$ = 250

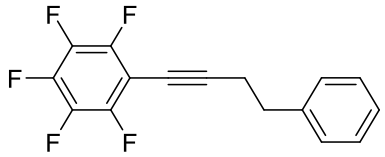
Hz),133.3, 131.9, 124.2, 120.5,100.3 (m), 100.0 (tm, J_{F-C} = 17 Hz), 74.2 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.8 – -135.9 (m, 2F), -152.1 – -152.2 (m, 1F), -161.6 – -161.7 (m, 2F). HRMS (ESI): calcd. for $C_{14}H_4F_5Br$ 345.9411, found: 345.9403.



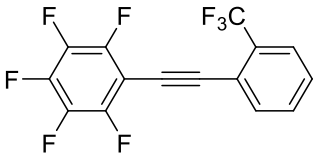
(**2-6i**):[32] 100.4 mg, 77% yield, white solid. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.07-8.05 (m, 2H), 7.65-7.63 (m, 2H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 166.3, 147.2 (dm, J_{F-C} = 253 Hz), 141.7 (d, J_{F-C} = 250 Hz), 137.7 (dm, J_{F-C} = 250 Hz), 131.8, 130.8, 129.6, 126.0, 100.4 (m), 99.8, 75.6, 52.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -135.5 – -135.6 (m, 2F), -151.6 – -151.7 (m, 1F), -161.4 – -161.5 (m, 2F). HRMS (ESI): calcd. for $C_{16}H_7F_5O_2$ 326.0365, found: 326.0372.



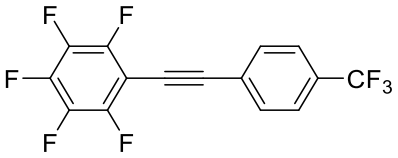
(**2-6j**): 91.8 mg, 76% yield, oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.94-2.88 (m, 1H), 2.04-1.99 (m, 2H), 1.81-1.73 (m, 4H), 1.65-1.61(m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.3 (dm, J_{F-C} = 251 Hz), 140.7 (dm, J_{F-C} = 250 Hz), 137.6 (dm, J_{F-C} = 248 Hz), 108.3 (m), 100.8 (m), 64.1 (m), 33.6, 30.9, 25.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -137.2 – -137.3 (m, 2F), -154.7 (t, J_F = 21 Hz, 1F), -162.5 – -162.6 (m, 2F). HRMS (ESI): calcd. for $C_{13}H_9F_5$ $[M-H]^-$ 259.0541, found: 259.0534.



(**2-6k**): 94.7 mg, 80% yield, oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.34-7.31 (m, 2H), 7.28-7.23 (m, 3H), 2.96 (t, J = 7 Hz, 2H), 2.79 (t, J = 7 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.5 (dm, $J_{F\text{-}C}$ = 250 Hz), 141.0 (dm, $J_{F\text{-}C}$ = 252 Hz), 137.6 (dm, $J_{F\text{-}C}$ = 250 Hz) 139.9, 128.5, 128.4, 126.5, 102.9 (m), 100.4 (tm, $J_{F\text{-}C}$ = 18 Hz), 65.4 (m), 34.5, 22.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.9 – -137.0 (m, 2F), -154.1 (t, J_F = 21 Hz, 1F), -162.3 – -162.4 (m, 2F). HRMS (ESI): calcd. for $C_{16}H_9F_5$ $[M+H]^+$ 297.0697, found: 297.0687



(**2-6l**): 64.5 mg, 48% yield, white solid. IR (ATR[cm^{-1}]) 2234 ($\nu_{C\equiv C}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, J = 8 Hz, 2H), 7.57 (t, J = 8 Hz, 1H), 7.52 (t, J = 8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.3 (dm, $J_{F\text{-}C}$ = 250 Hz), 141.9 (dm, $J_{F\text{-}C}$ = 249 Hz), 137.7 (dm, $J_{F\text{-}C}$ = 251 Hz), 134.2, 132.0 (q, $J_{F\text{-}C}$ = 31 Hz), 131.6, 129.4, 126.1 (q, $J_{F\text{-}C}$ = 5 Hz), 125.4 (q, $J_{F\text{-}C}$ = 272 Hz), 122.2, 119.6, 97.0 (m), 78.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -62.3 (s, 3F), -135.3 – -135.4 (m, 2F), -151.5 – -151.6 (m, 1F), -161.5 – -161.6 (m, 2F). HRMS (ESI): calcd. for $C_{15}H_4F_8$: 336.0180, found: 336.0170. Elemental analysis calcd for $C_{15}H_4F_8$: C 53.59, H 1.20; found: C 53.75, H 1.41.



(**2-6m**):[35] 67.2 mg, 50% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.72 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H) (2nd order AA'BB' spin system; values are approximate). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.2 (dm, $^{1}J_{F\text{-}C}$ = 251 Hz), 141.8 (dm, $J_{F\text{-}C}$ = 251 Hz), 137.7 (dm, $J_{F\text{-}C}$ = 250 Hz), 132.4, 132.2, 131.3 (q, $J_{F\text{-}C}$ = 33 Hz), 125.9 (q, $J_{F\text{-}C}$ = 273 Hz), 125.5 (q, $J_{F\text{-}C}$ = 4 Hz), 122.6, 99.7, 75.3 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -63.0 (t, J_F = 1 Hz, 3F), -135.4 – -135.5 (m, 2F), -151.3 – -151.4

(m, 1F), -161.3 – -161.4 (m, 2F). HRMS (ESI): calcd. for $C_{15}H_4F_8$: 336.0180, found: 336.0170.

2.5.5 Single-Crystal X-ray Diffraction Data

Crystal structure determination. Crystals suitable for single-crystal X-ray diffraction were selected, coated in perfluoropolyether oil, and mounted on MiTeGen sample holders. Diffraction data of **2-6a** and **2-6g** were collected on Bruker X8 Apex II 4-circle diffractometers with CCD area detectors using Mo-K_α radiation monochromated by multi-layer focusing mirrors. The crystals were cooled using an Oxford Cryostream low-temperature device. Data were collected at 100 K. The images were processed and corrected for Lorentz-polarization effects and absorption as implemented in the Bruker software packages. The structures were solved using the intrinsic phasing method (SHELXT),[36] refined with the SHELXL program[37] using the SHELXLE graphical user interface,[38] and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in structure factors calculations. All hydrogen atoms were assigned to idealised geometric positions. Diamond[39] software was used for graphical representation. Other structural information was extracted using Mercury[40] and OLEX2[41] software. Crystal data and experimental details are listed in Table 2-S1; full structural information has been deposited with the Cambridge Crystallographic Data Centre. CCDC-2000968 (**2-6a**) and 2000970 (**2-6g**).

Table 2-3: Single-crystal X-ray diffraction data and structure refinements of **2-6a** and **2-6g**.

Data	**2-6a**	**2-6g**
CCDC number	2000968	2000970
Empirical formula	$C_{17}H_{11}F_5$	$C_{14}H_4F_6$
Formula weight / g mol^{-1}	310.26	286.17
T / K	100(2)	100(2)
Radiation, λ / Å	Mo-K_α 0.71073	Mo-K_α 0.71073

Crystal size / mm ^{3}	0.83 × 0.26 × 0.21	0.75 × 0.26 × 0.17
Crystal color, habit	colorless block	colorless plate
μ / mm^{-1}	0.133	0.166
Crystal system	triclinic	triclinic
Space group	$P\ \bar{1}$	$P\ \bar{1}$
a / Å	7.187(6)	5.999(2)
b / Å	8.211(4)	7.593(5)
c / Å	12.336(7)	12.626(6)
α / °	91.51(2)	83.49(2)
β / °	99.48(3)	88.664(11)
γ / °	104.99(4)	85.089(17)
Volume / Å^3	691.7(8)	569.3(5)
Z	2	2
ρ_{calc} / g cm^{-3}	1.490	1.669
F(000)	316	284
θ range / °	2.575 − 26.512	2.999 – 26.477
Reflections collected	8583	8567
Unique reflections	2863	2359
Parameters / restraints	202 / 0	181 / 0
GooF on F^2	1.028	1.087
R_1 [I>2σ(I)]	0.0363	0.0352
wR^2 (all data)	0.1058	0.1098
Max. / min. residual electron	0.286 / -0.195	0.259 / -0.224

density / e ·Å^{-3}

Table 2-4: Intermolecular C–H···F, H···F, C···F, and F···F interaction distances (Å) and angles (°) in compounds **2-6a** and **2-6g** at 100 K less than or equal to the sum of the Van der Waals radii.

Compound	**C–H···F**	**H**···F	**C/F**···F	∠**(CHF)**
2-6a	C15–H15···F5	2.631(2)	3.536(3)	153.7(1)
	C8···C8		3.359(3)	
	C5···C14		3.294(3)	
	C16···F2		3.159(2)	
	F3···F4		2.909(2)	
2-6g	C11–H11···F4	2.6414(14)	3.496(2)	149.98(11)
	C10–H10···F5	2.5224(13)	3.316(2)	141.14(11)
	C13–H13···F6	2.5886(15)	3.420(2)	146.39(10)
	C13–H13···F2	2.5426(13)	3.213(2)	127.74(11)
	C3···C12		3.342(3)	
	C6···C9		3.399(3)	
	C3···F5		3.1262(19)	
	C6···F2		3.1440(19)	
	F2···F5		2.9205(17)	
	F3···F4		2.8556(18)	

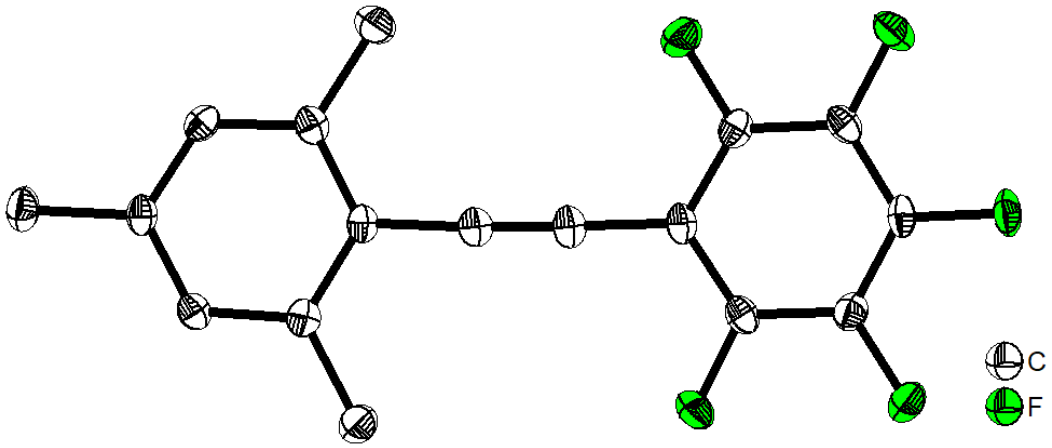


Figure 2-S1. The solid-state molecular structure of **2-6a** determined by single-crystal X-ray diffraction at 100 K. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity.

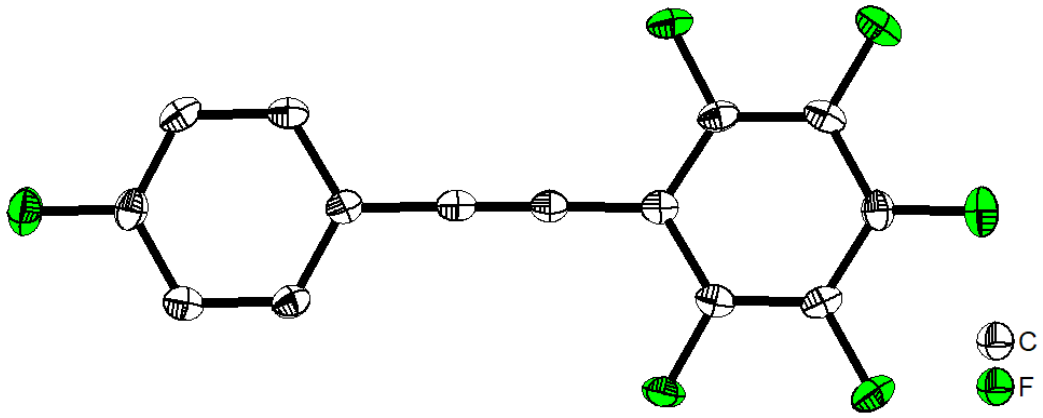


Figure 2-S2. The solid-state molecular structure of **2-6g** determined by single-crystal X-ray diffraction at 100 K. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity.

2.6 Reference

[1] a) Acetylene Chemistry: Chemistry, Biology and Material Science, ed. F. Diederich, P. J. Stang and R. R. Tykwinski, Wiley-VCH, Weinheim, **2005**; b) S. Toyota, *Chem. Rev*. **2010**, *110*, 5398-5424; c) S. Diez-Gonzalez, *Catal. Sci. Technol.* **2011**, *1*, 166-178; d) A. Palisse, S. F. Kirsch, *Org. Biomol. Chem.* **2012**, *10*, 8041-8047; e) I. V. Alabugin, B. Gold, *J. Org. Chem*. **2013**, *78*, 7777-7784; f) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783-1826; g) P. Siemsen, P. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657; *Angew. Chem.* **2000**, *112*, 2740-2767; h) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979-2017; i) R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2003**, *42*, 1566-1568; *Angew. Chem.* **2003**, *115*, 1604-1606.

[2] a) K. J. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46-49; b) R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2003**, *42*, 1566-1568; *Angew. Chem.* **2003**, *115*, 1604-1606; c) H. Plenio, *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956; *Angew. Chem.* **2008**, *120*, 7060-7063; d) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084-5121.

[3] a) Y. H. Xu, Q. C. Zhang, T. He, F. F. Meng, T. P. Loh, *Adv. Synth. Catal.* **2014**, *356*, 1539-1543; b) J. He, M. Wasa, K. S. L. Chan, J. Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387-3390; c) Y. Ano, M. Tobisu, N. Chatani, *Org. Lett.* **2012**, *14*, 354-357; d) Y. Ano, M. Tobisu, N. Chatani, *Synlett*. **2012**, 2763-2767; e) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984-12986; f) M. Tobisu, Y. Ano, N. Chatani, *Org. Lett.* **2009**, *11*, 3250-3252; g) S. H. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1868-1871; h) N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 4156-4159; i) F. Besselievre, S. Piguel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9553-9556; *Angew. Chem.* **2009**, *121*, 9717-9720; j) I. V. Seregin, V. Ryabova, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 7742-7743; k) K. Kobayashi, M. Arisawa, M. Yamaguchi, *J. Am. Chem. Soc.* **2002**, *124*, 8528-8529; l) V. G. Landge, C. H. Shewale, S. P. Midya, E. Balaraman, *Catal. Sci. Technol.* **2016**, *6*, 1946-1951.

[4] a) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780-4787; b) C. Feng, T. P. Loh, *Angew. Chem. Int. Ed.* **2014**, *53*, 2722-2726; *Angew. Chem.* **2014**, *126*, 2760-2764; c) Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743-6747; *Angew. Chem.* **2013**, *125*, 6875-6879; d) J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2010**, *49*, 7304-7307; *Angew. Chem.* **2010**, *122*, 7462-7465; e) J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165-4179; f) C. Feng, D. M. Feng, T. P. Loh, *Chem. Commum.* **2014**, *50*, 9865-

9868; g) C. Feng, D. M. Feng, T. P. Loh, *Org. Lett.* **2014**, *16*, 5956-5959; h) K. D. Collins, F. Lied, F. Glorius, *Chem. Commum.* **2014**, *50*, 4459-4461.

[5] a) Y. Wei, H. Zhao, J. Kan, W. Su, M. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522-2523; b) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358-2361; c) M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 1772-1775; d) S. H. Kim, J. Yoon, S. Chang, *Org. Lett.* **2011**, *13*, 1474-1477; e) F. Shibahara, Y. Dohke, T. Murai, *J. Org. Chem.* **2012**, *77*, 5381-5388; f) S. Ding, Y. Yan, N. Jiao, *Chem. Commun.* **2013**, *49*, 4250-4252; g) C. He, S. Guo, J. Ke, A. W. Lei, *J. Am. Chem. Soc.* **2012**, *134*, 5766-5769; h) J. X. Dong, F. Wang, J. S. You, *Org. Lett.* **2014**, *16*, 2884-2887; i) M. Shang, H. L. Wang, H. X. Dai, J. Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 11590-11593.

[6] a) T. Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512-1513; b) L. Yang, L. Zhao, C. J. Li, *Chem. Commun.* **2010**, *46*, 4184-4186; c) X. Jie, Y. Shang, P. Hu, W. Su, *Angew. Chem. Int. Ed.* **2013**, *52*, 3630-3633; *Angew. Chem.* **2013**, *125*, 3718-3721; d) S. H. Kim, S. H. Park, S. Chang, *Tetrahedron.* **2012**, *68*, 5162-5166; e) Y. J. Liu, Y. H. Liu, B. F. Shi, *Chem. Eur. J.* **2015**, *21*, 205-209.

[7] a) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 3313-3315; b) C. Theunissen, G. Evano, *Org. Lett.* **2014**, *16*, 4488-4491; c) K. Jouvin, J. Heimburger, G. Evano, *Chem. Sci.* **2012**, *3*, 756-760; d) A. Laouiti, K. Jouvin, M. M. Rammah, M. B. M. Rammah, G. Evano, *Synthesis.* **2012**, *44*, 1491-1500; e) K. Jouvin, R. Veillard, C. Theunissen, C. Alayrac, A.-C. Gaumont, G. Evano, *Org. Lett.* **2013**, *15*, 4592-4595; f) C. Theunissen, M. Lecomte, K. Jouvin, A. Laouiti, C. Guissart, J. Heimburger, E. Loire, G. Evano, *Synthesis.* **2014**, *46*, 1157-1166; g) C. Tresse, C. Guissart, S. Schweizer, Y. Bouhoute. A. C. Chany, M. L. Goddard, N. Blanchard, G. Evano, *Adv. Synth. Catal.* **2014**, *356*, 2051-2060; h) G. Evano, K. Jouvin, C. Theunissen, C. Guissart, A. Laouiti, C. Tresse, J. Heimburger, Y. Bouhoute, R. Veillard. M. Lecomte, A. Nitelet, S. Schweizer, N. Blanchard, C. Alayrac, A. C. Gaumont, *Chem. Commun.* **2014**, *50*, 10008-10018.

[8] For general references on the oxidation of organocopper reagents, see: a) D. S. Surry, D. A. Spring, *Chem. Soc. Rev.* **2006**, *35*, 218-225; b) S. J. Aves. D. R. Spring, The Chemistry of Functional Groups. The Chemistry of Organocopper Compounds, Vol. *24*, Z. Rappoport, I. Marek, Eds., John Wiley & Sons Ltd, Chichester, UK, **2009**; pp 585.

[9] For the formation of carbon−carbon bonds by oxidation of organocuprates, see: a) B. H. Lipshutz, K. Siegmann, E. Garcia, F. Kayser, *J. Am. Chem. Soc.* **1993**, *115*, 9276-9282;

b) D. S. Surry, X. Su, D. J. Fox, V. Franckevicius, S. J. F. Macdonald. D. R. Spring, *Angew. Chem. Int. Ed.* **2005**, *44*, 1870-1873; *Angew. Chem*. **2005**, *117*, 1904-1907; c) S. R. Dubbaka, M. Kienle, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 9093-9096; *Angew. Chem*. **2007**, *119*, 9251-9254; d) S. J. Aves, K. G. Pike, D. R. Spring, *Synlett* **2010**, 2839-2842. For another area of oxidative chemistry of organocopper reagents, namely the oxidation of vinylcopper species by oxenoids yielding to enolates, see: e) D. Zhang, J. M. Ready, *Org. Lett.* **2005**, *7*, 5681-5683; f) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky, I. Marek, *Nature* **2012**, *490*, 522-526; g) Y. Minko, M. Pasco, L. Lercher, I. Marek, *Nat. Protoc*. **2013**, *4*, 749-754.

[10] a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330; c) W. R. J. Dolbier, *J. Fluorine Chem.* **2005**, *126*, 157-163; d) N. M. Doherty, N. W. Hoffmann, *Chem. Rev.* **1991**, *91*, 553-573; e) A. D. Sun. J. A. Love, *Dalton Trans.* **2010**, *39*, 10362-10374; f) E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res.* **2011**, *44*, 333-348; g) M. F. Kuehnel, D. Lentz, T. Braun, *Angew. Chem. Int. Ed.* **2013**, *52*, 3328-3348; *Angew. Chem.* **2013**, 125, 3412-3432; h) J. Weaver, S. Senaweera, *Tetrahedron.* **2014**, *70*, 7413-7428; i) N. A. LaBerge, J. A. Love, *Top. Organomet. Chem.* **2015**, *52*, 55-112; j) O. Eisenstein, J. Milani, R. Perutz, *Chem. Rev.* **2017**, *117*, 8710-8753; k) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109,* 2119-2183.

[11] a) T. X. Neenan, G. M. Whitesides, *J. Org. Chem.* **1988**, *53*, 2489-2496; b) P. Nguyen, Z. Yuan, L. Agocs, G. Lesley, T. B. Marder, *Inorg. Chim. Acta* **1994**, *220*, 289-296.

[12] Y. Wei, H. Zhao, J. Kan, W. Su, M. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522-2523.

[13] a) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358-2361; b) M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 1772-1775.

[14] S. H. Kim, J. Yoon, S. Chang, *Org. Lett.* **2011**, *13*, 1474-1477.

[15] a) F. Shibahara, Y. Dohke, T. Murai, *J. Org. Chem.* **2012**, *77*, 5381-5388; b) S. Ding, Y. Yan, N. Jiao, *Chem. Commun.* **2013**, *49*, 4250-4252.

[16] X. Jie, Y. Shang, P. Hu, W. Su, *Angew. Chem. Int. Ed.* **2013**, *52*, 3630-3633; *Angew. Chem.* **2013**, 125, 3718-3721.

[17] G. Zou, J. Zhu, T. Tang, *Tetrahedron Lett.* **2003**, *44,* 8709-8711.

[18] a) F. Yang, Y. Wu, *Eur. J. Org. Chem.* **2007**, 3476-3479; b) L. H. Lu. P. Chellan, J. C.

Mao, *Tetrahedron* **2014**, *70*, 5980-5985; c) C. Feng, T. P. Loh *Chem. Commun*. **2010**, *46*, 4779-4781.

[19] C. D. Pan, F. Luo, J. Cheng, *Tetrahedron Lett.* **2009**, *50*, 5044-5046.

[20] a) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc*. **2016**, *138*, 5250-5253; b) Y.-M. Tian, X.-N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen, T. B. Marder, *J.Am. Chem. Soc*. **2018**, *140*, 17612-17623; c) Y. P. Budiman, A. Friedrich, U. Radius, and T. B. Marder, *ChemCatChem*. **2019**, *11*, 5387-5396; d) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius, and T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 6036-6050; e) L. Kuehn, D. G. Jammal, K. Lubitz, T. B. Marder, and U. Radius, *Chem. Eur. J.* **2019**, *25*, 9514-9521; f) L. Kuehn, M. Huang, U. Radius and T. B. Marder, *Org. Biomol. Chem.* **2019**, *17*, 6601-6606.

[21] J. Piera, J.-E. Backvall, *Angew. Chem. Int. Ed.* **2008**, *47*, 3506-3523; *Angew. Chem*. **2008**, *120*, 3558-3575.

[22] a) D. Ma, F. Liu, *Chem. Commun.* **2004**, 1934-1935; b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449; *Angew. Chem*. **2003**, *115*, 5558-5607; c) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657; *Angew. Chem*. **2000**, *112*, 2740-2765; d) J.-H. Li, J.-L. Li. D.-P. Wang. S.-F. Pi, Y.-X. Xie, M-B. Zhang, X.-C. Hu, *J. Org. Chem.* **2007**, *72*, 2053-2057; e) Y. Wei, H. Zhao, J. Kan, W. Su, M. Hong, *J. Am. Chem. Soc*. **2010**, *132*, 2522-2533; f) Y. Wei, J. Kan, W. Su, *Org. Lett.* **2009**, *11*, 3346-3349; (g) S. Ding, L. Xu, P. Li, *ACS Catal.* **2016**, *6*, 1329-1333.

[23] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1987**, S1-S19.

[24] C. E. Smith, P. S. Smith, R. L. Thomas, E. G. Robins, J. C. Collings, C. Y. Dai, A. J. Scott, S. Borwick, A. S. Batsanov, S. W. Watt, S. J. Clark, C. Viney, J. A. K. Howard, W. Clegg, T. B. Marder, *J. Mater. Chem.* **2004**, *14*, 413-420.

[25] C. Dai, P. Nguyen, T. B. Marder, A. J. Scott, W. Clegg, C. Viney, C. Viney, *Chem. Commun.* **1999**, 2493-2494.

[26] a) G. W. Coates, A. R. Dunn, L. M. Henling, D. A. Dougherty, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 248-251; *Angew. Chem.* **1997***, 109*, 290-293; b) J. Kendall, R. McDonald, M. J. Ferguson, R. R. Tykwinski, *Org. Lett.* **2008**, *10*, 2163-2166.

[27] S. W. Watt, C. Dai, A. J. Scott, J. M. Burke, R. L. Thomas, J. C. Collings, C. Viney, W. Clegg, T. B. Marder, *Angew. Chem. Int. Ed.* **2004**, *43*, 3061-3063; *Angew. Chem.* **2004**, *116*, 3123-3125;.

[28] a) J. C. Collings, J. M. Burke, P. S. Smith, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Org. Biomol. Chem.* **2004**, *2*, 3172-3178; b) M. Stein, R. Berger, W. Seichter, J. Hulliger, E. Weber, *J. Fluorine Chem.* **2012**, *135*, 231-239.

[29] A. Hori, in *The Importance of Pi-Interactions in Crystal Engineering: Frontiers in Crystal Engineering*, John Wiley & Sons, Chichester, UK, **2012**, pp. pp. 163-185.

[30] a) T. Dahl, *Acta Chem. Scand.* **1971**, *25*, 1031-1039; b) J. K. Cockcroft, R. E. Ghosh, J. J. Shephard, A. Singh, J. H. Williams, *CrystEngComm* **2017**, *19*, 1019-1023.

[31] a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc*. **2002**, *124*, 390-391; b) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem*. **2019**, *11*, 5387-5396.

[32] N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358-2361.

[33] X. Qi, J.-B. Jiang, X.-F. Wu, *Tetrahedron. Lett.* **2016**, *57*, 1706-1710.

[34] A. R. Gholap, K. Venkatasen, R. Pasricha, T. D. Rajgobal, J. Lahoti, K. V. Srinivasan, *J. Org. Chem.* **2005**, *70*, 4869-4872.

[35] Y. Wei, H. Zhao, J. Kan, W. Su, M. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522-2523.

[36] G. M. Sheldrick, *Acta Cryst.*, **2015**, *A71*, 3-8.

[37] G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112-122.

[38] C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *J. Appl. Cryst*., **2011**, *44*, 1281-1284.

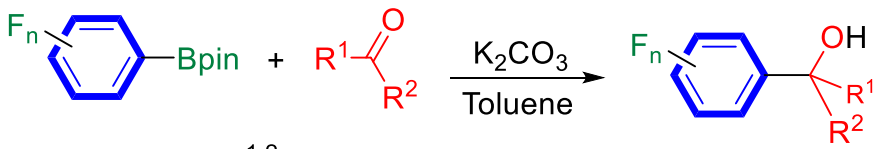
[39] Brandenburg, K. Diamond (version 4.4.0), Crystal and Molecular Structure Visualization, Crystal Impact H. Putz & K. Brandenburg GbR, Bonn (Germany), **2017**.

[40] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P. A. Wood, *J. Appl. Cryst.*, **2008**, *41*, 466-470.

[41] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.*, **2009**, *42*, 339-341.

Chapter 3

Transition Metal Catalyst-Free, Base-Promoted 1,2-Additions of Polyfluorophenylboronates to Aldehydes and Ketones



n = 1-5 $R^{1,2}$ = H, CH_3, Ar

Transition-metal-free
Simple conditions
33 examples
Up to 93% isolated yield

3 Transition Metal Catalyst-Free, Base-Promoted 1,2-Additions of Polyfluorophenylboronates to Aldehydes and Ketones

3.1 Abstract

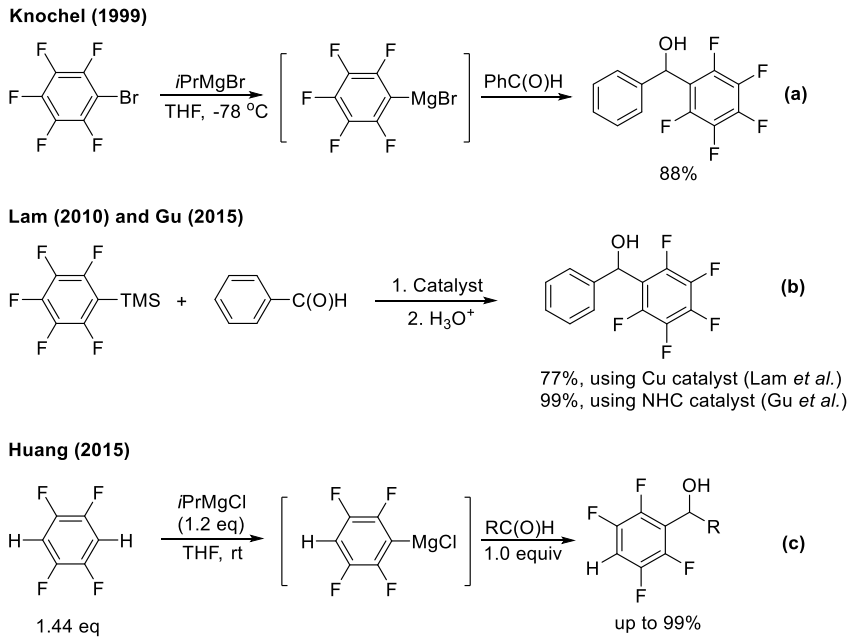
A novel protocol for the transition metal-free 1,2-addition of polyfluoroaryl boronate esters to aldehydes and ketones is reported, which provides secondary alcohols, tertiary alcohols, and ketones. The distinguishing features of this procedure include the employment of commercially available starting materials and the broad scope of the reaction with a wide variety of carbonyl compounds giving moderate to excellent yields. Intriguing structural features involving O–H···O and O–H···N hydrogen bonding, as well as arene-perfluoroarene interactions, in this series of racemic polyfluoroaryl carbinols have also been addressed.

3.2 Introduction

Over the past few decades, the transition metal catalyzed 1,2-addition of organometallic reagents to the C=O functionality of aldehydes and ketones has developed as a useful method for the synthesis of substituted secondary and tertiary alcohols.[1] Numerous reagents have been used for these reactions, including organomagnesium,[2] organozinc,[1,3] organolithium,[4] organosilane,[5] organostannane,[6] organocerium[7] and organoboron compounds.[8] In particular, organoboronate reagents offer significant advantages such as air and moisture stability, low toxicity, good functional group tolerance, and availability.[8] In 1998, Miyaura and co-workers[9] first reported the addition of arylboronic acids to aldehydes using a Rh catalyst. In subsequent studies, other rhodium,[10] palladium,[11] platinum,[12] nickel,[13] copper,[14] iron,[15] cobalt,[16] and ruthenium[17] complexes have been developed as precatalysts for such reactions. However, transition metals can be expensive, toxic, and difficult to remove completely from the corresponding product. A transition metal-free strategy would be highly desirable for these useful transformations. The reaction products for the addition of arylboronic acids to ketones, after hydrolysis, are tertiary alcohols, which are important building blocks for the synthesis of pharmaceuticals, agrochemical compounds, and natural products.[18] However, the nucleophilic addition of organometallic reagents to ketones can be challenging due to

the inherent steric congestion around the carbonyl group, frequently resulting in the generation of products arising from side reactions such as reduction and aldol condensation.[19] Therefore, the development of an efficient, general, and convenient protocol for the synthesis of tertiary alcohols is of considerable interest.

Moreover, an ideal strategy to synthesize ketones, important and ubiquitous structural motifs,[20] lies in the transition metal-catalyzed replacement of an aldehyde's C(O)–*H* group with a carbon electrophile.[21] Recently, Zheng and co-workers demonstrated the direct functionalization of aldehyde C–*H* bonds with aryl halides, using a precious metal palladium catalyst, which has proven to be a viable method to generate the corresponding ketone products.[22]



Scheme 3-1. Approaches to access polyfluoroaryl carbinols *via* the addition to aldehydes.

Polyfluoroarenes have gained extensive attention due to their important role in pharmaceutical, agrochemical, and advanced materials.[23] Thus, identifying practical and efficient concepts for the introduction of fluorine or fluorinated building blocks is highly desirable. Several studies have been reported regarding the polyfluorophenylation of aldehydes. For example, in 1999, Knochel and co-workers[24] used fluorinated aryl bromides to perform pentafluorophenylation of aldehydes (Scheme 3-1a). More recently, Lam and co-workers[25] used a copper catalyst (Scheme 3-1b) and Gu and co-workers[26] (Scheme 3-1b) used an *N*-heterocyclic carbene (NHC) organocatalyst to obtain fluorinated

aryl carbinols using polyfluorophenyl trimethylsilane as a nucleophile for the addition to aldehydes. In 2015, Huang and co-workers[27] (Scheme 3-1c) reported a Mg-mediated polyfluoroaryl addition to aldehydes. Although some advancements in this field have been reported, these methods suffer from the requirement for highly flammable Grignard reagents, transition metals or NHC catalysts. Moreover, methods reported by Lam and co-workers and Gu and co-workers are limited to pentafluorophenyl trimethylsilane or 1,4-bis (trimethylsilyl) tetrafluorobenzene as substrates.

Recently, we reported efficient methods to generate fluorinated arylboronic acid pinacol esters (Ar_F-Bpin) via C-F borylation of fluoroarenes using NHC-ligated Ni complex[28a,b] and C-Cl borylation of Ar_F-Cl using Pd catalyst under base free condition.[28c] Likewise, we reported optimized conditions for the Suzuki-Miyaura cross-coupling reaction of Ar_F-Bpin compounds with ArX (X = Br, I) using a combination of CuI and 1,10-phenanthroline as a catalyst precursor.[28d] Furthermore, we reported the palladium-catalyzed homocoupling of fluorinated arylboronates,[28e] and the copper-catalyzed oxidative cross-coupling of electron-deficient polyfluorophenyl boronate esters with terminal alkynes.[28f] We report herein the transition metal-free polyfluorophenylation of ketones and aldehydes with fluorinated aryl boronates, which provides a convenient and novel strategy for the synthesis of alcohols and ketones.

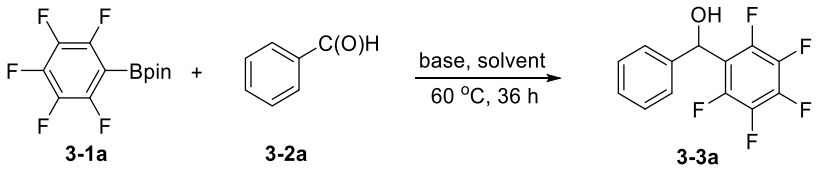
3.3 Results and Discussion

3.3.1 Optimization of Reaction Conditions

Addition of arylboronic acids to aldehydes using transition metal catalysts has been well developed. We expected that the use of more Lewis acidic pentafluorophenyl-Bpin with a base would generate a nucleophilic intermediate in the absence of a transition metal. To verify our hypothesis, we initially examined the reaction of pentafluorophenyl-Bpin (**3-1a**) and benzaldehyde (**3-2a**) as a model reaction. As shown in Table 3-1, secondary alcohol **3-3a** was observed as the addition product after hydrolysis when the mixture of **3-1a** and **3-2a** was heated in the presence of KOMe as the base (Table 3-1, entry 1). Encouraged by this first result, we screened the reaction parameters, including the base and the solvent, to improve the performance of the reaction. The employment of K_2CO_3 as the base dramatically increased the yield to 92% (Table 3-1, entry 6). The experimental results

revealed that heating is required as the room temperature reaction only afforded **3-3a** in trace amounts (Table 3-1, entry 7). Low conversions were observed when reactions were conducted in coordinating solvents such as DMF, THF, and 1,4-dioxane (Table 3-1, entries 8, 10, 11), and the lowest yield was obtained when CH_3CN was used as the solvent (Table 3-1, entry 9). In addition, the reaction exhibited very poor performance under aerobic conditions (Table 3-1, entry 12). Interestingly, increasing the amount of K_2CO_3 to 3 equiv. only led to a moderate increase in yield (Table 3-1, entry 13). Decreasing the amount of K_2CO_3 (0.8 equiv.) did not impact the performance of the reaction (Table 3-1, entry 14). No reaction took place when K_2CO_3 was absent (Table 3-1, entry 15), indicating that K_2CO_3 as the base is important for this reaction. Not surprisingly, adventitious water quenched the reaction (Table 3-1, entries 16-17). However, under anhydrous conditions, the transition metal-free polyfluorophenylation of benzaldehyde with pentafluorophenyl-Bpin is feasible and leads to high yields of the desired product.

Table 3-1: Optimization of the reaction conditions.[a]



3-1a 3-2a 3-3a

Entry	Base	Solvent	Yield (%)[b]
1	KOMe	Toluene	20
2	KF	Toluene	25
3	^{t}BuOLi	Toluene	52
4	Cs_2CO_3	Toluene	60
5	Na_2CO_3	Toluene	78
6	K_2CO_3	Toluene	92
7[c]	K_2CO_3	Toluene	trace
8	K_2CO_3	DMF	50
9	K_2CO_3	CH_3CN	15
10	K_2CO_3	THF	88
11	K_2CO_3	1,4-Dioxane	79
12[d]	K_2CO_3	Toluene	35
13[e]	K_2CO_3	Toluene	83
14[f]	**K_2CO_3**	**Toluene**	**92**
15	-	Toluene	0
16[g]	K_2CO_3	Toluene	66
17[h]	K_2CO_3	Toluene	25

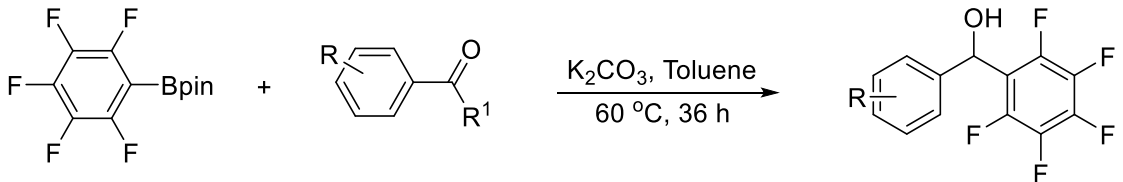
[a] conditions: **3-1a** (0.44 mmol), **3-2a** (0.4 mmol), base (1.0 equiv), degassed and dried solvent (3 mL), 60 °C, 36 h, under argon. [b] Yields were determined by GC-MS analysis *vs*. a calibrated internal standard and are averages of two runs. [c] room temperature. [d] under air. [e] K_2CO_3 (3 equiv). [f] K_2CO_3 (0.8 equiv). [g] K_2CO_3 (0.8 equiv), degassed wet toluene. [h] K_2CO_3 (0.8 equiv), wet toluene. Moisture and air are detrimental to the yield due to the instability of the fluorinated

aryl boronate.[23g]

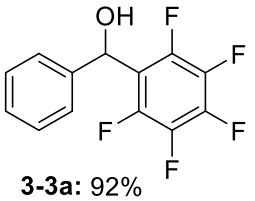
3.3.2 Investigation of Reaction Scope

Using these optimized conditions, we evaluated the scope and the limitations of this reaction. As shown in Table 3-2, a series of aldehydes bearing electron-withdrawing or -donating substituents at the *para*-, *meta*-, or *ortho*-position all worked well with pentafluorophenyl-Bpin to give the desired products (**3-3b-3k**). Notably, for reactions employing aldehydes bearing electron-donating groups, increasing the reaction temperature to 80 °C for 48 hours was required to generate the corresponding products in acceptable yields. It should be noted that reactions using 4-(diethoxymethyl)benzaldehyde resulted in cleavage of the diethoxymethyl group (**3-3l**). Furthermore, this methodology could be successfully extended to more complex aldehydes, such as those incorporating naphthyl and pyridyl groups (**3-3m** and **3-3n**). The structures of compounds **3-3f**, **3-3l**, **3-3m** and **3-3n** were unambiguously confirmed *via* single crystal X-ray analysis (*vide infra*). After a broad range of aromatic aldehydes were examined, reactions with aliphatic aldehydes were investigated using the optimized conditions. Gratifyingly, all reactions proceeded smoothly to afford the corresponding products (**3-3o-3q**). Importantly, aldehydes containing ester groups, which are well-known to be sensitive towards Grignard reagents, also afforded the desired alcohols in excellent yield (**3-3r**).

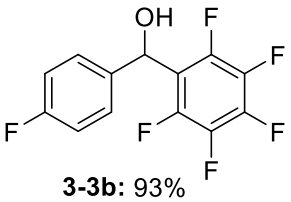
Table 3-2: Scope of the reaction with respect to the different aldehyde substrates **3-2**.[a]



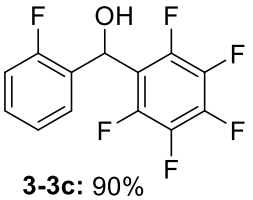
3-1a **3-2** (R^1 = H) **3-3**



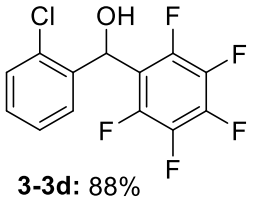
3-3a: 92%



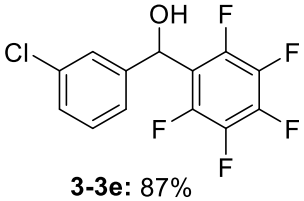
3-3b: 93%



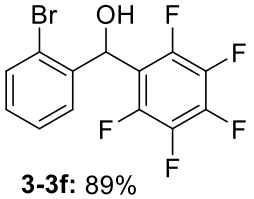
3-3c: 90%



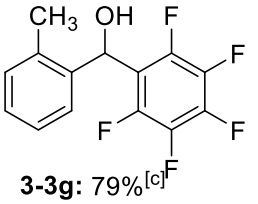
3-3d: 88%



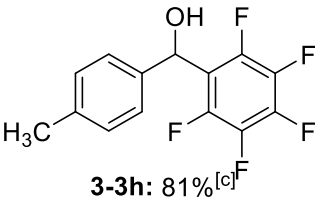
3-3e: 87%



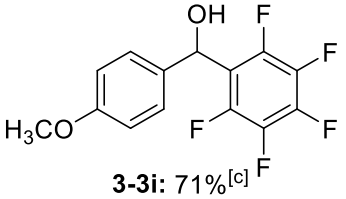
3-3f: 89%



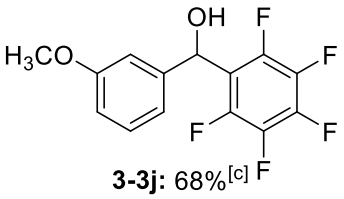
3-3g: 79%[c]



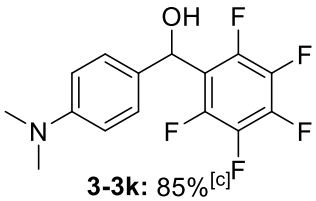
3-3h: 81%[c]



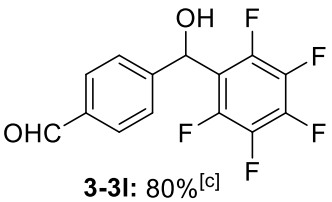
3-3i: 71%[c]



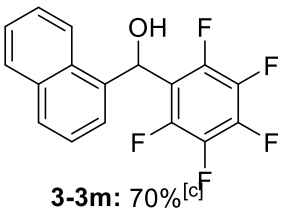
3-3j: 68%[c]



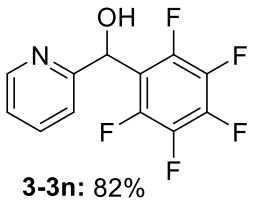
3-3k: 85%[c]



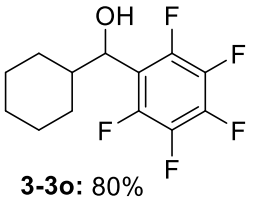
3-3l: 80%[c]



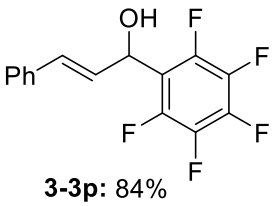
3-3m: 70%[c]



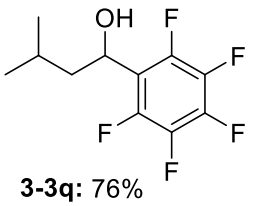
3-3n: 82%



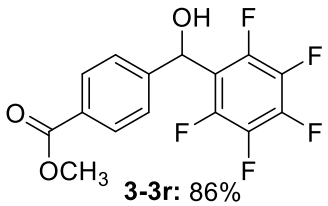
3-3o: 80%



3-3p: 84%



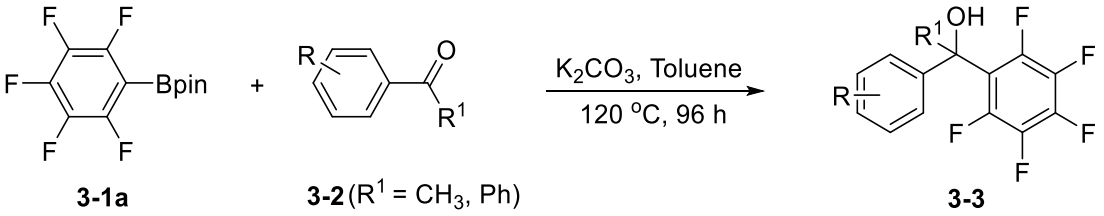
3-3q: 76%



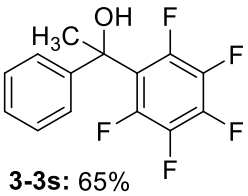
3-3r: 86%

[a] conditions: **3-1a** (0.44 mmol), **3-2** (0.4 mmol), K_2CO_3 (0.32 mmol), Toluene (3 mL), 60 °C, 36 h, Ar. [b] Isolated yields are reported. [c] 80 °C, 48 h.

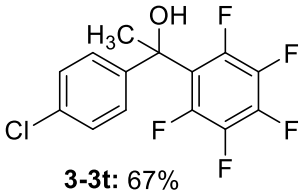
Table 3-3*:* Scope of the reaction with respect to the different ketone substrates **3-2**.[a]



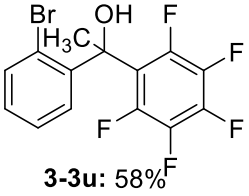
3-1a **3-2** (R^1 = CH_3, Ph) **3-3**



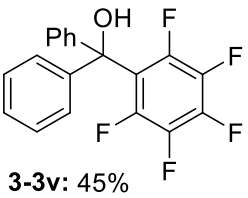
3-3s: 65%



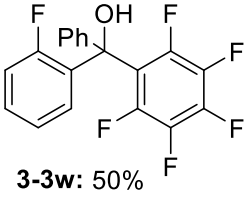
3-3t: 67%



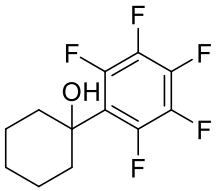
3-3u: 58%



3-3v: 45%



3-3w: 50%

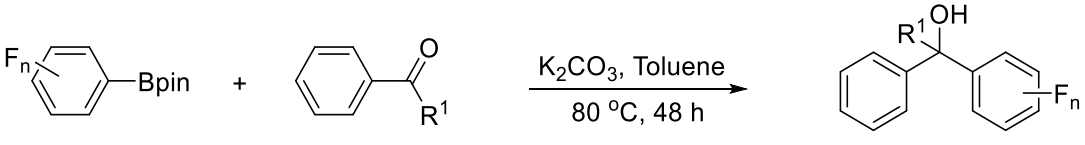


3-3x: 71%

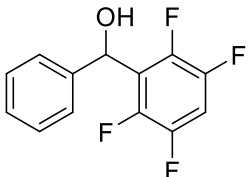
[a] conditions: **3-1a** (0.44 mmol), **3-2** (0.4 mmol), K_2CO_3 (0.32 mmol), Toluene (3 mL), 120 ℃, 96 h, Ar. [b] Isolated yields are reported.

We then briefly investigated the scope using simple ketones (Table 3-3). When reactions were performed at 120 °C and for prolonged reaction times, the corresponding products were provided in moderate yields (**3-3s-3u**). Modest reaction yields were obtained when sterically hindered benzophenone and (2-fluorophenyl)(phenyl)methanone were used (**3-3v-3w**). Importantly, cyclohexanone proceeded to give the desired products in good yield (**3-3x**).

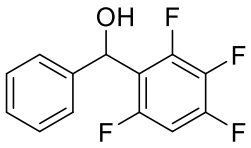
Table 3-4: Scope of the reaction with respect to different polyfluorophenyl boronate substrates **3-1**.[a]



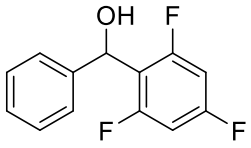
3-1 **3-2** (R^1 = H, CH_3) **3-4**



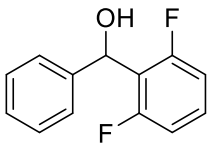
3-4a: 82%



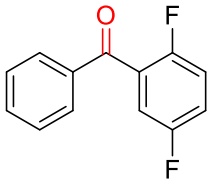
3-4b: 84%



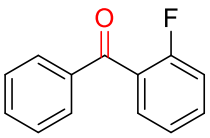
3-4c: 80%



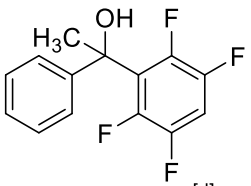
3-4d: 80%



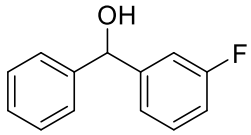
3-4e: 79%[c]



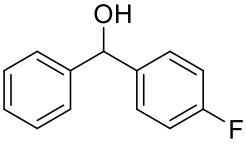
3-4f: 75%[c]



3-4g: 68%[d]



4h: ND



4i: ND

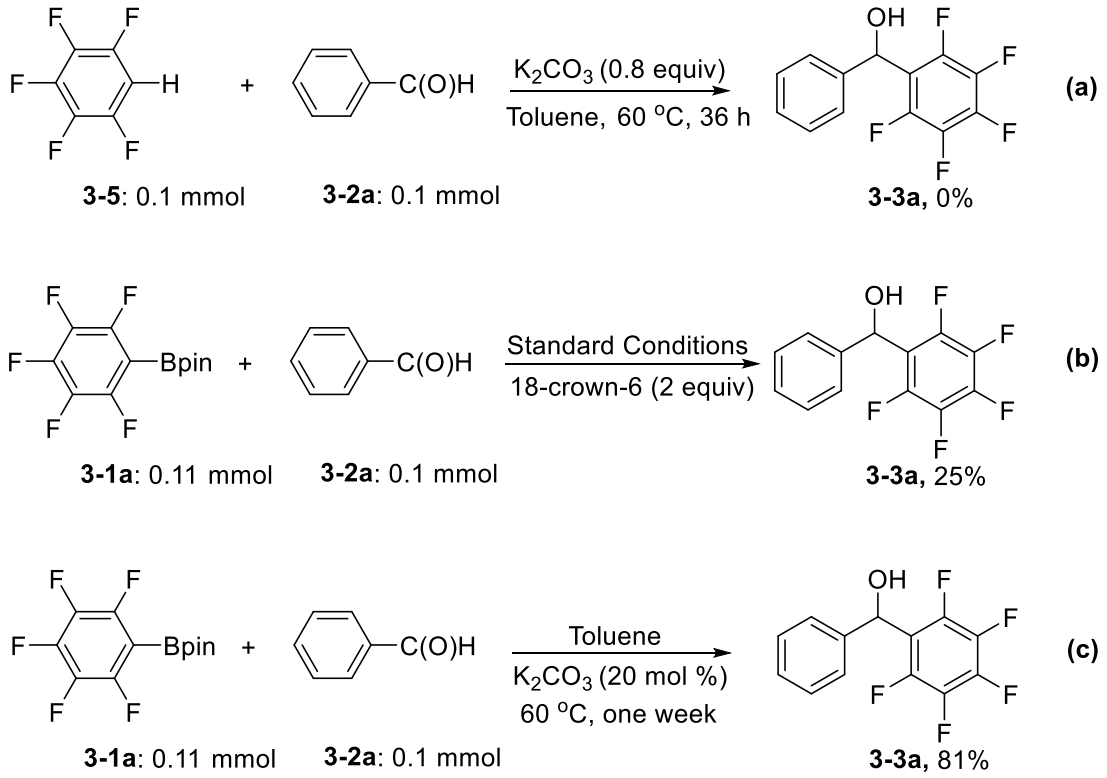
[a] Reaction conditions: **3-1a** (0.44 mmol), **3-2** (0.4 mmol), K_2CO_3 (0.32 mmol), toluene (3 mL), 80 °C, 48 h, Ar. [b] Isolated yields are reported. [c] *t*-BuOLi (0.32 mmol). [d] 120 °C, 96 h.

To explore further the utility of this reaction, we then examined the scope using other less substituted polyfluorophenyl boronate esters with benzaldehyde (Table 3-4). The compounds 2,3,5,6-tetrafluorophenyl-Bpin, 2,3,4,6-tetrafluorophenyl-Bpin, and 2,4,6-trifluorophenyl-Bpin also proved to be effective in these reactions and afforded the products in excellent yields (**3-4a**-**4c**). Furthermore, the reaction with 2,6-difluorophenyl-Bpin proceeded to give the desired product in 80% yield (**3-4d**). However, these reaction conditions were not suitable for the reaction of 2,5-difluorophenyl-Bpin and 2-fluorophenyl-Bpin with benzaldehyde. Surprisingly, reactions with these substrates resulted in the formation of ketones (**3-4e** and **3-4f**) when a strong base was used. Tetrafluorophenyl-Bpin reacted readily with acetophenone to yield product **3-4g**. Unfortunately, no reaction occurred when the aryl-Bpin compound did not have an *ortho*-fluorine substituent (**3-4h** and **3-4i**), as 3-fluorophenyl-Bpin, phenyl-Bpin, 4-CH_3-phenyl-Bpin and 4-CN-phenyl-Bpin all failed to provide any product. These results demonstrate that the *ortho*-fluorine group plays a key role in related conversions.

3.4 Mechanistic Study

3.4.1 Preliminary Mechanistic Studies

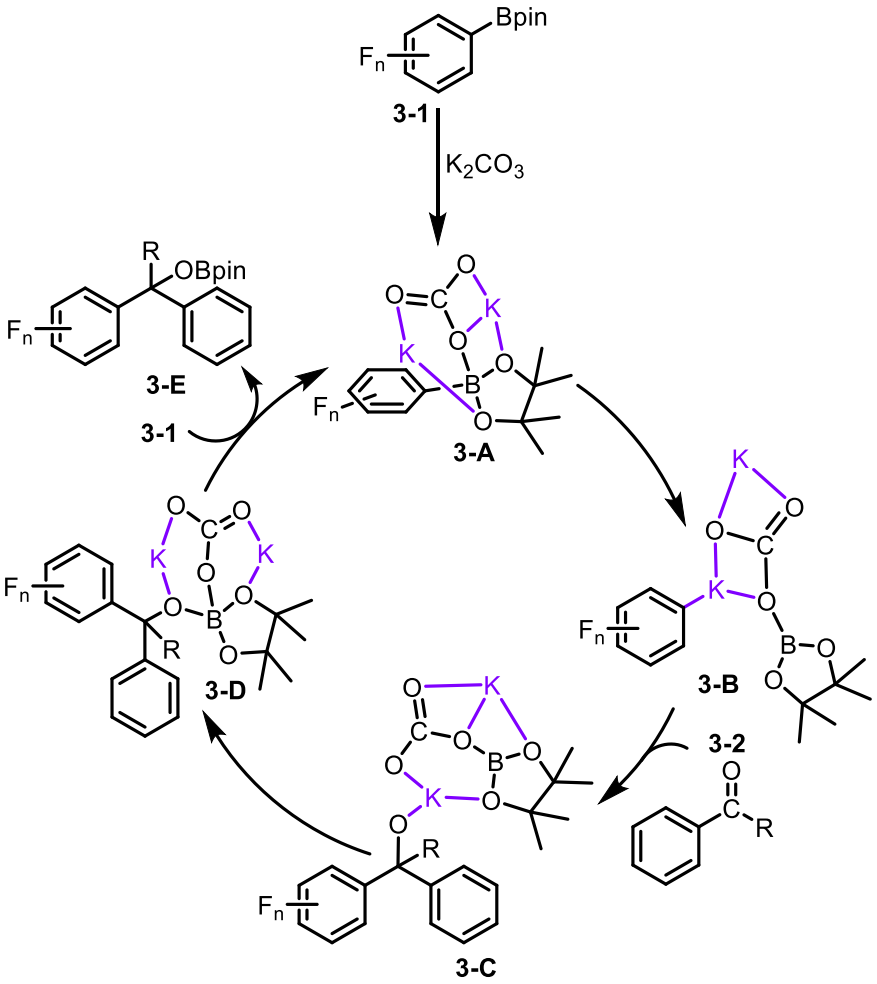
To gain further insight into the aforementioned reactions, several mechanistic studies were conducted. The reaction of **3-2a** with pentafluorobenzene **3-5** under standard conditions was examined, yet **3-3a** was not formed in any detectable amounts (Scheme 3-2a), indicating that the C-Bpin moiety is essential and deprotonation of the fluoroarene or nucleophilic attack at the fluoroarene by the base is not a plausible pathway. Interestingly, for the standard reaction between **3-1a** and **3-2a**, the yield dropped dramatically if 18-crown-6 ether and K_2CO_3 were added (Scheme 3-2b). This experimental result indicates that the presence of the potassium ion plays a crucial role for the outcome of the reaction. Furthermore, if the reaction of **3-1a** and **3-2a** was performed in the presence of only a catalytic amount of K_2CO_3 (20 mol%) (Scheme 3-2c), reaction rates were reduced, and a week was required to produce **3-3a** in good, isolated yield. This finding again indicates that the potassium ion (or the base) plays an important role in the reaction. Substituting *ortho*-fluorines by *ortho*-chlorines, using either C_6Cl_5Bpin 2,6-dichlorophenyl-1-Bpin as substrates, did not yield any product as shown by *in situ* GCMS studies. Likewise, 2,3,4-trifluorophenylBpin and 3,4,5-trifluorophenylBpin substrates with only one or no *ortho*-fluorine substituent also led to no detectable product formation. The presence of an *ortho*-methoxy group on the aldehyde, however, did not inhibit the reaction.



Scheme 3-2. Preliminary mechanistic studies.

3.4.2 Plausible Mechanism

Based on previous studies[28,29] and experimental observations, a mechanism for the 1,2-addition of polyfluorophenylboronates to aryl aldehydes in the presence of K_2CO_3 as base is proposed, as shown in Scheme 3-3. K_2CO_3 interacts with the Lewis-acidic Bpin moiety of substrate **3-1** to generate base adduct **3-A**, which weakens the carbon-boron bond and ultimately cleaves the B–C bond along with attachment of a potassium cation to the aryl group. The resulting Ar_F^- anion adduct **3-B** undergoes nucleophilic attack at the aldehyde carbon atom of substrate **3-2** to generate methanolate **3-C**. The methanolate oxygen atom then attacks the electrophilic Bpin group to obtain compound **3-D**. Transfer of K_2CO_3 from intermediate **3-D** to the boron atom of the more Lewis-acidic polyfluorophenyl-Bpin **3-1** finally closes the cycle and regenerates complex **3-A**. Thus, the primary reaction product is the O-borylated addition product **3-E**, which was detected by HRMS and NMR spectroscopy for the perfluorinated derivative (see section 3.7.7).



Scheme 3-3. Proposed mechanism of the 1,2-addition of polyfluorophenylboronates to aldehyde derivatives in the presence of K_2CO_3 as base.

3.4.3 Computational Studies

To corroborate this mechanism, a detailed DFT study was performed on the model 1,2-addition of **3-1a** to **3-2a**, the results of which are shown in Figure 3-1. In the initial step, K_2CO_3 coordinates to the Bpin moiety of **3-1a** and gives rise to the pentafluorophenyl-Bpin-base complex **6** with free energy decreasing by 27.2 kcal/mol. The energy of compound **6** is set as the zero point of the energy profile. The pentafluorobenzene anion (Ar_F^-) adduct **8** is formed endothermically by cleavage of the B–C(Ar_F) bond *via* transition state **7-ts** with an energy barrier of 26.4 kcal/mol. In the optimized structures of **7-ts**, K^+ cations coordinate to C, O and F atoms, whereas there is only K–O coordination in compound **6**. Subsequent cleavage of the B–C(Ar_F) bond can be facilitated by this pathway. The separated carbonate adduct and Ar_F^- group in adduct **8** are connected and

stabilized by K^+ cations. Nucleophilic attack of Ar_F^- at the aldehyde carbon atom *via* transition state **10-ts** occurs to achieve the coupling intermediate **11** with an energy of 17.6 kcal/mol. This low activation energy barrier can be attributed to the coordination of K^+ to the oxygen atom of the aldehyde, thus enhancing the electrophilicity of the aldehyde carbon atom. Subsequently, the methanolate oxygen atom attacks the Lewis-acidic boron atom to give the corresponding compound **13** irreversibly *via* transition state **12-ts**. The overall energy barrier for this step is 16.2 kcal/mol. Finally, K_2CO_3 in compound **13** coordinates to the boron of substrate **1a** *via* transition state **14-ts**, followed by cleavage of a B–O bond to give **16-ts** and eventually **17**, regenerating the active species **6**. As shown in Figure 1, the energy barriers for these two steps are very low, indicating that intermediate **13** transforms to product **17** swiftly. The step from pentafluorophenyl-Bpin-base compound **6** to product **17** is calculated to be exergonic by 14.3 kcal/mol**.** The base-assisted cleavage of Bpin and pentafluorophenyl (Ar_F) is calculated to be the rate determining step (RDS) with a free energy of activation of 26.4 kcal/mol.

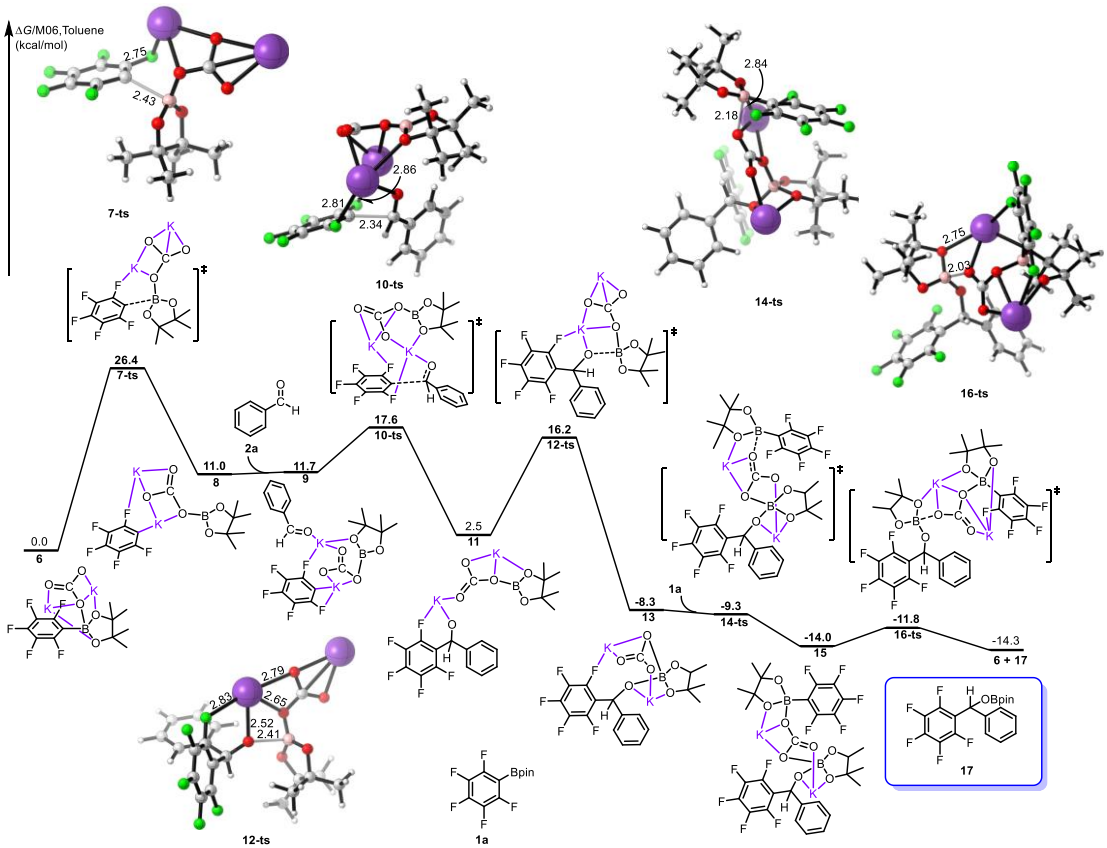


Figure 3-1. Free energy profile for the 1,2-addition of pentafluorophenyl-Bpin (**3-1a**) and benzaldehyde (**3-2a**) in the presence of K_2CO_3 as the base, calculated at the M06/(6-311++G(d, p), SMD)//B3LYP/(6-31+G(d)) level of theory. Relative free energies (ΔG) are given in kcal/mol, and bond lengths are given in Å.

As shown in Figure 3-1, the cation K^+ bonds with one or two F atoms in these intermediates and transition states, suggesting that the fluoride substituents possibly play an important role in the 1,2-addition of polyfluorophenylboronates to aryl aldehydes. Therefore, we calculated the activation free energies of the RDS using polyfluorophenylboronates with different numbers and positions of fluorine substituents as the substrate. The results given in Figure 3-2 clearly show that the energy barrier rises with a reduction in the number of F substituents. The position of the fluorine atoms also affects the energy barrier, and *ortho* fluorine has a stronger effect on the barrier than F substituents at other positions. The barrier for **24**, with an *ortho*-F substituent, is higher than that of **22** by 2.6 kcal/mol, whereas that of **26** with a *para*-F substituent rises to 39.0 kcal/mol. In fact, no reaction was observed under these conditions when **26** was used as the substrate, which is consistent with our calculated results. We conclude that the *ortho*-F substituent is vital in this reaction for interaction with K^+ along the reaction pathway, and that other F substituents also influence the reactivity for the 1,2-addition of polyfluorophenylboronates to aryl aldehydes *via* their electron-withdrawing effect. Thus, stronger electron-withdrawing groups located at the *para* or *meta* carbons of polyfluorophenylboronates may promote this reaction.

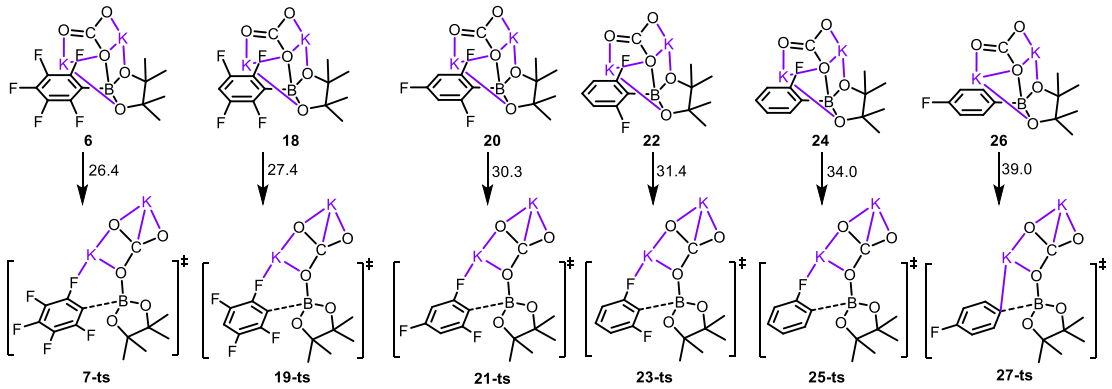


Figure 3-2. Free energies of activation of the cleavage of Bpin and Ar_F step calculated at the M06/(6-311++G(d, p), SMD)//B3LYP/(6-31+G(d)) level of theory. Relative free energies (ΔG) are given in kcal/mol.

In order to ascertain the role of the K^+ cation in these reactions, part of the free energy profile without the cation was also calculated at the same level of theory, and the results are given in Figure 3-3. Compared with the energy profile in Figure 3-1, in the absence of K^+, the process of the methanolate oxygen anion **33** attack at the Lewis-acidic boron in **30** becomes improbable, with an activation barrier of 41.4 kcal/mol, although the initial cleavage of Bpin and pentafluorophenyl (Ar_F) step has a lower free energy of activation.

Upon addition of 18-crown-6 to the reaction, the yields drop dramatically. As a counterion, K^+ clearly regulates the nucleophilicity of CO_3^{2-}, and promotes the reactivity by interaction with oxygen or fluorine atoms. Our DFT calculations indicate that both the *ortho*-F substituents on the polyfluorophenylboronates and the counterion K^+ are essential for the 1,2-addition of polyfluorophenylboronates to aryl aldehydes.

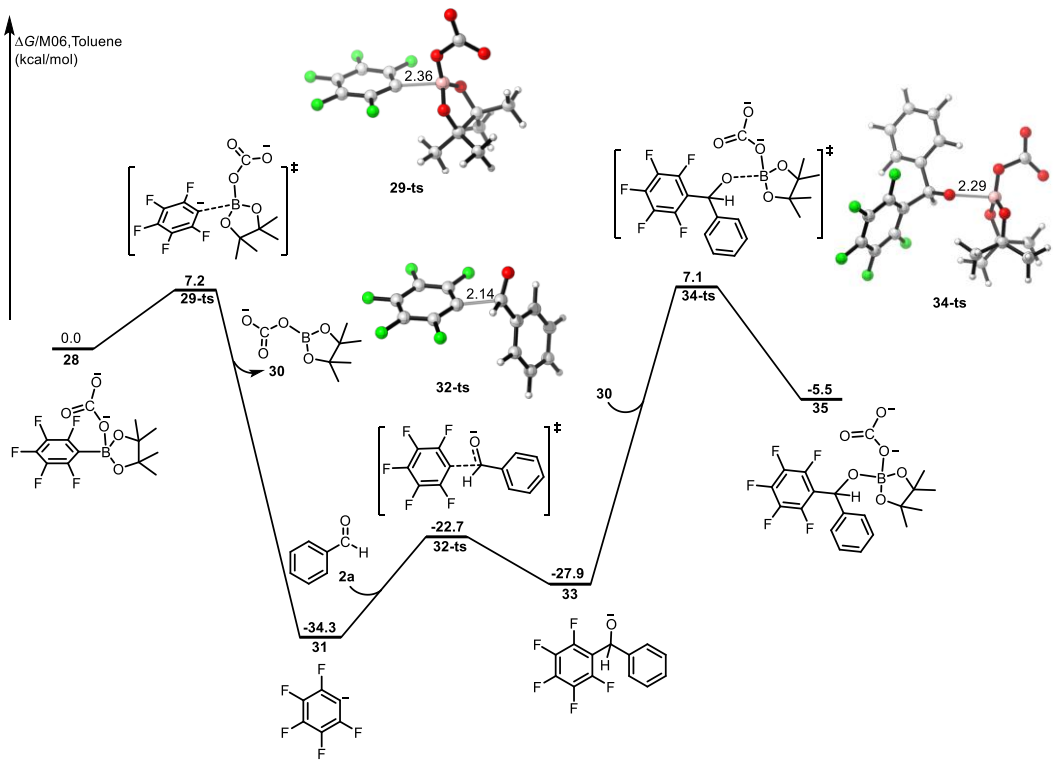


Figure 3-3. Free energy profile of 1,2-addition of polyfluorophenylboronates with aryl aldehydes in the absence of K^+ calculated by the M06/(6-311++G(d, p), SMD)//B3LYP/(6-31+G(d)) level of theory. Relative free energies (ΔG) are given in kcal/mol, bond lengths are given in Å.

3.5 Crystal and Molecular Structures of Products

The structures of **3-3f**, **3-3l**, **3-3m**, **3-3n**, and **3-4d** were unambiguously confirmed by single crystal X-ray diffraction. While the molecular structures are chiral (Figure 3-4), all the compounds represent racemic mixtures. Due to the presence of OH groups, the arrangement of the molecules in the crystal structures of all compounds is primarily determined by O–H···O or O–H···N hydrogen bonding (Table 3-5). The presence of π···π stacking interactions between pentafluorophenyl and bromophenyl or naphthyl moieties (3-**3f** and 3-**3m**), respectively, is also observed in these examples (Table 3-6). Such an attractive interaction between arenes and perfluorinated arenes results from the different

electronegativities of the hydrogen and fluorine atoms with respect to the carbon atoms of the aromatic rings and, hence, from opposite multipole moments of the aromatic groups. It is called the arene–perfluoroarene interaction and can be applied as a supramolecular synthon in crystal engineering.[30] This was previously confirmed by Marder and co-workers, who have shown that this type of interaction leads to the formation of highly ordered π-stacks of alternating arene and perfluoroarene molecules in co-crystals of arenes and perfluoroarenes.[30d,31]

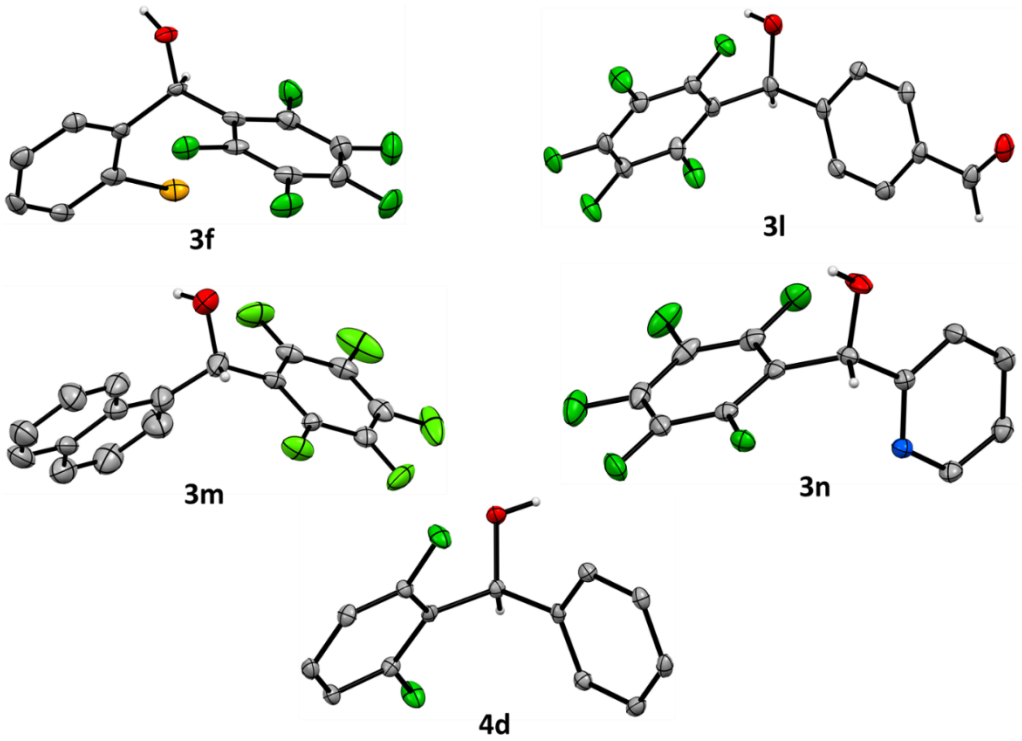


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Figure 3-4. Molecular structures of compounds **3f**, **3l**, **3m**, **3n** and **4d** in the solid state at 100 K. Atomic displacement ellipsoids are drawn with 50% probability. Only selected hydrogen atoms are shown for clarity. Colour code: grey – carbon, red – oxygen, blue – nitrogen, orange – bromine, green – fluorine, and white – hydrogen.

In the crystal structures of compounds **3-3f** and **3-3m**, the combination of both O–H···O hydrogen bonding and arene-perfluoroarene interaction leads to the intriguing formation of $[O–H···]_4$ hydrogen-bonded cyclic tetramers with graph set $\mathbf{R}_4^4(8)$ (Figure 3-5, Table 3-5).[32] The molecules of the tetramer interact *via* arene-perfluoroarene π···π stacking between the bromophenyl or naphthyl and pentafluorophenyl moieties on the outside of the cyclic $[O–H···]_4$ ring. The interplanar separations (3.281(7) – 3.687(14) Å) are typical for π···π stacking interactions,[30,31] the angles between the interacting planes are 4.96(19)

– 16.8(3) ° (Table 3-6). In the higher symmetry compound **3-3m** (space group $P2_1/c$ with $Z' = 2$, where Z' denotes the number of molecules in the asymmetric unit), arene-perfluoroarene interactions are also present between the tetramers, in addition to C–H···π, C–H···F, and F···F interactions (Figure 3-12). Each tetramer of **3-3m** is centrosymmetric and, hence, contains molecules of opposite chirality (*RRSS*), leading to a racemic mixture (Figure 3-5(b)). Tetramers are arranged in sheets parallel to the $\vec{b},\vec{c}$-plane (Figure 3-12). In contrast, compound **3-3f** crystallizes in the non-centrosymmetric space group *P*1. There are 16 symmetry-independent molecules in the asymmetric unit ($Z' = 16$) of 3-**3f**, which build up four symmetry-independent hydrogen-bonded cyclic tetramers (Figure 3-7). Each tetramer is constituted by molecules of the same chirality (*RRRR* or *SSSS*) (Figure 3-5(a)). Thus, the chirality of the four tetramers in the asymmetric unit, i.e., (*RRRR*)(*SSSS*)(*RRRR*)(*SSSS*), leads to a racemic mixture, as shown in Figures 3-5(a), 3-7 and 3-8. Tetramers of mixed chirality are arranged in sheets parallel to the $\vec{b},\vec{c}$-plane with bromine atoms all pointing up or down within the sheet (Figures 3-8 and 3-9). Parallel sheets face each other either with the bromine atoms or without. In fact, crystals of 3-**3f** represent one of the rare class of crystals for which $Z' > 1$.[33, 34] While searching for a structure of higher symmetry, the cell parameters of 3-**3f** were also determined at 200 K. As this resulted in a similar triclinic unit-cell metric as was observed at 100 K, the occurrence of a phase transition at temperatures between 100 K and 200 K is unlikely.

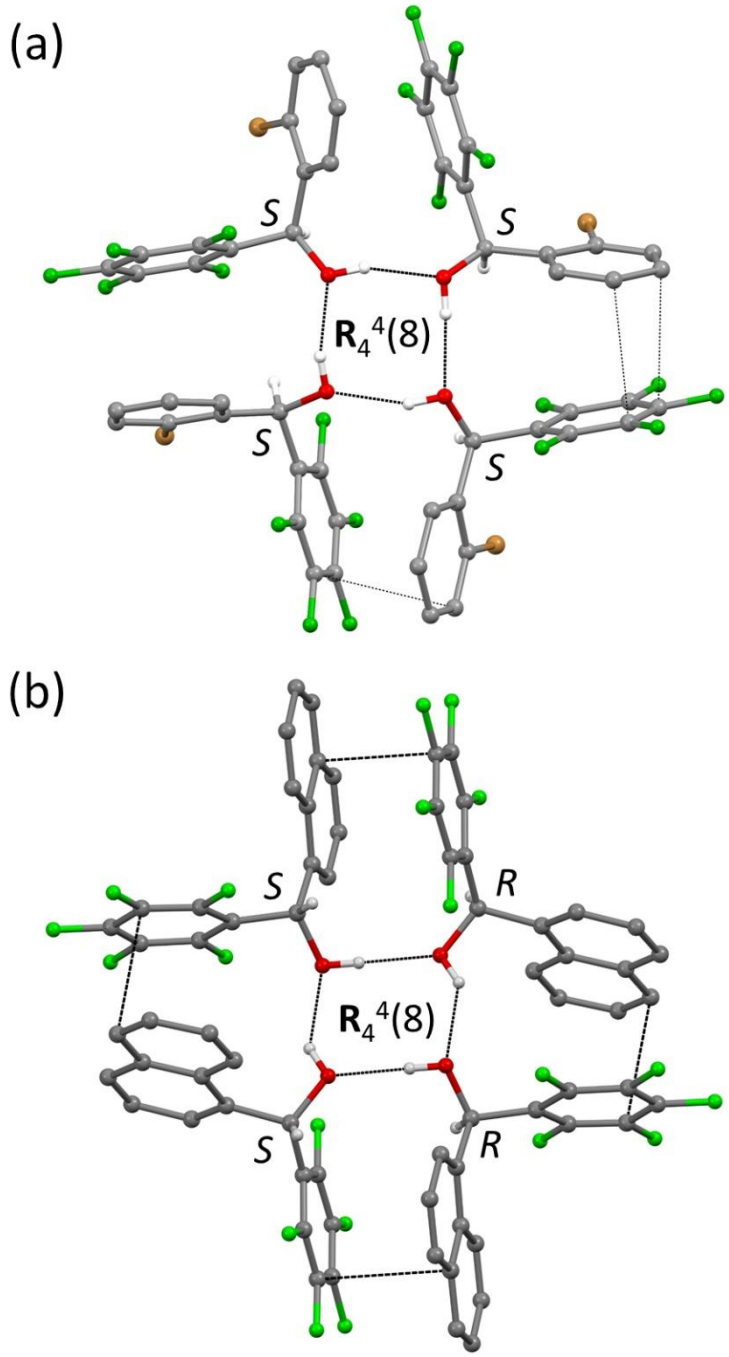


Figure 3-5. Compounds (a) **3-3f** and (b) **3-3m** self-assemble to form tetramers via O–H ··O hydrogen bonding and the corresponding graph set notation is $R_4^4(8)$.[31] π···π stacking interactions between the bromophenyl or naphthyl and pentafluorophenyl groups, respectively, within the tetrameric unit are indicated by close C···C contacts (dashed lines). (a) Each of the four symmetry-independent tetramers of **3-3f** consists of molecules of the same chirality (*RRRR* or *SSSS*). Only one tetramer (*SSSS*) is shown here. (b) In **3-3m**, the tetramer is centrosymmetric with (*RRSS*) chirality of the molecules.

Contrary to **3-3f** and **3-3m**, the dominance of hydrogen bonding and absence of arene-perfluoroarene interactions in compounds **3-3l** (space group $P\bar{1}$), **3-3n** and **3-4d** (both

space group *C*2/*c*) resulted in the formation of one-dimensional hydrogen-bonded chains (Figure 3-6). In **3-3l** and **3-3n**, the intermolecular O–H···O and O–H···N hydrogen bonding interaction takes place between the alcohol (O–H, donor) and the carboxaldehyde (O, acceptor) and pyridyl (N, acceptor) groups, respectively, the latter having a stronger hydrogen bond acceptor ability compared to the alcohol group (Table 3-5). Depending on the position of the acceptor atom in the molecule, hydrogen-bonded chains are straight (**3-3l**, Figure 3-6(a)) or zig-zag-like (3-**3n**, Figure 3-6(b)). In 3-**3l**, each one-dimensional chain contains molecules of one particular chirality (either *R* or *S*), and chains of opposite chirality exhibit extensive π-stacking interaction between the phenyl groups. In this way, double-stranded linear chains projecting the C_6F_5 groups on both sides are formed, as shown in Figure 3-6(a). The C_6F_5 groups from neighboring strands undergo interdigitation and exhibit partial offset π···π interactions between fluorinated moieties and C–F···π interactions between phenyl and pentafluorophenyl groups (Figures 3-10 and 3-11, Table 3-6). In **3-3n**, one-dimensional zig-zag chains are formed by molecules of alternating chirality (*RSRS*…) (Figure 3-6(b)). The pyridyl rings lie coplanar and the pentafluorophenyl groups interdigitate *via* partial offset π···π interactions to form a parallel ribbon-like arrangement (Figure 3-13, Table 3-6). This structure exhibits a bilayer architecture as there are alternating hydrophobic and hydrophilic regions (Figures 3-13 and 3-14).[35] In **3-4d**, corrugated one-dimensional chains are observed by the intermolecular O–H···O–H···hydrogen bonding interactions between the alcohol groups (Table 3-5), and molecules constituted of alternating pairs of same chirality (*RRSSRRSS*… as shown in Figure 3-6(c) and Figure 3-15). Other intermolecular interactions observed in **3-4d** include C–H···F, C–H···π, and very weak, strongly offset π···π interactions (Table 3-6).

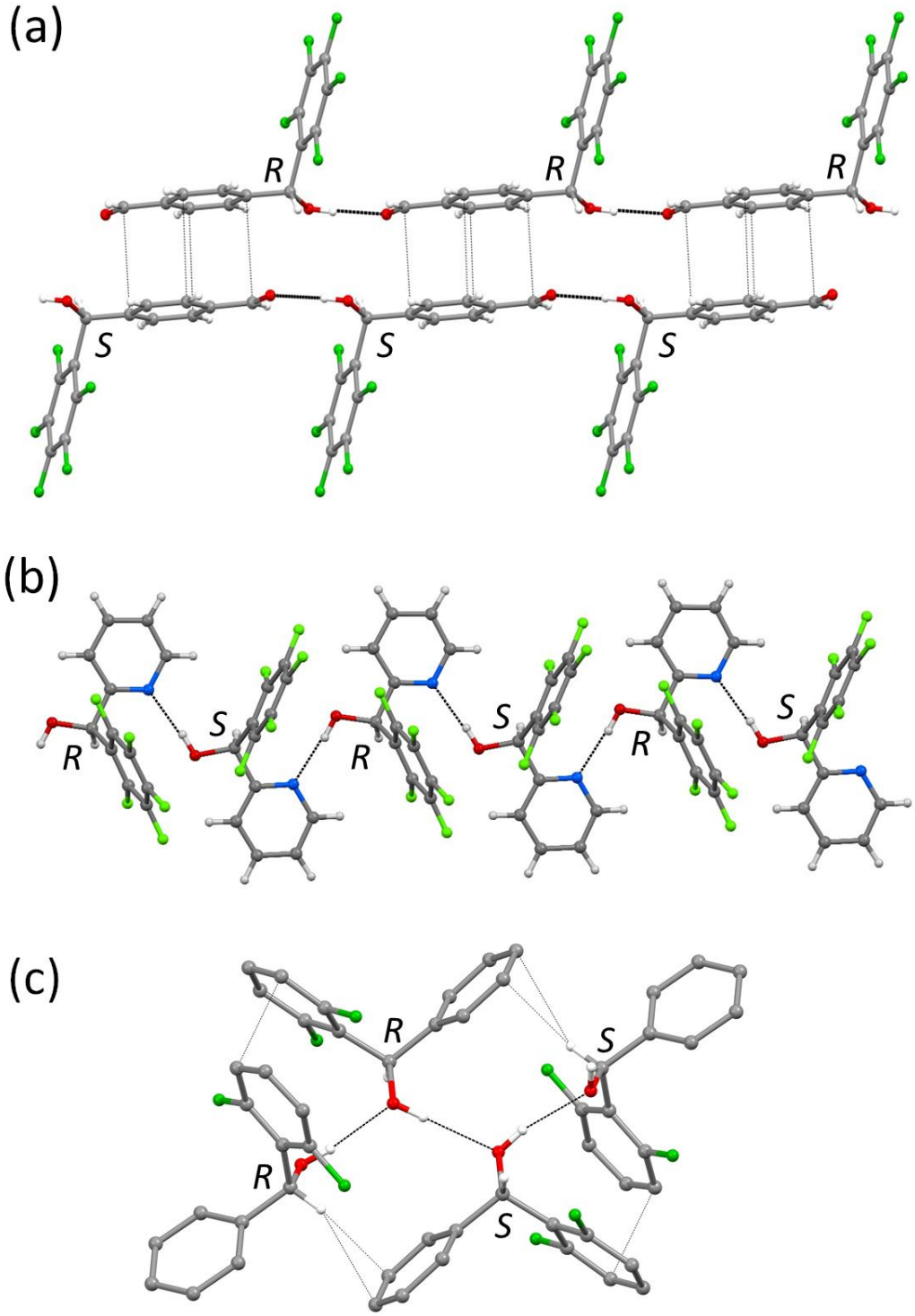


Figure 3-6. One-dimensional hydrogen-bonded chains are present in (a) **3-3l** (O–H ··O), (b) **3-3n** (O–H ··N), and (c) **3-4d** (O–H ··O). (a) In **3-3l**, chains containing molecules of opposite chirality stack parallel *via* π ··π interaction between the phenylcarboxaldehyde groups. (b) A zig-zag chain constituted by molecules of alternative chirality (*RSRS*…) is shown for compound **3-3n**. (c) Compound **3-4d** exhibits corrugated chains with (*RRSS*…) chirality of the molecules. Additional weak interactions (C–H···π and partial π···π stacking) are shown.

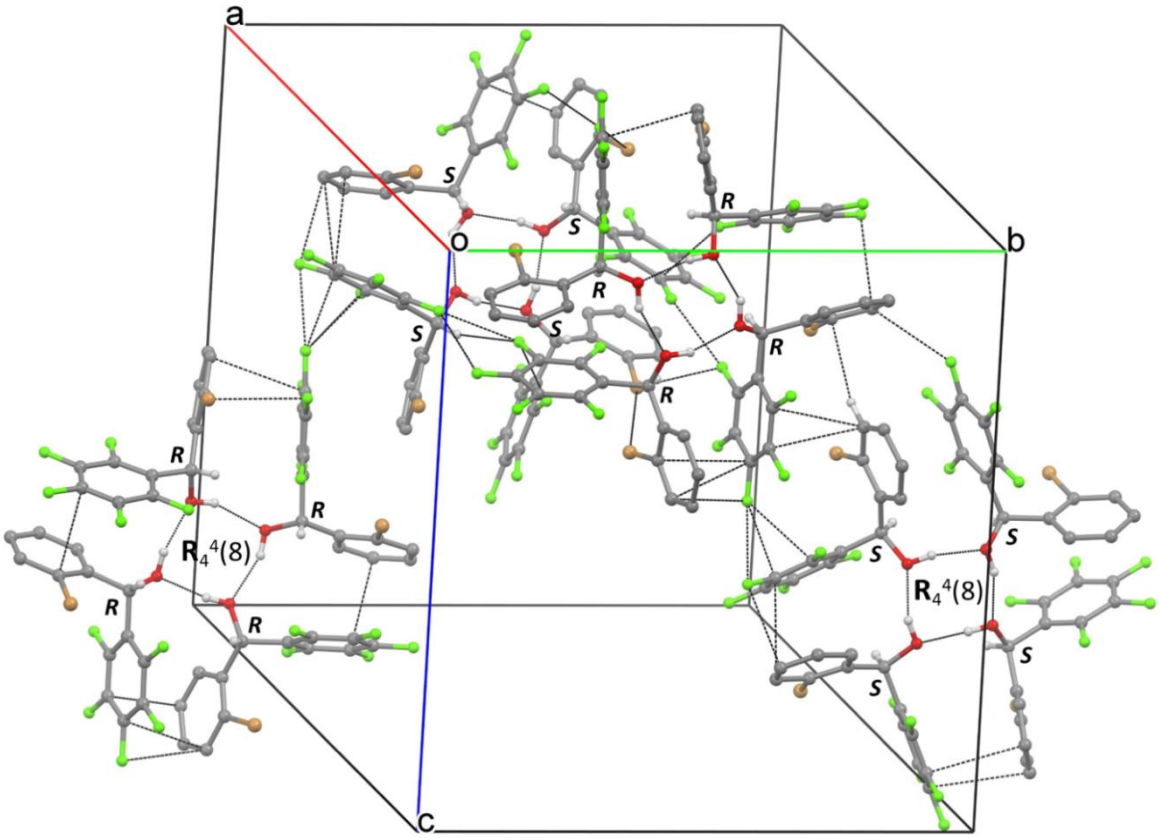


Figure 3-7. The asymmetric unit of **3-3f** and the unit cell metric are drawn. It consists of a racemic mixture of 16 symmetry-independent molecules which form four hydrogen-bonded tetramers of $\mathbf{R}_4^4(8)$ graphset. The chirality of all 16 molecules are shown. Each tetramer contains only one type of chirality. In addition to hydrogen bonding interactions, other interactions, such as π···π, C–F···π(C), C–H···π, F···F, F···Br, etc. are also observed. The interplanar separations and angles between the phenyl and pentafluorophenyl rings lie in the range of 3.281(7) – 3.687(14) Å and 4.96(19) – 16.8(3) °, respectively.

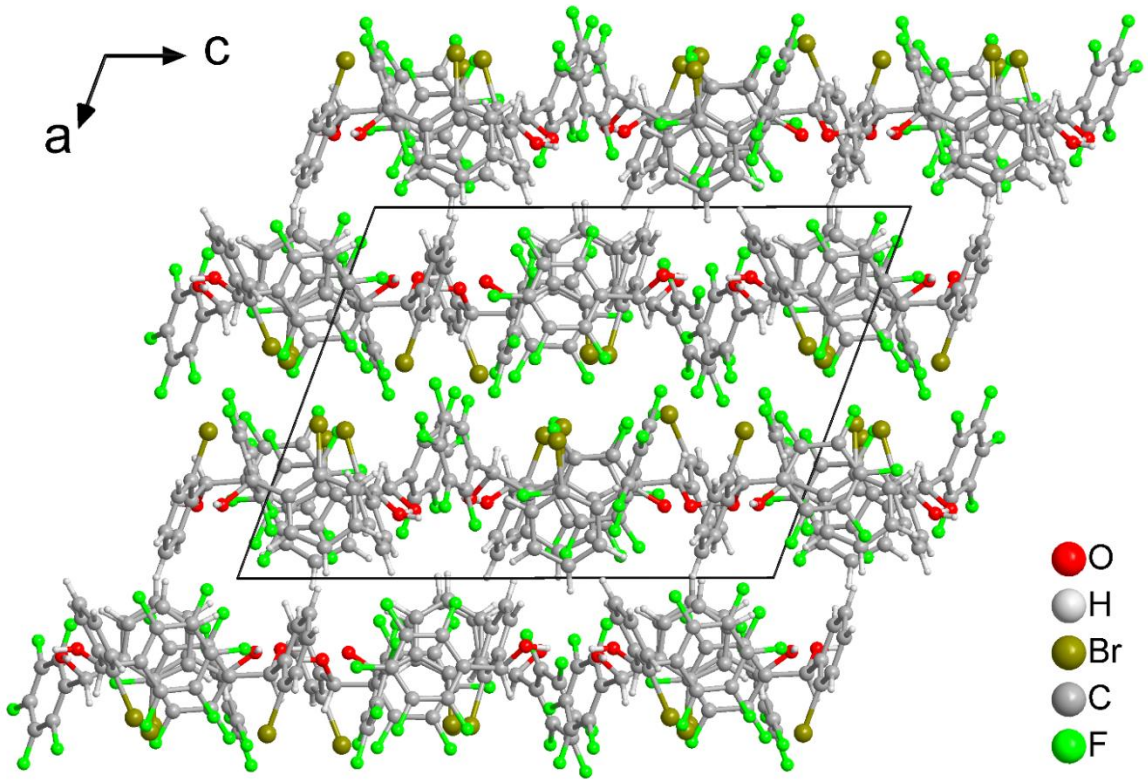


Figure 3-8. Tetramers of **3-3f** are arranged in sheets parallel to the $\vec{b}, \vec{c}$-plane with bromine atoms all pointing up or down within a sheet. Parallel sheets face each other either with the bromine atoms or without.

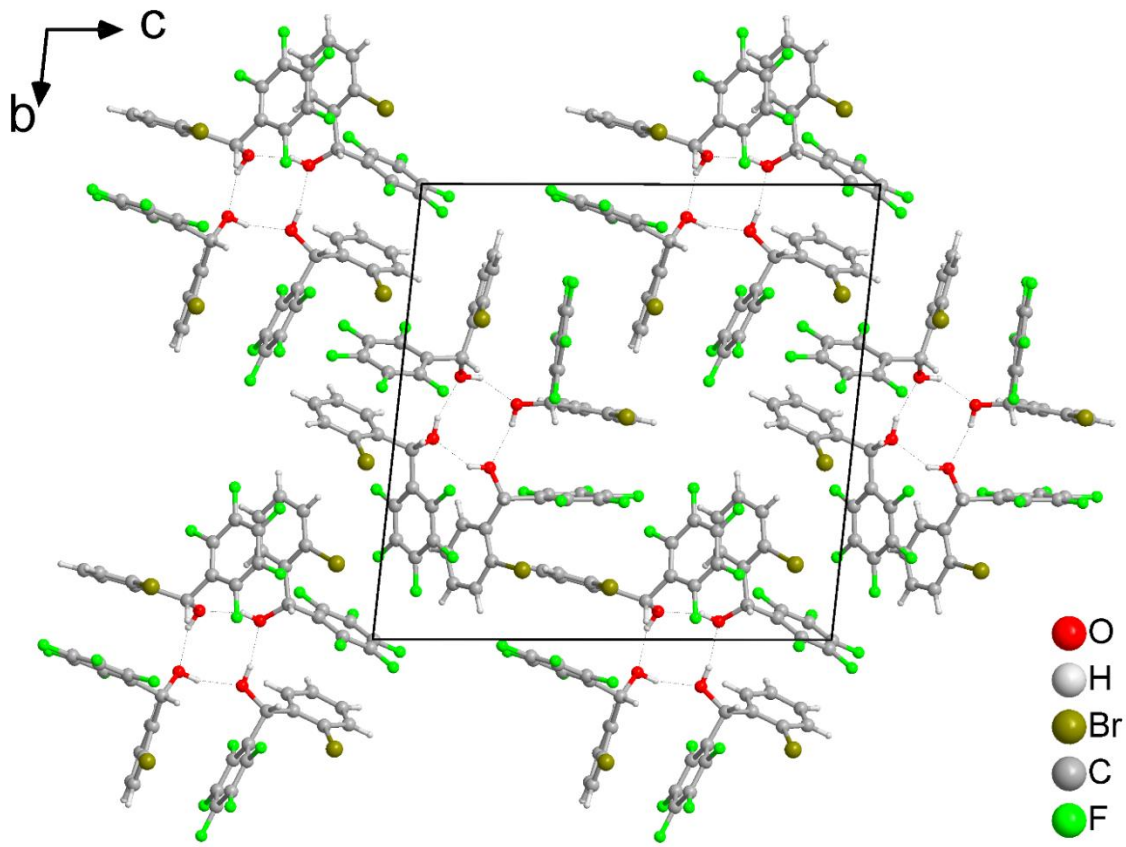


Figure 3-9. One of two symmetry-independent sheets of tetramers of **3-3f** containing two of four symmetry-independent tetramers. Tetramers within the sheet show alternating chirality.

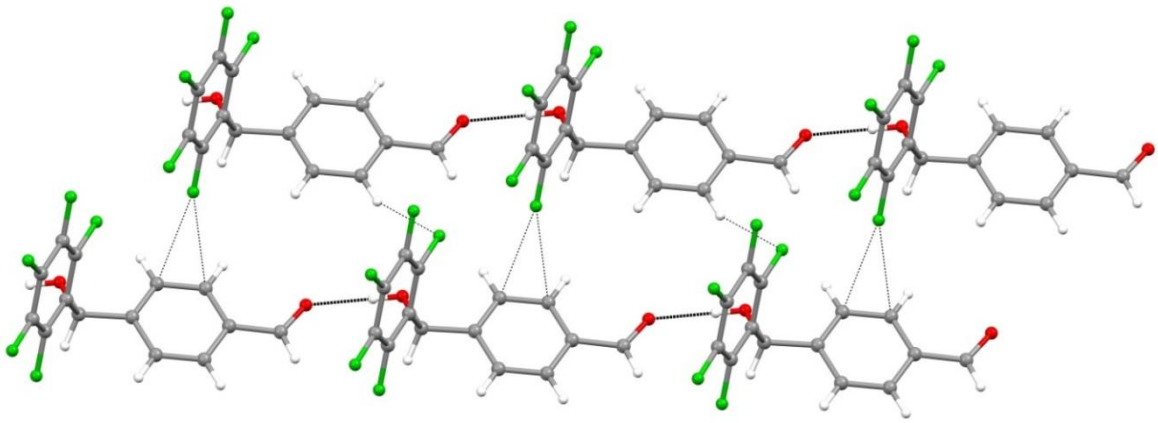


Figure 3-10. One-dimensional hydrogen bonded (O–H ··O) chains also exhibit C–F···π(C) and C–H ··F interactions between phenyl and pentafluorophenyl groups in **3-3l**.

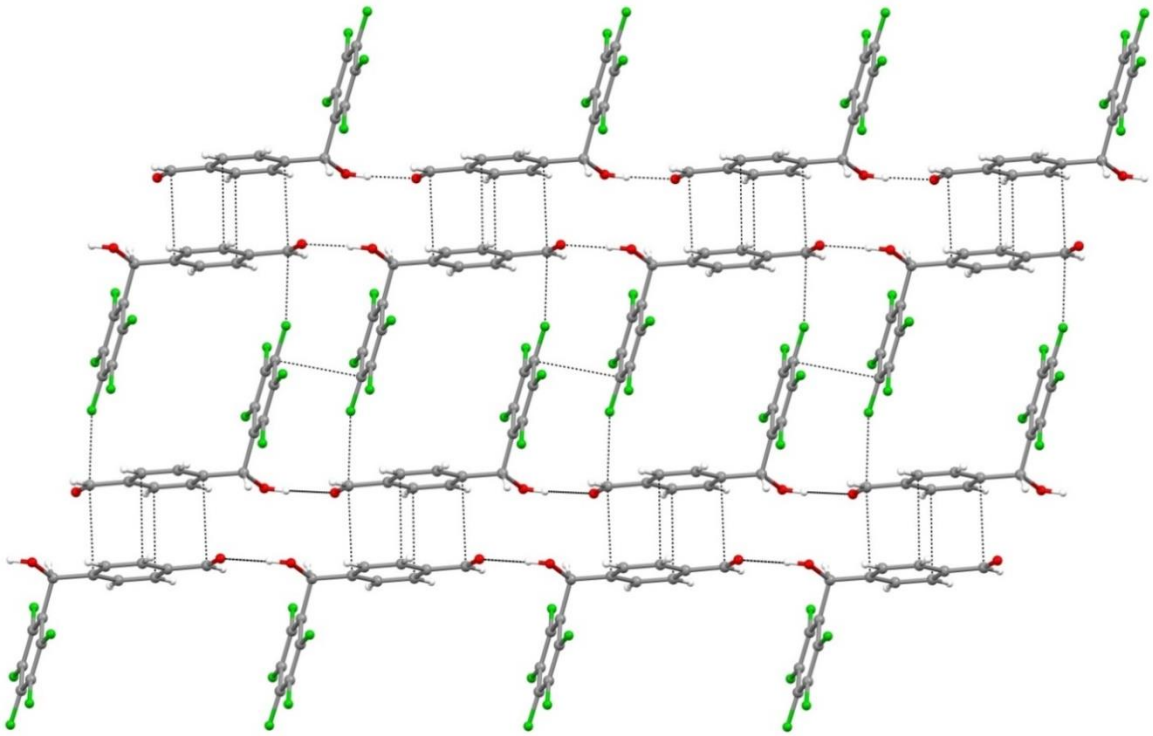


Figure 3-11. The π-stacked hydrogen-bonded chains further interdigitate[43] (viewed approximately along *a*-axis) and there exist partial π···π interactions between fluorinated moieties and C–F···π interactions between pentafluorophenyl and carbonyl groups in **3-3l**.

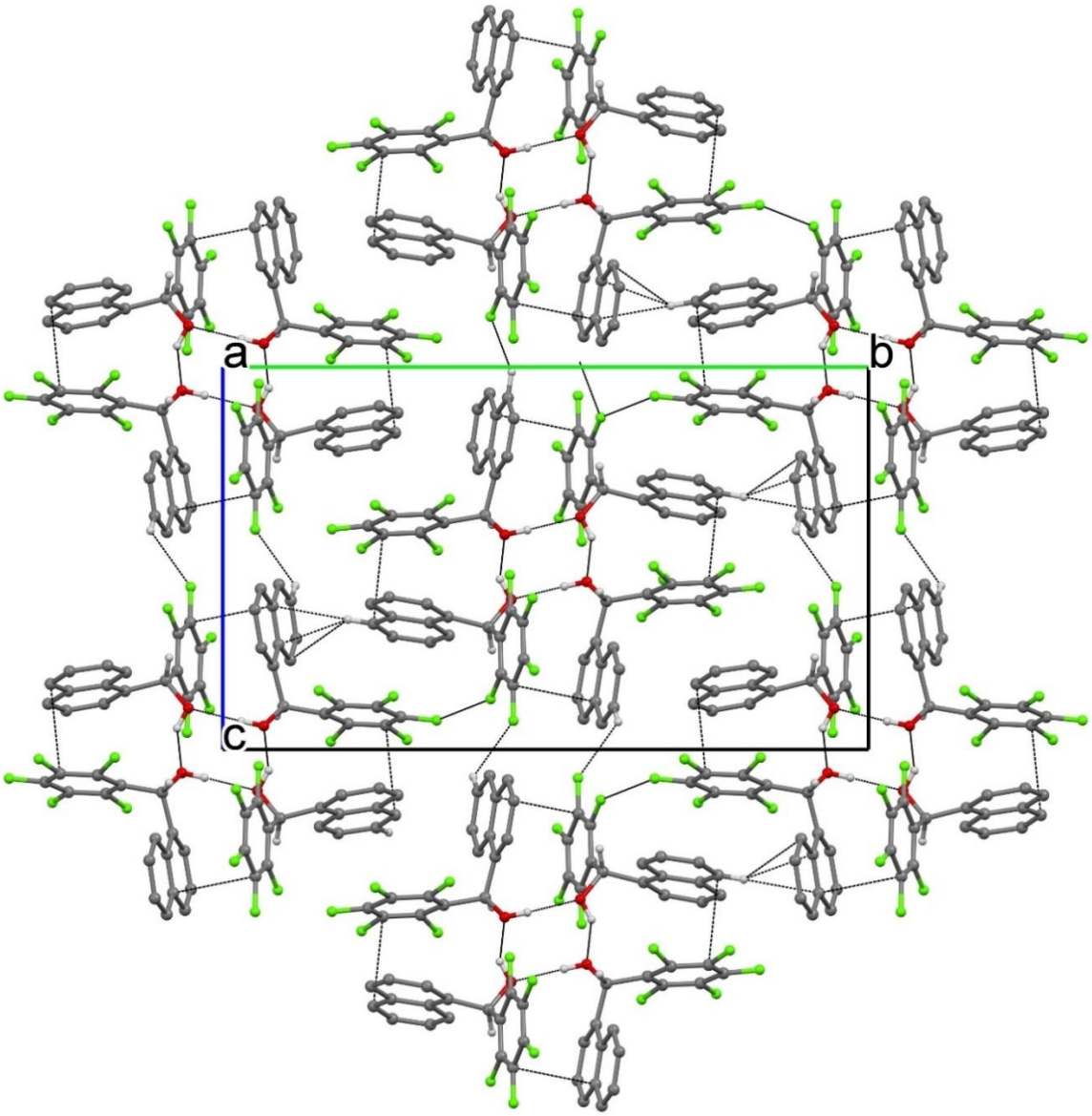


Figure 3-12. The crystal packing of compound **3-3m** is viewed along the *a*-axis. In addition to O–H···O hydrogen bonding, various intermolecular interactions, such as π···π, C–H···π, C–H ··F, and F ··F, are also observed. Interplanar separations and angles between the planes of naphthalene and pentafluorophenyl rings are 3.416(5) – 3.637(3) Å and 6.47(13) – 16.05(13) °.

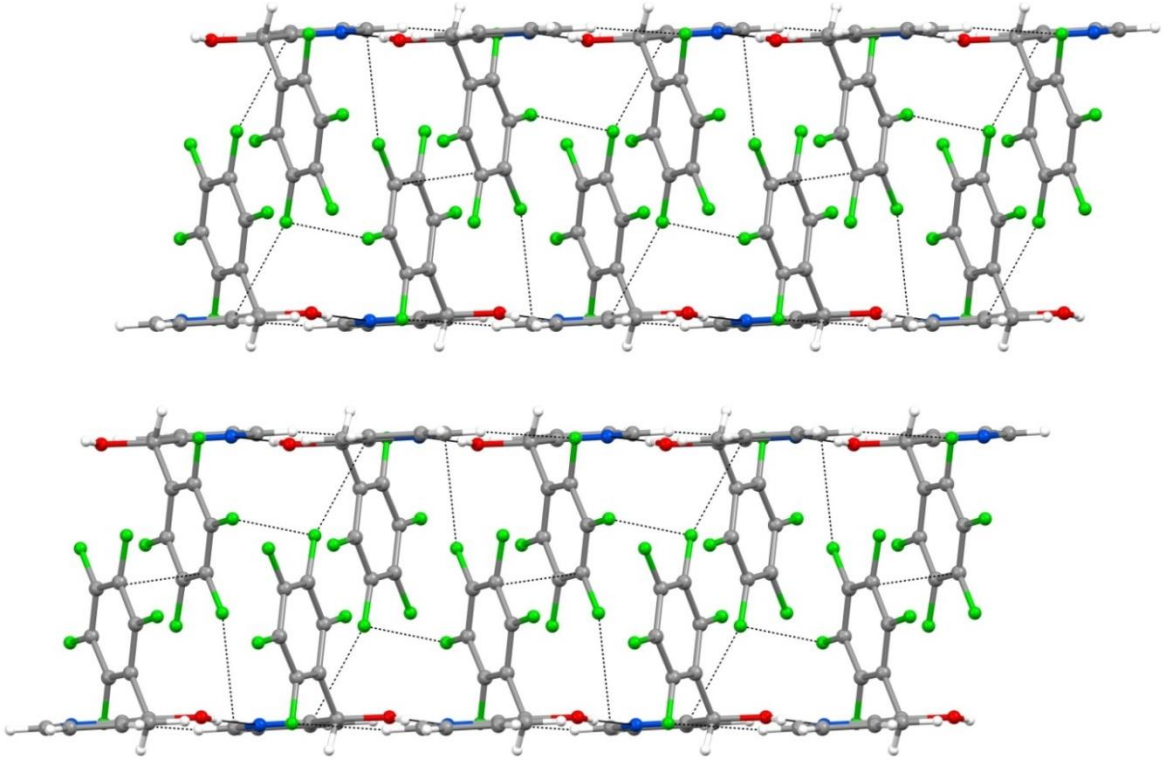


Figure 3-13. The crystal packing of **3-3n** is viewed along the *b*-axis. The pyridyl rings lie coplanar and the pentafluorophenyl groups interdigitate to form a parallel ribbon-like arrangement. Various types of weak interactions include, besides O–H ··N hydrogen bonding, C–H···π, C–F···π, and F ··F interactions ($d_{F\text{-}F}$ = 2.72 Å, $F_{vdW\text{-}radius}$ = 1.47 Å). Alternating hydrophobic and hydrophilic regions can be seen.

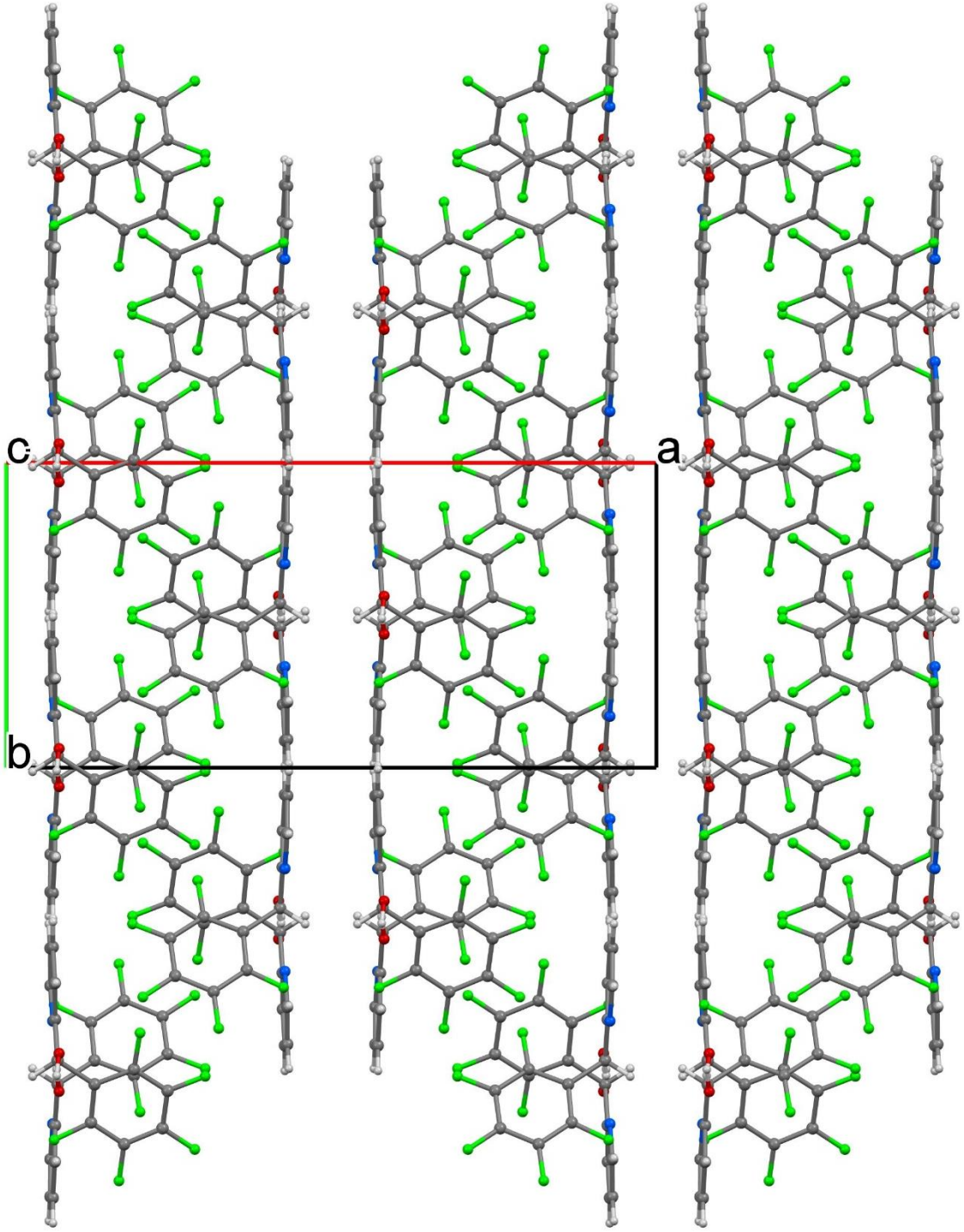


Figure 3-14. The crystal packing of **3-3n** is viewed along the *c*-axis. Alternating hydrophobic and hydrophilic regions can be seen.

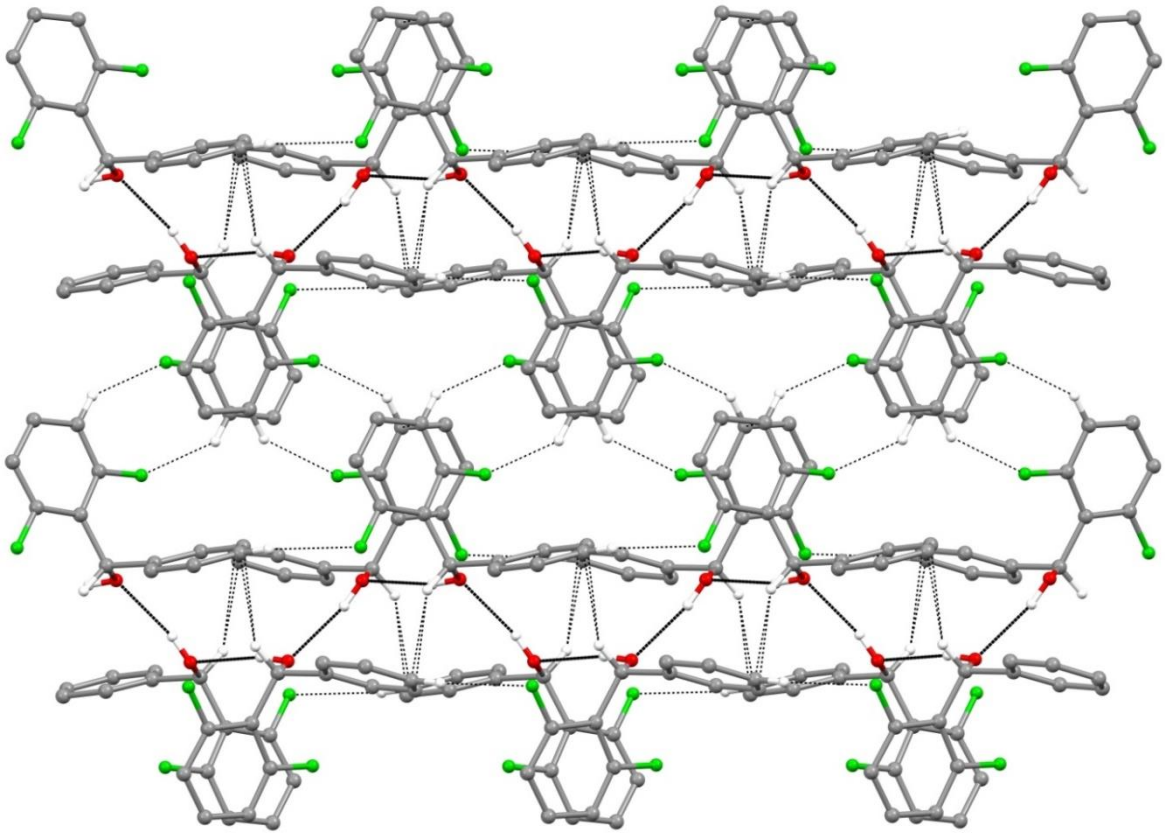


Figure 3-15. Crystal packing of **3-4d**, viewed along the *a*-axis, shows corrugated one-dimensional hydrogen bonded (O–H ··O) chains propagating along the *c*-axis. In addition, several other intermolecular interactions, including C–H ··F, C–H···π, and π···π, can be observed.

3.6 Conclusions

We have demonstrated here the simple conditions for the 1,2-addition of aldehydes and ketones with polyfluorophenylboronate compounds. This strategy has the following advantages: (1) transition metal-free catalyst system; (2) a variety of aromatic and aliphatic aldehydes were found to be suitable substrates for this reaction using pentafluorophenyl-Bpin in moderate to excellent yields; and (3) sterically hindered ketones also worked well to furnish the corresponding products. This method also introduces the use of polyfluoropenyl-Bpin compounds instead of Grignard reagents for polyfluorophenylation of arylaldehyde and ketone substrates. Further studies of the synthesis and applications of polyfluorophenyl boronates are underway in our laboratory and will be reported in due course.

3.7 Detailed Experiments and Characterization Data

3.7.1 General Information

All NMR spectra were recorded on a Bruker AC–500 spectrometer (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR, and 470 MHz for ^{19}F NMR) with $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm and ^{1}H NMR spectra were referenced via residual proton resonances of $CDCl_3$ (7.26 ppm), $^{13}C\{^{1}H\}$ spectra were referenced to $CDCl_3$ (77.16 ppm) and ^{19}F spectra are referenced to external $CFCl_3$. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. GCMS analyses were performed on an Agilent Technologies GCMS system (GC 7890A, EI-MS 5975C). HRMS were measured on a Thermo Scientific Exactive Plus equipped with an Orbitrap. ESI measurements were conducted using a HESI source with an aux-gas temperature of 50 ℃. Measurements were conducted using an APCI source with a corona needle; aux-gas temperature was 400 ℃. Chemical yields referred to pure isolated product. Automated flash chromatography was performed on silica gel (Biotage SNAP cartridge KP-Sil), obtained from Biotage, using a Biotage® Isolera Four Flash system. Unless otherwise stated, all reagents were commercially purchased and used without further purification. The degassed and dry solvents were used. B_2pin_2 was kindly provided by AllyChem Co. Ltd. (Dalian, China).

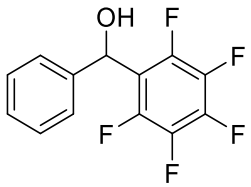
3.7.2 Borylation of Polyfluoroarenes

Pentafluorophenyl-Bpin, 2,3,5,6-tetrafluorophenyl-Bpin, 2,3,4,6-tetrafluorophenyl-Bpin and 2,4,6-trifluorophenyl-Bpin used were prepared according to the literature procedures.[36] In an argon filled glovebox, a solution of $[(COD)Ir(OMe)]_2$ (0.5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2 mol%), bispinacolatodiboron (B_2pin_2) (0.5 equiv.) and pentafluoroarene (1 equiv.) in hexane (dry and degassed) was stirred at room temperature in a sealed reaction vessel for 48h. The volatile materials were removed *in vacuo* to give the crude product, together with unreacted starting arene. The residue was then purified by flash chromatography on silica gel to provide the corresponding product (~90 %).

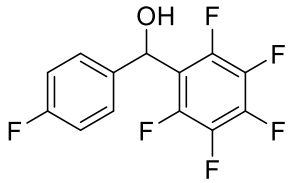
3.7.3 General Procedures

In an argon filled glovebox, a sealable reaction tube with a cap equipped with a magnetic stir bar was charged with polyfluorophenyl boronate esters **3-1** (0.45 mmol), aldehydes **3-2** (0.4 mmol) and K_2CO_3 (62.1 mg, 0.36 mmol) in toluene (3.0 mL, SPS and degassed) at room temperature. The sealed reaction vessel was placed in an oil bath at 60 ℃ for 36 h. After the reaction was completed, it was cooled to room temperature. The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: *n*-pentane and EtOAc) to give the desired product.

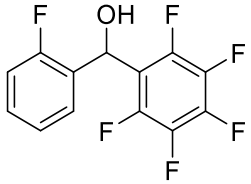
3.7.4 Characterization Data



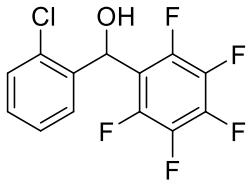
(**3-3a**):[37] 101 mg, 92% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40-7.36 (m, 4H), 7.34-7.31 (m, 1H), 6.23 (s, 1H), 2.92 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 140.8 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 140.6, 137.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 128.7, 128.3, 125.4 (t, $J_{F\text{-}C}$ = 1 Hz), 117.0 (tm, $J_{F\text{-}C}$ = 17 Hz), 67.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143 – -143.1 (m, 2F), -154.6 – -154.7 (m, 1F), -161.4 – -161.6 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_7F_5O$ 274.0417, Found: 274.0403.



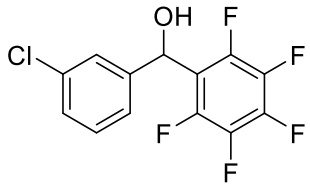
(**3-3b**):[37] 109 mg, 93% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38-7.34 (m, 2H), 7.07-7.02 (m, 2H), 6.21 (s, 1H), 2.73 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 162.5 (d, $^1J_{F\text{-}C}$ = 250 Hz), 144.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 140.9 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.7 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 136.3 (d, $J_{F\text{-}C}$ = 3 Hz), 127.2 (m), 116.7 (tm, $J_{F\text{-}C}$ = 18 Hz), 115.6 (d, $J_{F\text{-}C}$ = 22 Hz), 66.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -113.7 – -113.8 (m, 1F), -143.1 – -143.2 (m, 2F), -154.2 – -154.3 (m, 1F), -161.2 – -161.3 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_6F_6O$ 292.0323, Found: 292.0312.



(**3-3c**): 105 mg, 90% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.69-7.65 (m, 1H), 7.33-7.29 (m, 1H), 7.22-7.19 (m, 1H), 7.02-6.98 (m, 1H), 6.42 (s, 1H), 3.04 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 159.4 (d, $^{1}J_{F\text{-}C}$ = 250 Hz), 144.8 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 141.0 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 129.9 (d, $J_{F\text{-}C}$ = 8 Hz), 127.4 (d, $J_{F\text{-}C}$ = 13 Hz), 126.9 (m), 124.2 (d, $J_{F\text{-}C}$ = 4 Hz), 115.7 (tm, $J_{F\text{-}C}$ = 15 Hz), 115.3 (d, $J_{F\text{-}C}$ = 21 Hz), 62.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -117.8 – -117.9 (m, 1F), -142.8 – -142.9 (m, 2F), -154.4 – -154.5 (m, 1F), -161.7 – -161.9 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_6F_6O$ 292.0323, Found: 292.0311.

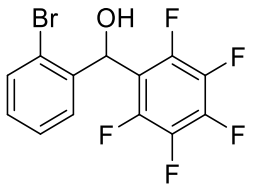


(**3-3d**):[37] 108 mg, 88% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.81-7.79 (m, 1H), 7.36-7.27 (m, 3H), 6.36 (s, 1H), 3.32 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.1 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 141.1 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.4, 131.7, 129.5, 129.4, 127.5 (t, $J_{F\text{-}C}$ = 3 Hz), 126.8, 115.0 (tm, $J_{F\text{-}C}$ = 17 Hz), 64.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -141.6 – -141.7 (m, 2F), -153.9 (t, J_F = 21 Hz, 1F), -161.7 – -161.9 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_6F_5ClO$ 308.0027, Found: 308.0014.

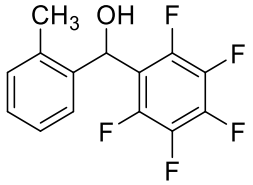


(**3-3e**): 108 mg, 87% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.39 (s, 1H), 7.32-7.27 (m, 2H), 7.25-7.23 (m, 1H), 6.19 (s, 1H), 2.92 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.7 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 142.5, 141.1 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.7 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 134.7, 130.0, 128.4, 125.6, 123.5, 116.3 (tm, $J_{F\text{-}C}$ = 15 Hz), 66.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.8 – -142.9 (m, 2F), -153.7 – -153.8 (m,

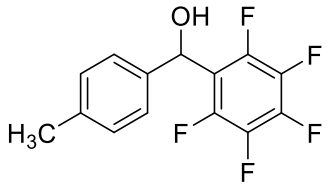
1F), -160.9 – -161.1 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_6F_5ClO$ 308.0027, Found: 308.0017.



(**3-3f**): 125 mg, 89% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.80-7.78 (m, 1H), 7.51 (dd, *J* = 8 Hz, 1 Hz, 1H), 7.39 (tm, *J* = 8 Hz, 1H), 7.20 (tm, *J* = 8 Hz, 1H), 6.29 (s, 1H), 3.24 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.1 (dm, $^1J_{F-C}$ = 250 Hz), 143.2 (dm, $^1J_{F-C}$ = 250 Hz), 138.9, 137.6 (dm, $^1J_{F-C}$ = 250 Hz), 132.8, 129.8, 128.1 (t, J_{F-C} = 3 Hz), 127.4, 121.5, 114.9 (tm, J_{F-C} = 15 Hz), 66.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -141.0 (m, 2F), -153.7 (t, J_F = 20 Hz, 1F), -161.6 – -161.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_6F_5BrO$ 351.9522, Found: 351.9511.

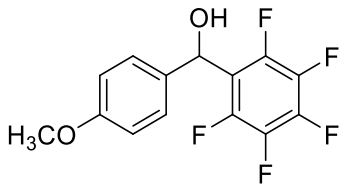


(**3-3g**):[37] 91 mg, 79% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.54-7.52 (m, 1H), 7.27-7.24 (m, 2H), 7.19-7.17 (m, 1H), 6.30 (s, 1H), 2.63 (s, 1H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.8 (dm, $^1J_{F-C}$ = 250 Hz), 140.8 (dm, $^1J_{F-C}$ = 250 Hz), 137.9, 137.6 (dm, $^1J_{F-C}$ = 250 Hz), 135.4, 130.8, 128.4, 126.2, 125.7 (t, J_{F-C} = 3 Hz), 115.8 (tm, J_{F-C} = 15 Hz), 65.3, 18.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.0 – -142.1 (m), -154.4 – -154.5 (m), -161.5 – -161.7 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_9F_5O$ 288.0574, Found: 288.0563.

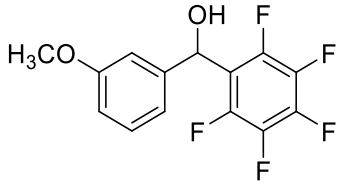


(**3-3h**):[37] 93 mg, 81% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28-7.27 (m, 2H), 7.20-7.18 (m, 2H), 6.17 (s, 1H), 3.20 (s, 1H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.6 (dm, $^1J_{F-C}$ = 250 Hz), 140.7 (dm, $^1J_{F-C}$ = 250 Hz), 138.2, 137.7 (dm, $^1J_{F-C}$ = 251 Hz), 137.6, 129.4, 125.3, 117.1 (tm, J_{F-C} = 15 Hz), 67.5, 21.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143.1 – -143.2 (m, 2F), -155.1 (t, J_F = 21

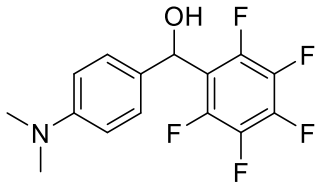
Hz, 1F), -161.7 – -161.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_9F_5O$ 288.0574, Found: 288.0563.



(**3-3i**):[37] 86 mg, 71% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.30-7.28 (m, 2H), 6.88-6.85 (m, 2H), 6.14 (s, 1H), 3.79 (s, 3H), 3.24 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 159.5, 144.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 140.7 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 132.7, 126.8, 117.2 (tm, $J_{F\text{-}C}$ = 15 Hz), 114.0, 67.3, 55.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143.2 – -143.3 (m, 2F), -155.2 (t, J_F = 21 Hz, 1F), -161.7 – -161.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_9F_5O_2$ 304.0523, Found: 304.0512.

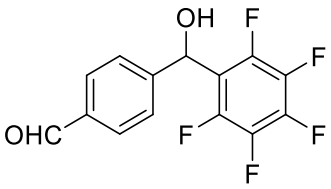


(**3-3j**):[37] 86 mg, 71% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28-7.25 (m, 1H), 6.97 (s, 1H), 6.92-6.91 (m, 1H), 6.85-6.83 (m, 1H), 6.17 (s, 1H), 3.80 (s, 3H), 3.01 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 159.9, 144.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 142.3, 140.8 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 129.8, 117.6, 116.9 (tm, $J_{F\text{-}C}$ = 15 Hz), 113.3, 111.3, 67.3, 55.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143.0 – -143.1 (m, 2F), -154.7 (t, J_F = 21 Hz, 1F), -161.5 – -161.6 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_9F_5O_2$ 304.0523, Found: 304.0509.

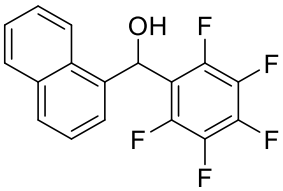


(**3-3k**): 108 mg, 85% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.26-7.24 (m, 2H), 6.74-6.73 (m, 2H), 6.13 (s, 1H), 2.96 (s, 6H), 2.77 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 150.2, 144.5 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 140.5 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 128.7, 126.7, 117.4 (tm, $J_{F\text{-}C}$ = 15 Hz), 112.7, 67.9, 40.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.9 – -143.0 (m, 2F), -155.6 (s, 1F), -161.5 – -

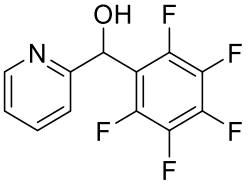
161.6 (m, 2F). HRMS (ASAP): Calcd. for $C_{15}H_{12}F_5NO$ $[M+H]^+$ 318.0912, Found: 318.0903.



(**3-3l**): 97 mg, 80% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.00 (s, 1H), 7.90-7.88 (m, 2H), 7.59-7.58 (m, 2H), 6.33 (s, 1H), 2.91 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 191.9, 147.2, 144.7 (dm, $^1J_{F-C}$ = 250 Hz), 141.2 (dm, $^1J_{F-C}$ = 250 Hz), 137.7 (dm, $^1J_{F-C}$ = 250 Hz), 136.0, 130.1, 126.0, 116.4 (tm, J_{F-C} = 15 Hz), 66.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.6 – -142.7 (m, 2F), -153.3 (m, 1F), -160.7 – -160.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_7F_5O_2$ $[M+H]^+$ 303.0439, Found: 303.0430.

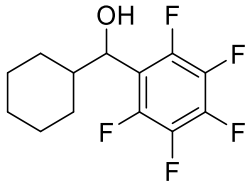


(**3-3m**):[37] 91 mg, 70% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.04 (d, J = 9 Hz, 1H), 7.91-7.85 (m, 1H), 7.85 (d, J = 10 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.58-7.51 (m, 2H), 7.49-7.46 (m, 1H), 6.85 (s, 1H), 2.94 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.0 (dm, $^1J_{F-C}$ = 250 Hz), 141.9 (dm, $^1J_{F-C}$ = 250 Hz), 137.7 (dm, $^1J_{F-C}$ = 250 Hz), 134.9, 133.9, 130.3, 129.4, 129.0, 126.8, 125.9, 125.1, 123.9 (t, J_{F-C} = 2 Hz), 122.7, 116.1 (tm, J_{F-C} = 15 Hz), 65.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.0 – -142.1 (m, 2F), -154.2 (t, J_F = 21 Hz, 1F), -161.3 – -161.4 (m, 2F). HRMS (ASAP): Calcd. for $C_{17}H_9F_5O$ 324.0574, Found: 324.0561.

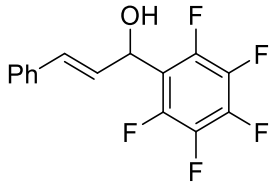


(**3-3n**): 90 mg, 82% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.59 (d, J = 4 Hz, 1H), 7.72-7.69 (m, 1H), 7.30-7.28 (m, 1H), 7.16 (d, J = 8 Hz, 1H), 6.17 (s, 1H), 5.52 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 157.3, 147.9, 145.3 (dm, $^1J_{F-C}$

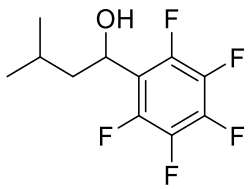
= 250 Hz), 141.1 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.6 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.3, 123.2, 120.4, 116.7 (tm, $J_{F\text{-}C}$ = 18 Hz), 65.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143.3 – -143.4 (m, 2F), -154.3 – -154.4 (m, 1F), -161.7 – -161.9 (m, 2F). HRMS (ASAP): Calcd. For $C_{12}H_6F_5NO$ $[M+H]^+$ 276.0442, Found: 276.0435.



(**3-3o**): 90 mg, 80% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.66 (d, *J* = 9 Hz, 1H), 2.45 (s, 1H), 2.16-2.13 (m, 1H), 1.83-1.78 (m, 2H), 1.68-1.66 (m, 2H), 1.29-1.13 (m, 4H), 1.05-1.03 (m, 1H), 0.96-0.88 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.7 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 140.3 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.4 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 116.5 (tm, $J_{F\text{-}C}$ = 16 Hz), 71.4, 43.3, 29.7, 28.9, 26.1, 25.6, 25.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.9 – -143.0 (m, 2F), -155.7 (t, J_F = 19 Hz, 1F), -162.2 – -162.3 (m, 2F). HRMS (ASAP): Calcd. for $C_{13}H_{13}F_5O$ $[M-H]^+$ 279.0803, Found: 279.0800.

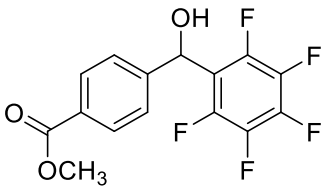


(**3-3p**):[37] 101 mg, 84% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40-7.38 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.27 (m, 1H), 6.71-6.68 (m, 1H), 6.55-6.50 (m, 1H), 5.75 (d, *J* = 6 Hz, 1H), 2.57 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.8 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 140.8 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 137.7 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 135.7, 132.8, 128.6, 128.4, 127.5, 126.7, 116.1 (tm, $J_{F\text{-}C}$ = 15 Hz), 66.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -143.4 – -143.5 (m, 2F), -154.9 (t, J_F = 20 Hz, 1F), -161.7 – -161.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{15}H_9F_5O$ 300.0574, Found: 300.0564.

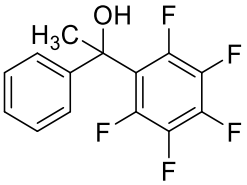


(**3-3q**): 77 mg, 76% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.13-5.10 (m, 1H), 2.34 (s, 1H), 1.94-1.88 (m, 1H), 1.68-1.59 (m, 2H), 0.96-0.93 (m, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.7 (dm, $^{1}J_{F\text{-}C}$ = 250 Hz), 140.4 (dm, $^{1}J_{F\text{-}C}$ = 250

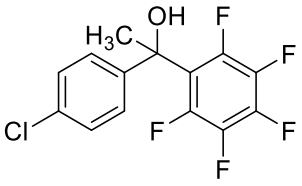
Hz), 137.5 (dm, $^{1}J_{F-C}$ = 250 Hz), 117.4 (tm, J_{F-C} = 15 Hz), 64.7 (m), 45.8, 25.1, 22,5, 22.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -144.2 – -144.3 (m, 2F), -155.6 – -155.7 (m, 1F), -161.9 – -162.1 (m, 2F). HRMS (ASAP): Calcd. for $C_{11}H_{11}F_5O$ $[M-H]^+$ 253.0646 , Found: 253.0643.



(**3-3r**): 114 mg, 86% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.95-7.93 (m, 2H), 7.45-7.43 (m, 2H), 6.26 (s, 1H), 3.87 (s, 3H), 3.80 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 167.1, 145.9, 144.7 (dm, $^{1}J_{F-C}$ = 250 Hz), 141.0 (dm, $^{1}J_{F-C}$ = 250 Hz), 137.6 (dm, $^{1}J_{F-C}$ = 250 Hz), 129.8, 129.4, 125.4, 116.7 (tm, J_{F-C} = 17 Hz), 66.5, 52.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -142.7 – -142.8 (m, 2F), -154.3 (t, J_F = 21 Hz, 1F), -161.4 – -161.5 (m, 2F). HRMS (ASAP): Calcd. for $C_{15}H_9F_5O_3$ $[M+H]^+$ 333.0545, Found: 333.0535.

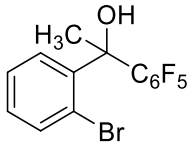


(**3-3s**): 81 mg, 70% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.36-7.27 (m, 5H), 2.82 (s, 1H), 2.01 (t, J = 4 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 146.8, 145.2 (dm, $^{1}J_{F-C}$ = 250 Hz), 140.5 (dm, $^{1}J_{F-C}$ = 250 Hz), 137.9 (dm, $^{1}J_{F-C}$ = 250 Hz), 128.6, 127.7, 124.1, 120.7 (tm, J_{F-C} = 14 Hz), 76.9, 31.7 (t, J_{F-C} = 6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.0 – -139.1 (m, 2F), -155.0 – -155.1 (m, 1F), -161.6 – -161.8 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_9F_5O$ $[M-OH]^+$ 271.0541, Found: 271.0534.

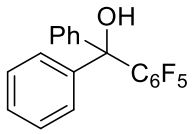


(**3-3t**): 92 mg, 71% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32-7.26 (m, 4H), 3.02 (s, 1H), 1.99 (t, J = 4 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.4, 145.2 (dm, $^{1}J_{F-C}$ = 250 Hz), 140.6 (dm, $^{1}J_{F-C}$ = 250 Hz), 138.9 (dm, $^{1}J_{F-C}$ = 250 Hz), 133.6, 128.7, 125.7, 120.1 (tm, J_{F-C} = 15 Hz), 76.5, 31.7 (t, J_{F-C} = 6 Hz). ^{19}F NMR (470

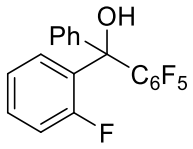
MHz, $CDCl_3$): δ (ppm) = -138.9 – -139.1 (m, 2F), -154.4 – -154.5 (m, 1F), -161.2 – -161.4 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_8F_5ClO$ 322.0184, Found: 322.0172.



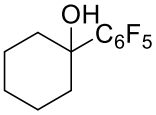
(**3-3u**): 89 mg, 61% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.88-7.86 (m, 1H), 7.53-7.51 (m, 1H), 7.42-7.39 (m, 1H), 7.19-7.16 (m, 1H), 3.27 (s, 1H), 2.11 (t, *J* = 3 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.2 (dm, $^1J_{F-C}$ = 250 Hz), 144.4, 140.6 (dm, $^1J_{F-C}$ = 250 Hz), 137.7 (dm, $^1J_{F-C}$ = 250 Hz), 134.6, 129.5, 127.7, 126.7 (t, J_{F-C} = 2 Hz), 120.1, 119.7 (tm, J_{F-C} = 15 Hz), 76.2, 28.9 (t, J_{F-C} = 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.1 – -139.2 (m, 2F), -155.4 – -155.5 (m, 1F), -162.3 – -162.5 (m, 2F). HRMS (ASAP): Calcd. for $C_{14}H_8F_5BrO$ 365.9679, Found: 365.9668.



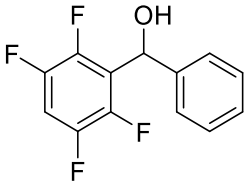
(**3-3v**): 84 mg, 60% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38-7.36 (m, 6H), 7.31-7.29 (m, 4H), 3.56 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.1 (dm, $^1J_{F-C}$ = 250 Hz), 144.3, 140.7 (dm, $^1J_{F-C}$ = 250 Hz), 138.1 (dm, $^1J_{F-C}$ = 250 Hz), 128.4, 128.3, 126.9, 121.1 (tm, J_{F-C} = 12 Hz), 80.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -136.4 – -136.5 (m, 2F), -154.5 – -154.6 (m, 1F), -161.5 – -161.7 (m, 2F). HRMS (ASAP): Calcd. for $C_{19}H_{11}F_5O$ 350.0730, Found: 350.0719.



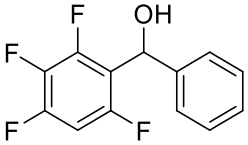
(**3-3w**): 93 mg, 63% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.41-7.33 (m, 6H), 7.11-7.05 (m, 2H), 6.94-6.90 (m, 1H), 3.69 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 160.9 (d, $^1J_{F-C}$ = 250 Hz), 145.1 (dm, $^1J_{F-C}$ = 250 Hz), 142.5, 140.5 (dm, $^1J_{F-C}$ = 250 Hz), 137.7 (dm, $^1J_{F-C}$ = 250 Hz), 131.9 (d, J_{F-C} = 11 Hz), 130.4 (d, J_{F-C} = 9 Hz), 128.6, 128.5, 126.7, 124.0 (d, J_{F-C} = 3 Hz), 119.9 (tm, J_{F-C} = 15 Hz), 116.0 (d, J_{F-C} = 22 Hz), 78.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -111.5 – -111.6 (m, 1F), -137.5 – -137.6 (m, 2F), -154.6 – -154.7 (m, 1F), -161.8 – -161.9 (m, 2F). HRMS (ASAP): Calcd. for $C_{19}H_{10}F_6O$ 368.0636, Found: 368.0625.



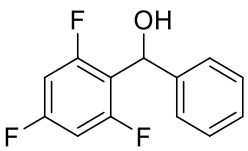
(**3-3x**): 76 mg, 71% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.38 (s, 1H), 2.08-2.00 (m, 4H), 1.86-1.69 (m, 3H), 1.63-1.59 (m, 2H), 1.35-1.27 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.2 (dm, $^{1}J_{F-C}$ = 250 Hz), 139.7 (dm, $^{1}J_{F-C}$ = 250 Hz), 137.8 (dm, $^{1}J_{F-C}$ = 250 Hz), 121.6 (tm, J_{F-C} = 12 Hz), 75.4, 37.3 (t, J_{F-C} = 4 Hz), 25.1, 21.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -140.1 – -140.2 (m, 2F), -156.5 – -156.6 (m, 1F), -162.1 – -162.2 (m, 2F). HRMS (ASAP): Calcd. for $C_{12}H_{11}F_5O$ 266.0730, Found: 266.0721.



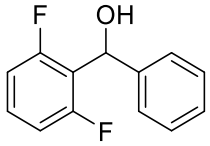
(**3-4a**): 84 mg, 82% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.42-7.36 (m, 4H), 7.34-7.30 (m, 1H), 7.05-6.98 (m, 1H), 6.26 (s, 1H), 2.97 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 146.1 (dm, $^{1}J_{F-C}$ = 250 Hz), 144.1 (dm, $^{1}J_{F-C}$ = 250 Hz), 140.7, 128.7, 128.2, 125.5, 122.7 (t, J_{F-C} = 15 Hz), 105.5 (t, J_{F-C} = 23 Hz), 67.9 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -138.5 – -138.6 (m, 2F), -143.6 – -143.7 (m, 2F). HRMS (ASAP): calcd. for $C_{13}H_8F_4O$ 256.0511, Found: 256.0500.



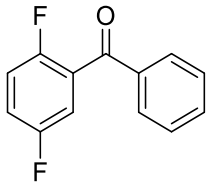
(**3-4b**): 86 mg, 84% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40-7.35 (m, 4H), 7.32-7.29 (m, 1H), 6.81-6.76 (m, 1H), 6.19 (s, 1H), 2.77 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 154.8 (dm, $^{1}J_{F-C}$ = 250 Hz), 150.2 (dm, $^{1}J_{F-C}$ = 250 Hz), 149.6 (dm, $^{1}J_{F-C}$ = 250 Hz), 141.1 (m), 137.3 (dm, $^{1}J_{F-C}$ = 250 Hz), 128.6, 128.0, 125.4 (t, J_{F-C} = 1 Hz), 117.0 (tm, J_{F-C} = 19 Hz), 101.3 (m), 67.4 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -117.8 – -117.9 (m, 1F), -132.4 – -132.5 (m, 1F), -135.2 – -135.3 (m, 1F), -164.2 – -164.4 (m, 1F). HRMS (ASAP): calcd. for $C_{13}H_8F_4O$ 256.0511, Found: 256.0499.



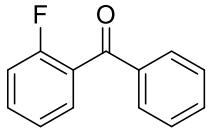
(**3-4c**): 76 mg, 80% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40-7.34 (m, 4H), 7.31-7.27 (m, 1H), 6.71-6.65 (m, 2H), 6.19 (s, 1H), 2.77 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 162.2 (dt, $^{1}J_{F-C}$ = 250 Hz, J_{F-C} = 16 Hz), 161.1 (ddd, $^{1}J_{F-C}$ = 250 Hz, J_{F-C} = 15 Hz, 11 Hz), 141.8, 128.5, 127.7, 125.5 (t, J_{F-C} = 1 Hz), 115.9 (td, J_{F-C} = 17 Hz, 5 Hz), 100.8 (dd, J_{F-C} = 54 Hz, 2 Hz), 67.2 (t, J_{F-C} = 3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -108.1 – -108.2 (m, 1F), -111.1 – -111.2 (m, 2F). HRMS (ASAP): calcd. for $C_{13}H_9F_3O$ 238.0600, Found: 238.0595.



(**3-4d**): 70 mg, 80% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.44-7.42 (m, 2H), 7.39-7.32 (m, 2H), 7.31-7.23 (m, 2H), 6.94-6.88 (m, 2H), 6.27 (s, 1H), 2.90 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 160.8 (dd, $^{1}J_{F-C}$ = 250 Hz, J_{F-C} = 8 Hz), 142.1, 129.6 (t, J_{F-C} = 11 Hz), 128.4, 127.6, 125.6 (t, J_{F-C} = 1 Hz), 119.5 (t, J_{F-C} = 16 Hz), 112.0 (m), 67.6 (t, J_{F-C} = 3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -114.4 – -114.5 (m, 2F). HRMS (ASAP): calcd. for $C_{13}H_{10}F_2O$ 220.0694, Found: 220.0691.

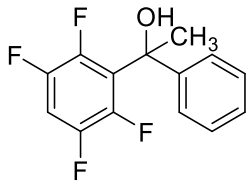


(**3-4e**):[38,39] 69 mg, 79% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.85-7.83 (m, 2H), 7.64-7.61 (m, 1H), 7.51-7.47 (m, 2H), 7.28-7.20 (m, 2H), 7.17-7.12 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 191.9 (m), 158.4 (dd, $^{1}J_{F-C}$ = 250 Hz, J_{F-C} = 2 Hz), 155.9 (dd, $^{1}J_{F-C}$ = 250 Hz, J_{F-C} = 2 Hz), 136.7, 133.8, 129.8 (d, J_{F-C} = 1 Hz), 128.6, 128.1 (dd, J_{F-C} = 18 Hz, 7 Hz), 119.5 (dd, J_{F-C} = 24 Hz, 9 Hz), 117.6 (dd, J_{F-C} = 25 Hz, 8 Hz), 116.9 (dd, J_{F-C} = 25 Hz, 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -117.0 – -117.1 (m, 1F), -117.6 – -117.7 (m, 1F). HRMS (ASAP): calcd. for $C_{13}H_8F_2O$ $[M+H]^+$ 219.0618, Found: 219.0614.



(**3-4f**):[40,41] 60 mg, 75% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.85-7.83 (m, 2H), 7.60-7.44 (m, 5H), 7.22-7.24 (m, 1H), 7.17-7.12 (m, 1H). $^{13}C\{^{1}H\}$ NMR

(125 MHz, $CDCl_3$): δ (ppm) = 193.5, 160.1 (d, $^1J_{F-C}$ = 250 Hz), 137.4 (d, J_{F-C} = 1 Hz), 133.5, 133.1 (d, J_{F-C} = 8 Hz), 130.7 (d, J_{F-C} = 3 Hz), 129.8 (d, J_{F-C} = 1 Hz), 128.5, 127.0 (d, J_{F-C} = 15 Hz), 124.3 (d, J_{F-C} = 4 Hz), 116.3 (d, J_{F-C} = 21 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -111.0 – -111.1 (m, 1F). HRMS (ASAP): calcd. for $C_{13}H_9FO$ $[M+H]^+$ 201.0710, Found: 201.0706.



(**3-4g**): 73 mg, 68% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.35-7.34 (m, 4H), 7.30-7.27 (m, 1H), 7.08-7.01 (m, 1H), 3.21 (s, 1H), 2.03 (t, J = 4 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 147.1, 146.4 (dm, $^1J_{F-C}$ = 250 Hz), 144.8 (dm, $^1J_{F-C}$ = 250 Hz), 128.5, 127.6, 126.1 (t, J_{F-C} = 12 Hz), 124.2, 105.2 (t, J_{F-C} = 22 Hz), 77.1, 31.5 (t, J_{F-C} = 7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -138.5 – -138.6 (m, 2F), -139.6 – -139.7 (m, 2F). HRMS (ASAP): calcd. for $C_{14}H_{10}F_4O$ $[M-OH]^+$ 253.0635, Found: 253.0630.

3.7.5 Single Crystal X-Ray Diffraction

Single crystals suitable for X-ray diffraction were selected, coated in perfluoropolyether oil, and mounted on MiTeGen sample holders. Diffraction data were collected on Bruker X8 Apex II 4-circle diffractometers with CCD area detectors using Mo-Kα radiation monochromated by graphite or multi-layer focusing mirrors. The crystals were cooled using an Oxford Cryostream low-temperature device. Diffraction data were collected at 100 K. The images were processed and corrected for Lorentz-polarization effects and absorption effects by employing the Bruker software packages. The structure was solved using the intrinsic phasing method (SHELXT)[42d] and expanded using Fourier techniques. All the non-hydrogen atoms were refined in anisotropic approximation, with hydrogen atoms 'riding' in idealized positions, by full-matrix least squares against F^2 on all data, using SHELXL[42a,c] software and the SHELXLE[42b] graphical user interface. Crystal data and experimental details are listed in Table 3-S1; full structural information has been deposited with the Cambridge Crystallographic Data Centre. CCDC-2045652 (**3-3f**), 2045653 (**3-3l**), 2045654 (**3-3m**), 2045655 (**3-3n**), and 2045656 (**3-4d**).

Table 3-S1. Single-crystal X-ray diffraction data and structure refinements of 3-3f, 3-3l, 3-3m, 3-3n, and 3-4d

Compounds	**3-3f**	**3-3l**	**3-3m**	**3-3n**	**3-4d**
CCDC number	2045652	2045653	2045654	2045655	2045656
Empirical formula	$C_{13}H_6BrF_5O$	$C_{14}H_7F_5O_2$	$C_{17}H_9F_5O$	$C_{12}H_6F_5NO$	$C_{13}H_{10}F_2O$
Formula weight (g mol^{-1})	353.09	302.20	324.24	275.18	220.21
Temperature (K)	100(2)	100(2)	100(2)	100(2)	100(2)
Radiation, λ (Å)	Mo-Kα 0.71073	Mo-Kα 0.71073	Mo-Kα 0.71073	Mo-Kα 0.71073	Mo-Kα 0.71073
Crystal color, habit	Colorless, block	Colorless, block	Colorless, block	Colorless, block	Colorless, block
Crystal size (mm^3)	0.17×0.26×0.34	0.57×0.55×0.28	0.30×0.33×0.41	0.54×0.39×0.23	0.44×0.35×0.22
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P*1	$P\bar{1}$	$P2_1/c$	*C*2/*c*	*C*2/*c*
Unit cell dimensions					
a (Å)	14.964(6)	6.9938(7)	8.422(5)	22.136(7)	20.058(3)
b (Å)	19.077(8)	7.7520(8)	23.486(13)	10.023(3)	10.796(3)
c (Å)	19.488(8)	11.9114(12)	14.108(9)	9.945(3)	9.2708(17)
α (°)	90.142(12)	71.116(2)	90	90	90
β (°)	109.530(7)	87.313(2)	99.583(17)	105.237(8)	98.046(8)
γ (°)	106.160(7)	82.190(2)	90	90	90
Volume ($Å^3$)	5008(4)	605.36(11)	2751(3)	2128.8(12)	1987.9(7)
Z	16	2	8	8	8
Calc. density (Mg m^{-3})	1.873	1.658	1.565	1.717	1.472
μ (mm^{-1})	3.337	0.161	0.143	0.170	0.117
F(000)	2752	304	1312	1104	912
θ range (°)	1.493 - 26.370	2.800 - 27.103	1.701 - 26.369	1.907 - 26.371	2.051 - 26.372
Reflections collected	165215	25240	62274	51503	15767
Independent reflections	40933	2658	5627	2178	2035
Minimum/maximum transmission	0.486 / 0.533	0.679 / 0.717	0.621 / 0.702	0.711 / 0.746	0.691 / 0.746
Parameters / restraints	2963 / 208	191 / 0	618 / 615	173 / 0	148 / 0
Goof on F^2	1.003	1.070	1.089	1.072	1.037
R_1 [$I>2\sigma(I)$]	0.0351	0.0388	0.0945	0.0300	0.0397
wR^2 (all data)	0.0755	0.1099	0.2297	0.0842	0.1057
Maximum/minimum residual electron density (e $·Å^{-3}$)	1.476 / –0.515	0.475 / –0.204	0.757 / －0.594	0.282 / –0.194	0.484 / –0.217

Table 3-5. Parameters for hydrogen bonding in 3-3f, 3-3l, 3-3m, 3-3n and 3-4d

Donor(D)–H ··Acceptor(A) [a]	**H ··A (Å)** [a]	**D ··A (Å)**	**D–H ··A (°)**
Compound **3-3f**			
O1–H1A ··O2	1.90	2.693(5)	157.4
O2–H2A ··O3	1.87	2.702(6)	171.0
O3–H3A ··O4	1.90	2.704(5)	160.2
O4–H4A ··O1	1.97	2.765(6)	156.5
O5–H5A ··O8	1.91	2.697(6)	156.2
O8–H8A ··O7	1.86	2.681(6)	166.6
O7–H7A ··O6_1/11	2.02/2.07	2.703(14)/2.646(16)	138.4/125.4
O6_1/11–H6_1/11 ··O5	1.87/1.84	2.700(19)/2.666(11)	171.0/166.8
O9–H9A ··O12	1.95	2.698(6)	148.1
O10–H10A ··O9	1.97	2.756(5)	155.7
O11–H11A ··O10	1.95	2.711(6)	150.3
O12–H12A ··O11	1.92	2.740(5)	166.1
O13–H13A ··O14	1.88	2.690(5)	162.0
O14–H14A ··O15	1.90	2.716(5)	163.0
O15–H15A ··O16	1.89	2.699(6)	161.0
O16–H16A ··O13	1.88	2.677(6)	158.8
Compound **3-3l**			
O1–H1 ··O2	1.90	2.7412(16)	176.4
Compound **3-3m**			
O1_1–H1a_1 ··O1a_3	1.99	2.65(2)	135.3
O1_1–H1a_1 ··O1_3	2.11	2.72(2)	129.1
O1a_3–H1ab_3 ··O1_1	1.91	2.65(2)	145.6

O1a_3–H1ab_3 ··O1a_1	1.82	2.41(3)	125.4
Compound **3-3n**			
O1–H1 ··N1	1.95	2.7880(17)	173.5
Compound **3-4d**			
O1–H1A ··O1	2.16	2.9815(17)	165.4
O1–H1B ··O1	2.04	2.8661(16)	167.3

[a]The donor–H distance was constrained to be 0.84 Å for all H atoms. H atoms were refined riding in idealized positions.

Table 3-6. Aryl···aryl (π···π) distances (Å) and angles (٩) in 3-3f, 3-3l, and 3-3m at 100 K

Aryl···aryl	Centroid-centroid distance	Interplanar separation	Offset shift [a]	Plane normal angle
Compound **3-3f**				
$Ar_{Br1}\cdots Ar_F$	3.648(4)	3.529(5)/3.330(7)	0.924(11)/1.490(12)	9.6(3)
$Ar_{Br2}\cdots Ar_F$	3.536(4)	3.470(4)/3.284(5)	0.682(9) / 1.311(8)	11.04(19)
$Ar_{Br3}\cdots Ar_F$	3.800(4)	3.570(5)/3.348(6)	1.301(11)/1.797(9)	9.9(2)
$Ar_{Br4}\cdots Ar_F$	3.648(4)	3.525(5)/3.386(6)	0.940(11)/1.357(10)	9.5(2)
$Ar_{Br5}\cdots Ar_F$	3.657(3)	3.538(4)/3.362(5)	0.927(9)/1.439(9)	8.75(19)
$Ar_{Br6\_1}\cdots Ar_F$	3.694(14)	3.640(14)/3.687(14)	0.631(14)/0.23(5)	10.7(8)
$Ar_{Br6\_11}\cdots Ar_F$	3.719(15)	3.717(14)/3.682(14)	0.12(5)/0.518(15)	9.9(8)
$Ar_{Br7}\cdots Ar_F$	3.783(5)	3.285(8)/3.659(6)	1.875(12)/0.959(13)	16.8(3)
$Ar_{Br8}\cdots Ar_F$	3.523(4)	3.416(4)/3.514(4)	0.729(10)/0.25(1)	8.0(2)
$Ar_{Br9}\cdots Ar_F$	3.674(5)	3.494(6)/3.276(8)	1.138(12)/1.663(12)	8.9(3)
$Ar_{Br10}\cdots Ar_F$	3.719(4)	3.528(5)/3.317(5)	1.179(10)/1.682(9)	11.43(19)
$Ar_{Br11}\cdots Ar_F$	3.728(4)	3.554(5)/3.362(5)	1.128(10)/1.611(9)	8.8(2)
$Ar_{Br12}\cdots Ar_F$	3.564(4)	3.484(4)/3.343(6)	0.754(11)/1.237(10)	9.7(2)
$Ar_{Br13}\cdots Ar_F$	3.739(4)	3.357(6)/3.635(4)	1.646(10)/0.877(10)	13.3(2)

$Ar_{Br14}\cdots Ar_F$	3.610(4)	3.593(4)/3.523(4)	0.35(1)/0.788(10)	12.5(2)
$Ar_{Br15}\cdots Ar_F$	3.706(5)	3.559(5)/3.281(7)	1.034(12)/1.723(11)	12.9(3)
$Ar_{Br16}\cdots Ar_F$	3.592(4)	3.577(4)/3.539(4)	0.330(9)/0.614(9)	4.96(19)
Compound **3-3l**				
Ar···Ar	3.6667(10)	3.3379(13)	1.5176(19)	0.00(7)
$Ar_F \cdots Ar_F$	4.6778(14)	3.375(2)	3.238(3)	0.00(1)
Compound **3-3m**[b]				
$Ar_d\cdots Ar_F$	3.650(3)	3.637(3)/3.564(3)	0.305(7)/0.787(6)	16.05(13)
$Ar\cdots Ar_{F\_d}$	3.538(3)	3.448(3)/3.357(4)	0.794(5)/1.119(7)	6.47(13)
$Ar_d\cdots Ar_F$ (T···T)	3.886(3)	3.613(4)/3.416(5)	1.431(5)/1.854(7)	6.89(13)
Compound **3-3n**				
$Ar_F \cdots Ar_F$	4.2972(15)	3.193(2)	2.876(2)	0.0(5)
Compound **3-4d**				
Ar···Ar	4.8860(13)	3.177(3)	3.712(2)	0.00(1)
$Ar_{HF} \cdots Ar_{HF}$	4.5100(14)	3.358(2)	3.010(3)	17.65(7)

[a]The offset shift, also called inter-centroid shift, is the distance within a plane of an aryl ring between the centroid of the respective aryl ring and the intersection point with the normal to the plane through the centroid of the other aryl ring.
[b] Only interactions with the main parts (85%) of the disordered (d) pentafluorophenyl and naphthalene moieties are reported here.

3.7.6 Computational Methods

(Computations have been made by Prof. Xiaoling Luo) All the calculations were performed with the Gaussian09 programs.[44] The geometries of the different structures were optimized at the DFT level using the B3-LYP[45-46] hybrid functional with 6-31+G(d) basis set. Frequency analysis was carried out at the same level to verify the stationary points as an intermediate or transition state and to obtain the thermodynamic energy corrections assuming a standard state of 1 atm and 298.15 K. Intrinsic reaction coordinates (IRC)[47] were calculated to confirm the connection between the transition state and the

correct reactant/product. The solvent effects were taken into consideration by single point calculations of the gas-phase stationary points with the SMD[48-50] continuum salvation model. To obtain more accurate energy information, single-point calculations were carried out with the M06[51] functional and 6-311++G(d,p) basis set in toluene solvent (using the SMD solvent model). All of the three-dimensional molecular diagrams of the molecules were generated with CYLView.[52]

Table 3-7. Absolute calculated electronic energies, correction of enthalpies, and free energies

Geometry	$E_{(elec\text{-}B3LYP)}$[1]	$G_{(corr\text{-}B3LYP)}$[2]	$H_{(corr\text{-}B3LYP)}$[3]	$E_{(M06\ toluene)}$[4]	IF[5]
6	-2602.91354	0.19189	0.276362	-2602.613003	
7-ts	-2602.862623	0.187452	0.27543	-2602.566437	-135.94
8	-2602.899113	0.183295	0.276536	-2602.586769	
9	-2948.493833	0.283666	0.395715	-2948.028436	
10-ts	-2948.48623	0.2872	0.395038	-2948.022579	-104.87
11	-2948.514631	0.289305	0.397303	-2948.048797	
12-ts	-2948.483194	0.291873	0.396411	-2948.029586	-71.99
13	-2948.526205	0.29542	0.397854	-2948.072049	
14-ts	-4087.664887	0.503267	0.650296	-4086.926819	-74.41
15	-4087.674391	0.503786	0.651069	-4086.934931	
16-ts	-4087.667933	0.502938	0.650055	-4086.930499	-106.81
17	-1484.742692	0.286987	0.373107	-1484.297391	
18	-2503.68739	0.201261	0.283462	-2503.387159	
19-ts	-2503.634465	0.196446	0.282443	-2503.338675	-135.57
20	-2404.458457	0.210645	0.290577	-2404.158042	
21-ts	-2404.40159	0.205886	0.289656	-2404.105012	-137.3
22	-2305.218418	0.220156	0.297974	-2304.918703	
23-ts	-2305.159478	0.215332	0.297033	-2304.863907	-141.31
24	-2205.970598	0.228529	0.305459	-2205.671805	
25-ts	-2205.908151	0.223326	0.304145	-2205.612351	-104.72
26	-2205.963365	0.228374	0.305711	-2205.664144	
27-ts	-2205.892339	0.222338	0.304343	-2205.595884	-114.48
28	-1402.96216	0.191335	0.268364	-1402.767999	

29-ts	-1402.951039	0.18894	0.266972	-1402.754229	-132.93
30	-675.200515	0.156661	0.211906	-675.04524	
31	-727.84762	0.011433	0.055189	-727.754167	
32-ts	-1073.433312	0.110004	0.173384	-1073.176777	-121.88
33	-1073.441942	0.113864	0.175008	-1073.188879	
34-ts	-1748.560884	0.292987	0.387263	-1748.200815	-108.2
35	-1748.578555	0.295372	0.389196	-1748.223167	

[1] The electronic energy calculated by B3-LYP/6-31+g(d) in gas phase. [2] The thermal correction to Gibbs free energy calculated by B3-LYP/6-31+g(d) in gas phase. [3] The thermal correction to enthalpy calculated by B3-LYP/6-31+g(d) in gas phase. [4] The electronic energy calculated by M06/6-311++G(d,p) in toluene. [5] The B3-LYP calculated imaginary frequencies for the transition states.

B3LYP geometries for all the optimized compounds and transition state.

6

C	-2.27197500	0.88043600	-1.53236400
C	-2.65585600	-0.62458300	-1.26977200
O	-1.50658800	-1.11901800	-0.57012800
O	-1.52181800	1.20667900	-0.35807100
B	-0.82930300	-0.00536400	0.14312500
C	0.81156600	-0.00311700	-0.20654500
C	1.57578400	1.16182700	-0.26982500
C	1.54782400	-1.16102800	-0.45624800
C	2.93231300	1.20292500	-0.58179700
C	2.90348000	-1.18470400	-0.77289900
C	3.60583200	0.01408700	-0.84209000
O	-1.03623900	-0.09693500	1.60633000
C	-0.02050700	-0.16995300	2.61978200
O	0.33486200	-1.32923400	2.92791100
O	0.33160600	0.93346200	3.09209100
C	-3.88967900	-0.76451400	-0.35566100
H	-4.81443900	-0.45330500	-0.85606700
H	-4.00876800	-1.81920100	-0.07493400
H	-3.76934400	-0.18045300	0.56199600
C	-2.86422200	-1.46237000	-2.53519300
H	-3.13209500	-2.49061300	-2.26257100
H	-3.67923300	-1.05863100	-3.14923800
H	-1.95640700	-1.50483400	-3.14221000
C	-3.46281000	1.83876300	-1.63913700
H	-3.10237700	2.85735100	-1.82798000
H	-4.12221100	1.56149300	-2.47087500
H	-4.05557800	1.85240900	-0.71940700
C	-1.37274000	1.05628800	-2.77092000

H	-1.92916100	0.90706000	-3.70377100
H	-0.96944700	2.07510200	-2.77334300
H	-0.52928100	0.35996600	-2.75615700
F	1.00950400	2.37975900	-0.00637500
F	3.59563500	2.37278600	-0.63053400
F	4.91280700	0.02264500	-1.14748600
F	3.53950500	-2.34771000	-1.00564700
F	0.95227900	-2.39118300	-0.38382100
K	-1.04721800	-2.87445200	1.41987500
K	-1.04337900	2.67075900	1.79668500

7-ts

C	0.46292300	2.80457500	-0.28914600
C	0.93411000	2.36303100	1.16428300
O	0.87683100	0.91600700	1.09949800
O	0.74813000	1.63109200	-1.08854900
B	0.85999100	0.54819300	-0.24076000
C	-1.31576800	-0.51892500	-0.33293200
C	-2.26133100	-0.08870200	-1.25197100
C	-1.86771100	-1.09607000	0.79104800
C	-3.64089400	-0.16870500	-1.05798600
C	-3.22770800	-1.21845600	1.06731000
C	-4.12723600	-0.73266400	0.12163900
O	1.51143300	-0.64889100	-0.66281000
C	2.83025300	-0.92611000	-0.45547200
O	3.66663800	-0.00183500	-0.32608100
O	3.09202800	-2.18298700	-0.43336200
C	2.39361100	2.73219200	1.47641400
H	2.52668100	3.81639300	1.57357700
H	2.67368000	2.26678300	2.42853100
H	3.07010100	2.35019600	0.70696100
C	0.03030000	2.83613500	2.30474800
H	0.41221200	2.44826600	3.25580400
H	0.01638800	3.93156600	2.36603700
H	-0.99545900	2.47979900	2.18548300
C	1.24801100	3.97521600	-0.88729600
H	0.87359700	4.18332900	-1.89564900
H	1.12174100	4.88282900	-0.28394900
H	2.31424600	3.74801700	-0.96396200
C	-1.04009200	3.10287600	-0.38850800
H	-1.29525600	4.03636500	0.12697000
H	-1.31041400	3.20420500	-1.44443900
H	-1.64393300	2.29651200	0.03300100
F	-1.86829200	0.45997600	-2.44177900
F	-4.52419900	0.27623100	-1.98186400
F	-5.45583100	-0.82835800	0.33350600

F	-3.69504800	-1.80380000	2.19687600
F	-1.01943300	-1.67657400	1.74561600
K	5.61649200	-1.62245000	-0.19876500
K	0.45353000	-2.92102000	-0.21376700
8			
C	5.27663600	1.00011600	-0.46195400
C	5.40606700	-0.48068100	0.08284100
O	4.12362500	-0.67871900	0.74640200
O	3.83438000	1.14029100	-0.63301200
B	3.24118600	0.20198900	0.18236900
C	-3.10863500	1.35634300	-0.42346400
C	-4.37302000	1.75597400	-0.03626100
C	-3.02269700	0.02479900	-0.71918100
C	-5.47480000	0.90413400	0.06419200
C	-4.04871500	-0.90520200	-0.61153400
C	-5.30537500	-0.45243300	-0.22182000
O	1.89177800	0.27594500	0.43221300
C	1.06562400	-0.83599600	0.76323300
O	1.37994000	-1.95077400	0.31481000
O	0.03991600	-0.49648300	1.40842900
C	5.49761700	-1.53551300	-1.02858300
H	6.46620600	-1.49763500	-1.53953600
H	5.37924300	-2.52811800	-0.58281300
H	4.70507100	-1.40857800	-1.77337500
C	6.51783300	-0.69971100	1.10688100
H	6.50898800	-1.74351300	1.43793600
H	7.50013300	-0.49181600	0.66590700
H	6.38874600	-0.06699400	1.98856800
C	5.95120700	1.25762500	-1.80756200
H	5.77862700	2.29543300	-2.11263500
H	7.03429900	1.10170600	-1.73613400
H	5.55559600	0.60653200	-2.59064200
C	5.70937700	2.06356700	0.55700400
H	6.79481400	2.06027400	0.70533400
H	5.41738500	3.05163200	0.18562200
H	5.22789800	1.91042000	1.52872800
F	-4.60299700	3.06369700	0.31317600
F	-6.69539600	1.34037300	0.44678400
F	-6.33777700	-1.31272000	-0.11097600
F	-3.84415100	-2.24808800	-0.83563000
F	-1.78009700	-0.51937500	-1.13495500
K	-1.19472100	-2.64939000	0.40126200
K	-0.40122600	1.89915500	0.28674400
9			
C	-4.83159700	0.03947600	0.36536300

C	-3.49213300	0.24315000	0.68414400
C	-2.43332400	-0.53403600	0.27153600
C	-2.82305300	-1.58400600	-0.52603000
C	-4.12916000	-1.88013400	-0.90604300
C	-5.15007300	-1.04698000	-0.44920900
C	-0.37872300	0.88334000	-1.84999700
H	-1.27348100	0.58003400	-2.42326600
C	-0.44116900	2.23293200	-1.25529700
C	0.62058800	2.74491200	-0.48514200
C	-1.59250300	3.00967300	-1.46242400
C	0.51966500	4.01975600	0.06988800
H	1.51168400	2.14438100	-0.32993100
C	-1.68897500	4.28654800	-0.90766900
H	-2.41496600	2.60399800	-2.04707200
C	-0.63356800	4.79065300	-0.14099000
H	1.34062500	4.41833400	0.66043400
H	-2.58369000	4.88211100	-1.06469900
H	-0.70650500	5.78474200	0.29266300
F	-1.85890200	-2.46842500	-1.03805700
F	-4.43643200	-2.93252400	-1.69759100
F	-6.43029900	-1.28964000	-0.79055800
F	-5.81969700	0.84875200	0.80924500
F	-3.24472100	1.35183000	1.51118600
O	0.57984300	0.12177200	-1.76178100
O	3.65752800	0.84274600	0.57060500
C	4.62415000	0.58634500	-0.48781100
C	4.65022600	-0.99420000	-0.54638300
O	3.32079500	-1.34269300	-0.05939500
B	2.87710000	-0.28772200	0.72954200
C	4.08528000	1.23626000	-1.76957700
H	3.94488600	2.30785800	-1.59133100
H	4.78897400	1.12321300	-2.60195000
H	3.12057900	0.81270200	-2.06457400
C	5.95184100	1.23396700	-0.09535100
H	5.83277500	2.32221900	-0.06045200
H	6.29170000	0.90220100	0.88859700
H	6.73099800	1.00304200	-0.83178500
C	5.65526100	-1.62696700	0.42654800
H	5.47767500	-2.70628700	0.46994000
H	6.68824300	-1.45871100	0.10277300
H	5.54061200	-1.22988100	1.44038800
C	4.83004000	-1.58777200	-1.94256100
H	5.79602600	-1.29241200	-2.36837800
H	4.81309300	-2.68189100	-1.88306500
H	4.04022100	-1.26755500	-2.62751400

C	1.30141900	-1.49565800	2.38753300
O	1.53720200	-2.59471600	1.88829000
O	0.70973000	-1.07937200	3.38076300
O	1.78250000	-0.29397100	1.53411200
K	0.76793500	-2.38861300	-0.62091400
K	-0.65111500	0.86371200	2.22826100

10-ts

C	-4.54637200	-0.41225900	0.76349200
C	-3.33810500	0.25411600	0.57317800
C	-2.37179400	-0.11990500	-0.33549000
C	-2.67609700	-1.25320400	-1.05445500
C	-3.85607600	-1.98087500	-0.93371900
C	-4.80613100	-1.54372100	-0.01036800
C	-0.58362500	1.06853900	-1.27705500
H	-1.03388200	0.68935200	-2.20450900
C	-0.97613300	2.47374700	-0.94180800
C	-0.12585800	3.27618800	-0.16589300
C	-2.15157600	3.03132400	-1.46687100
C	-0.46165700	4.60508900	0.10757200
H	0.81990900	2.86415100	0.17869300
C	-2.48809300	4.35632200	-1.19500200
H	-2.81087600	2.41333700	-2.07218700
C	-1.64721400	5.14533100	-0.39992900
H	0.20746000	5.22231000	0.70212400
H	-3.40627000	4.77581800	-1.59775900
H	-1.91059400	6.17819900	-0.18761800
F	-1.75561900	-1.74898500	-1.98136500
F	-4.10047400	-3.08522100	-1.66895500
F	-5.95916200	-2.21708500	0.14230800
F	-5.45672000	-0.00721700	1.67205100
F	-3.10710800	1.34515100	1.40033900
O	0.47453200	0.55807700	-0.83552700
O	4.02001300	0.37935600	1.33521400
C	4.84093600	0.64420500	0.16679500
C	4.67583600	-0.68770000	-0.66440800
O	3.34898100	-1.13929700	-0.25567200
B	3.09113500	-0.58237300	0.99253600
C	4.24355600	1.87427700	-0.53299100
H	4.22527000	2.70725400	0.17799800
H	4.84292700	2.17960700	-1.39819300
H	3.21687900	1.68841700	-0.86576800
C	6.26656500	0.94184900	0.62838100
H	6.27687000	1.87010400	1.20943800
H	6.66248900	0.14491400	1.26248800
H	6.93545600	1.07288600	-0.23090000

C	5.66487900	-1.78797200	-0.25705100
H	5.36450100	-2.73152700	-0.72454600
H	6.68418900	-1.55188500	-0.58188700
H	5.67182100	-1.94027800	0.82686000
C	4.68288500	-0.50636700	-2.18128300
H	5.63773800	-0.08548700	-2.51738800
H	4.56110900	-1.47872500	-2.67344500
H	3.87881300	0.15521800	-2.51497800
C	1.15081400	-2.02615600	1.78849700
O	1.51918500	-2.95555800	1.05640000
O	0.15020500	-1.84525800	2.49447100
O	2.03232600	-0.83270200	1.80841200
K	0.95562400	-2.07751000	-1.33046900
K	-0.38773600	0.64195700	1.94486700
11			
C	-4.57005300	-0.52949400	0.97168100
C	-3.34564900	0.06554300	0.68935500
C	-2.79054200	0.11619700	-0.59074600
C	-3.55133400	-0.48849100	-1.59300200
C	-4.78212100	-1.10006400	-1.35250300
C	-5.29673900	-1.12143900	-0.06020900
C	-1.36341900	0.66500100	-0.86330400
H	-1.27959800	0.67893000	-1.96956100
C	-1.24796900	2.15370800	-0.45533700
C	-0.01404700	2.63591400	0.00206400
C	-2.30409900	3.06609200	-0.59744200
C	0.15914700	3.98645400	0.32670200
H	0.81757500	1.93902800	0.06898300
C	-2.13892400	4.41514400	-0.27074800
H	-3.26997500	2.72357800	-0.96319000
C	-0.90635900	4.88176200	0.19792500
H	1.12803600	4.33987400	0.67338000
H	-2.97477900	5.10218600	-0.38060700
H	-0.77771800	5.93057600	0.45311300
F	-3.10373500	-0.50559700	-2.87133500
F	-5.47150300	-1.66845300	-2.35561200
F	-6.47669500	-1.70542800	0.19250400
F	-5.05539500	-0.54118400	2.22434400
F	-2.68220500	0.61538900	1.74379100
O	-0.42919200	-0.15664300	-0.28967200
O	4.51886000	0.22993500	1.08804600
C	5.12505300	0.67400700	-0.15479700
C	4.69150900	-0.46229300	-1.16321400
O	3.43319400	-0.91895200	-0.57925000
B	3.47349000	-0.61306600	0.77892900

C	4.51917800	2.04516900	-0.48788100
H	4.69708500	2.72309500	0.35333700
H	4.97485900	2.48307400	-1.38293400
H	3.43759300	1.98093000	-0.64836300
C	6.63216400	0.80570000	0.05854100
H	6.83003200	1.59927800	0.78682400
H	7.06894500	-0.11885000	0.44345700
H	7.13784300	1.07128700	-0.87775000
C	5.64386300	-1.66566500	-1.17006300
H	5.18743100	-2.48338700	-1.73767200
H	6.60130500	-1.41513000	-1.63968800
H	5.83738900	-2.03203100	-0.15707100
C	4.42473400	0.00799000	-2.59197700
H	5.33166200	0.43590500	-3.03496200
H	4.12547000	-0.84331500	-3.21490000
H	3.63221200	0.75975800	-2.63348300
C	1.84176600	-2.28350400	1.77295800
O	2.19402500	-3.11587800	0.92493500
O	0.97067400	-2.27405100	2.65026200
O	2.56076600	-0.97988100	1.71918700
K	0.99258900	-2.07938200	-1.18248800
K	0.00159100	0.12966500	2.31128400

12-ts

C	1.89045500	2.92142600	-0.25955200
C	2.13961800	2.72834400	1.29886300
O	2.23954700	1.61858200	-0.79508900
O	2.00559600	1.29308700	1.47715200
B	2.14545000	0.71290600	0.23655800
O	2.52961100	-0.62853100	0.06541200
C	3.63837400	-1.04055900	-0.62428700
O	4.68272500	-0.34817200	-0.59777600
O	3.49295300	-2.16249400	-1.22074000
C	3.56846900	3.08554500	1.73776300
H	3.75494900	4.16447600	1.68188900
H	3.70549900	2.76704900	2.77693800
H	4.31273800	2.56528100	1.12630100
C	1.12625000	3.43028200	2.20249300
H	1.35322500	3.20298200	3.25006100
H	1.17374400	4.51879400	2.07318000
H	0.10520500	3.09903500	1.99908700
C	2.78935300	3.96647100	-0.92377800
H	2.56979300	4.00469000	-1.99667800
H	2.60450300	4.96380200	-0.50576700
H	3.84893800	3.72641200	-0.80426400
C	0.42454900	3.18806200	-0.62443900

H	0.08546800	4.16240400	-0.25446700
H	0.32872600	3.18254800	-1.71613100
H	-0.22022400	2.39872600	-0.23396500
C	-3.89777800	-0.83607500	-1.79066000
C	-2.82175400	-0.93308100	-0.91654600
C	-2.47539500	0.06991900	-0.00799300
C	-3.30320200	1.19337000	-0.01905400
C	-4.39051400	1.33159000	-0.88340400
C	-4.69060000	0.31027100	-1.77783500
C	-1.17276300	-0.00880700	0.83901700
H	-1.15257800	0.93312300	1.42669800
C	-1.27863000	-1.13186400	1.90456200
C	-0.09042300	-1.70315000	2.38673100
C	-2.49301100	-1.56927700	2.45365200
C	-0.11709200	-2.69171100	3.37614200
H	0.85545600	-1.33823800	1.99749900
C	-2.52515200	-2.56273300	3.43844600
H	-3.43007100	-1.13537200	2.11119500
C	-1.33602200	-3.13279900	3.90204800
H	0.81773300	-3.10976400	3.74478500
H	-3.48067000	-2.89077400	3.84215700
H	-1.35862800	-3.90364800	4.66881200
F	-3.07300800	2.21828600	0.83327800
F	-5.15160000	2.44025900	-0.85716800
F	-5.73234900	0.42278200	-2.61893400
F	-4.18317800	-1.83734300	-2.64592600
F	-2.09523100	-2.08456200	-0.98485100
O	-0.10308700	-0.11906800	0.00354600
K	0.72419900	-2.32606400	-0.88250400
K	5.95106900	-2.00180100	-2.04595700

13

C	-2.77645200	-1.03077300	-1.83590800
C	-2.02983700	-2.19903700	-1.08119300
O	-2.68870200	0.04941800	-0.89683100
O	-1.01744600	-1.50285700	-0.35248700
B	-1.49844500	-0.14750500	-0.04837100
O	-1.76316200	-0.10227800	1.40337600
C	-2.23819300	0.93610300	2.21767200
O	-2.21538600	0.63768700	3.44165100
O	-2.60966000	2.00371800	1.67569200
C	-2.95040000	-2.92977900	-0.08045500
H	-3.71029600	-3.54198100	-0.58090100
H	-2.33422300	-3.60262100	0.53090400
H	-3.45450000	-2.21857800	0.58143200
C	-1.36323300	-3.23042400	-1.99724400

H	-0.87672000	-4.00348100	-1.39032100
H	-2.09767100	-3.72590000	-2.64519800
H	-0.59764300	-2.76808700	-2.62553900
C	-4.25396400	-1.30244300	-2.13722800
H	-4.68806900	-0.44910400	-2.67307400
H	-4.37429700	-2.18898900	-2.77272800
H	-4.82945800	-1.44716700	-1.21913800
C	-2.05675700	-0.61884800	-3.13490100
H	-2.14281200	-1.38527600	-3.91441300
H	-2.51774300	0.29932500	-3.52199600
H	-0.99727700	-0.41752000	-2.95255100
C	3.08564400	-1.37432200	-1.37021600
C	2.21427100	-0.30935900	-1.15622300
C	1.66113500	-0.02602600	0.09672300
C	2.03336800	-0.89119800	1.12326600
C	2.89704700	-1.96778400	0.94724200
C	3.43191000	-2.21193300	-0.31234400
C	0.63845300	1.10578600	0.33083000
H	0.38521600	1.07042200	1.39600100
C	1.24214500	2.48616900	0.06825400
C	1.08385400	3.13974800	-1.16160200
C	1.95182200	3.13326200	1.08892100
C	1.62529100	4.41312800	-1.36442900
H	0.55136500	2.63679000	-1.96288200
C	2.49761600	4.40385000	0.88798200
H	2.06483100	2.64646100	2.05578200
C	2.33507400	5.04947200	-0.34126200
H	1.50174500	4.90433400	-2.32705900
H	3.03848600	4.89268400	1.69439600
H	2.75515400	6.03945900	-0.49971700
F	1.52251600	-0.73000200	2.38016300
F	3.20025100	-2.77628900	1.98073700
F	4.26691300	-3.24210400	-0.50670700
F	3.59176100	-1.60473100	-2.59186300
F	1.90565600	0.44573400	-2.22472900
O	-0.51162200	0.91133900	-0.44375500
K	-2.54950400	2.69329300	-0.72126700
K	-1.04484700	-1.65468800	3.26768700

14-ts

C	1.48107000	3.56279300	-0.48309300
C	1.63257800	2.68805100	-1.78999800
O	0.82984900	2.65782700	0.42348300
O	1.80481600	1.36737600	-1.26742400
B	1.17347400	1.28001000	0.04602700
O	-0.00237100	0.37060400	-0.09034100

C	-0.88228100	-0.05335400	0.87674000
O	-1.57730800	-1.05392300	0.49078700
O	-0.94527300	0.52819200	1.97924000
C	0.36445900	2.71277500	-2.66496500
H	0.21412100	3.68229300	-3.15406000
H	0.46929500	1.95582900	-3.45270900
H	-0.52940900	2.48144200	-2.07838400
C	2.84659100	3.04130100	-2.65551900
H	2.87793700	2.38319100	-3.53200900
H	2.79259100	4.07665800	-3.01534700
H	3.78284400	2.91072900	-2.10659100
C	0.60715300	4.81049600	-0.64488000
H	0.55678500	5.35689800	0.30520700
H	1.02381300	5.49175500	-1.39744100
H	-0.41386900	4.55137500	-0.93600400
C	2.84210600	3.96487500	0.11702300
H	3.36585200	4.69961000	-0.50564200
H	2.67645800	4.42520100	1.10016500
H	3.48871200	3.09293000	0.25122800
C	5.42859900	-0.65892300	-1.35313400
C	4.62318100	-0.38620000	-0.25071100
C	3.36170500	-0.96329800	-0.07538300
C	2.95200400	-1.82868800	-1.08844200
C	3.72752200	-2.12098800	-2.20635200
C	4.97981800	-1.53264900	-2.34076200
C	2.43241400	-0.61448700	1.10444200
H	1.53372800	-1.22619300	0.96929800
C	3.03685600	-1.01416500	2.45104900
C	3.72332600	-0.09479000	3.25600500
C	2.88384000	-2.32936200	2.91078800
C	4.24596600	-0.48434500	4.49320000
H	3.86320600	0.92040800	2.89778300
C	3.40847000	-2.72281600	4.14470700
H	2.33696800	-3.04938300	2.30479200
C	4.09218700	-1.79989800	4.94167200
H	4.78464600	0.23813000	5.10223600
H	3.27398800	-3.74588000	4.48682200
H	4.49930400	-2.10212500	5.90314400
F	1.72348100	-2.41763300	-1.03833000
F	3.26473900	-2.95281300	-3.15895200
F	5.74444300	-1.80104300	-3.40801600
F	6.63357800	-0.08036700	-1.47546100
F	5.10451900	0.48633000	0.65218000
O	2.09280500	0.74762000	1.10217700
C	-4.06972800	-3.46346200	0.54778100

C	-3.91110800	-3.35999200	-1.02222800
O	-3.39140100	-2.01037400	-1.20493300
O	-4.24832000	-2.07626100	0.92716800
B	-3.67629300	-1.28333900	-0.03837900
C	-3.92206600	0.28673500	-0.05176700
C	-3.59245800	1.09632800	-1.14052600
C	-4.46497900	0.96592200	1.04674300
C	-3.78061100	2.47384800	-1.16985000
C	-4.66557100	2.34606400	1.05911000
C	-4.32333200	3.10548600	-0.05493600
C	-2.81675800	-3.98492800	1.26803200
H	-2.96465100	-3.87018600	2.34691100
H	-2.64545700	-5.04716700	1.05598000
H	-1.93100000	-3.40535300	0.99754600
C	-5.29813100	-4.24521100	1.01700100
H	-5.24159800	-5.29288300	0.69650100
H	-5.34110600	-4.22747800	2.11095600
H	-6.22723800	-3.81192500	0.63851200
C	-5.24448700	-3.42364900	-1.78164800
H	-5.07030400	-3.16866500	-2.83279500
H	-5.68759900	-4.42498400	-1.73985900
H	-5.96695300	-2.70747400	-1.37779000
C	-2.91987200	-4.35154600	-1.63324700
H	-3.25703900	-5.38384000	-1.48287300
H	-2.84467600	-4.18444400	-2.71495800
H	-1.92372400	-4.25556700	-1.19127300
F	-4.82153700	0.30379200	2.15750600
F	-5.18383600	2.95330300	2.14085100
F	-4.50948100	4.43408300	-0.05425500
F	-3.43650700	3.19639200	-2.25146000
F	-3.02811900	0.55116000	-2.25660200
K	0.72278300	2.10386900	3.01686000
K	-0.80574100	-1.17676900	-2.03249700

15

C	1.47875000	3.70467900	-0.03358300
C	1.72915200	3.00949800	-1.42837700
O	0.86344200	2.64946500	0.73117400
O	1.98688700	1.64925600	-1.05477600
B	1.29023300	1.36352100	0.18177200
O	0.12384900	0.44884600	-0.17639500
C	-0.82342500	-0.01879400	0.64069200
O	-1.47788000	-0.99276800	0.04567300
O	-1.03420000	0.39207700	1.78408600
C	0.48697500	3.04791200	-2.33956900
H	0.28251600	4.05545700	-2.71961200

H	0.67104900	2.39779800	-3.20427500
H	-0.40534600	2.68829800	-1.81855400
C	2.93846200	3.54393100	-2.20150200
H	3.03739100	3.00333800	-3.14997500
H	2.82341200	4.61015000	-2.43376500
H	3.86612700	3.40598200	-1.63997000
C	0.52487000	4.90149800	-0.07403100
H	0.41069000	5.32276200	0.93237100
H	0.91423000	5.69546200	-0.72324900
H	-0.46712700	4.61330200	-0.43070100
C	2.78864600	4.10975200	0.66672800
H	3.28054800	4.95084500	0.16459700
H	2.56231900	4.42630300	1.69330000
H	3.48914400	3.27053400	0.71263200
C	5.57570200	-0.34516200	-1.27290300
C	4.72416900	-0.23745500	-0.17667200
C	3.46235600	-0.83826000	-0.14043900
C	3.09868300	-1.54772300	-1.28461600
C	3.92212100	-1.67224600	-2.39939600
C	5.17450700	-1.06819300	-2.39403600
C	2.48217500	-0.67226400	1.03428300
H	1.60261600	-1.27031000	0.77291300
C	3.02709000	-1.24425300	2.34258200
C	3.65575200	-0.43576400	3.29950000
C	2.87216100	-2.61133200	2.61028300
C	4.12015900	-0.98558000	4.49856600
H	3.79768100	0.61994800	3.09024300
C	3.33936400	-3.16403100	3.80559500
H	2.36997200	-3.24774500	1.88406700
C	3.96516000	-2.35136800	4.75541400
H	4.61480400	-0.34803200	5.22777700
H	3.20513200	-4.22538400	3.99792200
H	4.32708200	-2.77780000	5.68736700
F	1.87463900	-2.13835300	-1.36936500
F	3.50534600	-2.35670400	-3.48092500
F	5.98401000	-1.17745200	-3.45561700
F	6.77872600	0.24902600	-1.26078300
F	5.15873200	0.49713100	0.86229500
O	2.11174000	0.67537000	1.20952200
C	-3.54583200	-3.56089300	0.25083300
C	-3.82668500	-3.16267500	-1.24866500
O	-3.08700800	-1.93631600	-1.37840800
O	-3.46080800	-2.28477400	0.89323800
B	-2.99713900	-1.30800300	-0.04078100
C	-3.78440900	0.14374800	0.05598900

C	-3.69283900	1.08346800	-0.96940900
C	-4.58446100	0.54357300	1.13102300
C	-4.34192700	2.31404300	-0.97800200
C	-5.25593700	1.76753800	1.17100800
C	-5.13692400	2.65949600	0.11001100
C	-2.20634200	-4.30212300	0.43269200
H	-1.98315600	-4.35798900	1.50371700
H	-2.24459000	-5.32399500	0.03523100
H	-1.38320000	-3.76653700	-0.05069900
C	-4.66222900	-4.36864300	0.91967200
H	-4.82832800	-5.32252300	0.40221200
H	-4.38398300	-4.58903600	1.95637800
H	-5.60183200	-3.81083000	0.93981900
C	-5.31268900	-2.86481500	-1.51895300
H	-5.40850900	-2.40079300	-2.50736100
H	-5.92190500	-3.77627800	-1.50778700
H	-5.71725000	-2.16883900	-0.77784900
C	-3.31390100	-4.16184800	-2.29032400
H	-3.80755400	-5.13531600	-2.18085800
H	-3.53126200	-3.79170900	-3.30015600
H	-2.23369600	-4.31824800	-2.20592600
F	-4.74467300	-0.24473900	2.21043200
F	-6.01360900	2.10261100	2.23315200
F	-5.77651900	3.84150600	0.13650800
F	-4.20273600	3.16966200	-2.01065300
F	-2.90171900	0.83402900	-2.06398200
K	0.59412200	1.74635000	3.20938700
K	-0.76476900	-0.89373800	-2.44852300

16-ts

C	1.74961600	-3.46780700	-1.39753700
C	2.01912300	-3.40549000	0.16252000
O	1.27412000	-2.12794100	-1.69321700
O	2.33988800	-2.01158200	0.36008300
B	1.76417300	-1.27282800	-0.67168700
O	-1.99581800	-0.07607300	0.93371500
C	-0.61411700	-0.01434200	0.87375800
O	-0.08957700	-0.76195200	-0.00844400
O	-0.03394200	0.70935700	1.71292900
C	0.78774700	-3.74545500	1.01768600
H	0.54018900	-4.81222400	0.96150400
H	1.01287100	-3.50212800	2.06158300
H	-0.08347700	-3.15515400	0.72332800
C	3.21080500	-4.24202300	0.63476100
H	3.33731000	-4.11704100	1.71561400
H	3.04738000	-5.30833500	0.43508800

H	4.14048500	-3.93390300	0.15018200
C	0.68021300	-4.47626100	-1.82222100
H	0.53136200	-4.42595300	-2.90810600
H	0.98755900	-5.50050600	-1.58025300
H	-0.27815100	-4.28981600	-1.32761000
C	3.02337300	-3.68740800	-2.22855200
H	3.42350500	-4.69995800	-2.10354200
H	2.78646500	-3.54054300	-3.28811000
H	3.80272200	-2.96819200	-1.95949500
C	6.42656500	-0.40381100	-0.00347200
C	5.18136000	0.02803700	-0.45435200
C	4.15316200	0.39351600	0.41952500
C	4.44907500	0.32003200	1.78206900
C	5.68604800	-0.10353700	2.26292700
C	6.68191700	-0.47098700	1.36375100
C	2.76983300	0.85703000	-0.05973000
H	2.10582300	0.87253200	0.81021700
C	2.85620900	2.27237000	-0.62499300
C	2.94461100	2.51352800	-2.00098500
C	2.87137600	3.35988000	0.25965400
C	3.05305800	3.82166200	-2.48264000
H	2.92483300	1.67354600	-2.68711300
C	2.98172800	4.66725300	-0.22057500
H	2.79123000	3.18102400	1.33007700
C	3.07427300	4.90260700	-1.59617300
H	3.12305400	3.99569800	-3.55396400
H	2.99186900	5.50059400	0.47810100
H	3.16042300	5.91880700	-1.97314700
F	3.52095500	0.66776800	2.69683800
F	5.92247800	-0.16172400	3.58484700
F	7.87949100	-0.88041500	1.80897200
F	7.38486000	-0.75281300	-0.87930100
F	4.99711800	0.07566600	-1.78703300
O	2.23723300	-0.02197000	-1.03905600
C	-2.40794700	2.27768200	-1.61406700
C	-3.25915800	2.97820900	-0.48841000
O	-3.10576400	2.07244900	0.61194200
O	-2.58362200	0.87747200	-1.31276000
B	-2.95711800	0.69310800	0.09424800
C	-4.35428200	-0.21054900	0.27337300
C	-5.13626000	-0.12803400	1.42419200
C	-4.80608100	-1.15436700	-0.64533500
C	-6.29596000	-0.86626500	1.64441400
C	-5.95827000	-1.92160600	-0.48285400
C	-6.71783500	-1.77065500	0.67330500

C	-0.91213400	2.61875600	-1.52756800
H	-0.34583300	1.96585300	-2.20086200
H	-0.71099900	3.65286000	-1.82961100
H	-0.51674300	2.46870600	-0.51973300
C	-2.90734500	2.53557700	-3.04012500
H	-2.88944500	3.60657400	-3.27683600
H	-2.25357400	2.03186500	-3.76339300
H	-3.92429100	2.16252800	-3.18752600
C	-4.75461200	3.08643300	-0.84298300
H	-5.30918900	3.39625700	0.04993200
H	-4.93338300	3.82881100	-1.62949100
H	-5.16256100	2.12760500	-1.17617800
C	-2.74555200	4.35822500	-0.06556500
H	-2.76760400	5.06458500	-0.90435700
H	-3.38839200	4.76406200	0.72532400
H	-1.72027900	4.31048600	0.31226500
F	-4.09312600	-1.41089300	-1.78686900
F	-6.33453800	-2.81322900	-1.41854000
F	-7.83189400	-2.49675000	0.85657300
F	-7.00332800	-0.72719000	2.78090400
F	-4.76604700	0.70132900	2.45009000
K	-2.10589500	1.67069500	3.00688600
K	-1.27650100	-1.24948800	-2.24053600
17			
C	-4.00064800	-0.33220600	-0.79214500
C	-3.71036500	-0.34294100	0.76461900
O	-2.92200500	0.50349600	-1.30547900
O	-2.26370400	-0.14139000	0.80776100
B	-1.90990000	0.46139700	-0.37944500
C	-4.34511300	0.83778900	1.51186900
H	-5.43429300	0.73613800	1.57105600
H	-3.94744300	0.86803800	2.53165300
H	-4.11330500	1.79328400	1.02944100
C	-4.03728400	-1.65344200	1.47647400
H	-3.77480400	-1.57174900	2.53663100
H	-5.10913400	-1.87440400	1.40871300
H	-3.48062000	-2.49418300	1.05564800
C	-5.33273600	0.29644100	-1.19573400
H	-5.43252700	0.27563500	-2.28612200
H	-6.17307300	-0.26274800	-0.76725200
H	-5.40350300	1.33755300	-0.87198300
C	-3.84743200	-1.71066900	-1.45008900
H	-4.66239100	-2.38583000	-1.16672400
H	-3.86548800	-1.58659900	-2.53765100
H	-2.89700400	-2.18345300	-1.18061600

C	2.60390000	-1.72384700	-1.28367300
C	1.81963700	-0.58738800	-1.10061400
C	1.23235400	-0.27803700	0.13173000
C	1.48173100	-1.16563600	1.18086100
C	2.26668900	-2.30710600	1.02775300
C	2.82783200	-2.58912600	-0.21415000
C	0.35641800	0.95886900	0.33848800
H	-0.08988000	0.87227000	1.33266000
C	1.16695500	2.25028300	0.28342600
C	1.12947700	3.09801200	-0.82874000
C	1.97120900	2.59033400	1.38061400
C	1.89372100	4.26909800	-0.84315700
H	0.50115500	2.84036200	-1.67427800
C	2.73623700	3.75831200	1.36375600
H	1.99648300	1.94333600	2.25573400
C	2.69989000	4.60182000	0.24864500
H	1.85702700	4.92183400	-1.71173400
H	3.35323000	4.01202600	2.22201600
H	3.29229800	5.51306500	0.23379300
F	0.96585600	-0.92921200	2.40495000
F	2.47980000	-3.13274800	2.06353200
F	3.58235200	-3.68252700	-0.38007600
F	3.14727000	-1.99046000	-2.48045900
F	1.64297400	0.22024100	-2.15786800
O	-0.67758300	0.98132300	-0.64404000

18

C	2.23586900	-0.89264300	-1.34664000
C	2.58542700	0.61772200	-1.06332100
O	1.36882900	1.11524500	-0.49251100
O	1.36497800	-1.20841700	-0.25634100
B	0.62298700	0.00728200	0.15995600
C	-0.97174600	-0.00315100	-0.35230900
C	-1.72148100	-1.17293100	-0.48610700
C	-1.68210000	1.15210900	-0.68207100
C	-3.03954100	-1.20463100	-0.93223400
C	-2.99966000	1.15355800	-1.13031100
C	-3.70415400	-0.03400200	-1.26912600
O	0.68595400	0.11536700	1.63626400
C	-0.41534000	0.19683700	2.55383800
O	-0.78394900	1.35928100	2.83422300
O	-0.82029800	-0.90321300	2.99105200
C	3.71820500	0.77429900	-0.02898800
H	4.69137400	0.46584400	-0.42934200
H	3.80148900	1.83235400	0.25223300
H	3.50838500	0.19714500	0.87670200

C	2.92084000	1.44027000	-2.31152900
H	3.15483800	2.47352500	-2.02689800
H	3.79646900	1.03223000	-2.83222100
H	2.08001000	1.46849300	-3.00894400
C	3.43466300	-1.84664900	-1.31164300
H	3.09930800	-2.86954800	-1.52211100
H	4.17839500	-1.57893200	-2.07234000
H	3.92523800	-1.84261500	-0.33345600
C	1.47616800	-1.08756900	-2.67312000
H	2.12914300	-0.94518200	-3.54243900
H	1.08028000	-2.10875500	-2.70743600
H	0.63245200	-0.39656700	-2.75787000
F	-1.17662200	-2.38804500	-0.15993300
F	-3.68079300	-2.39191300	-1.03449200
F	-3.60164100	2.32821300	-1.42930800
F	-1.09622900	2.38538700	-0.55728100
K	0.70624300	2.89049100	1.41887200
K	0.66167000	-2.65403100	1.84669300
H	-4.73211600	-0.04533900	-1.61240900

19-ts

C	0.12417100	2.78847800	-0.29409900
C	0.63787500	2.37005800	1.15225300
O	0.65748300	0.92253600	1.08506500
O	0.45936900	1.63218700	-1.09939700
B	0.63969800	0.55668700	-0.25483900
C	-1.50837300	-0.62278100	-0.30314000
C	-2.49882400	-0.23715600	-1.19568800
C	-2.00704700	-1.22972100	0.83238700
C	-3.86466700	-0.39289000	-0.95509300
C	-3.35565200	-1.41442600	1.12704600
C	-4.31844600	-0.98115100	0.22286300
O	1.33629500	-0.60868800	-0.68988300
C	2.66490300	-0.83501400	-0.48407400
O	3.46492900	0.12150600	-0.35622000
O	2.97599600	-2.08041400	-0.46218100
C	2.07973200	2.81656700	1.44525500
H	2.15567000	3.90623600	1.54276700
H	2.39807000	2.36544800	2.39222100
H	2.76508100	2.47270900	0.66563700
C	-0.27464400	2.79245600	2.30569300
H	0.14230000	2.42794100	3.25131200
H	-0.34983700	3.88544600	2.36660400
H	-1.27991300	2.37794400	2.20134500
C	0.83976800	3.99875000	-0.90046400
H	0.43938100	4.19026600	-1.90210100

H	0.67746300	4.89719200	-0.29195800
H	1.91477400	3.82593100	-0.99466000
C	-1.39325100	3.00928800	-0.37184800
H	-1.68724200	3.93014100	0.14592400
H	-1.68408600	3.09386400	-1.42373000
H	-1.94904400	2.17434400	0.05943100
F	-2.16286500	0.33525600	-2.39446600
F	-4.78063800	0.02186600	-1.87314300
F	-3.74712700	-2.02836900	2.27988300
F	-1.10621700	-1.77114500	1.76553200
K	5.47290900	-1.42247700	-0.21026600
K	0.36403200	-2.92031000	-0.23513700
H	-5.37723100	-1.10819700	0.41819300

20

C	2.14090500	-1.11386400	-1.19806800
C	2.48651400	0.42358600	-1.18342000
O	1.27151300	1.00991900	-0.70443600
O	1.27462500	-1.23776900	-0.06802300
B	0.52248800	0.02920800	0.13097900
C	-1.06495900	-0.07197100	-0.36804500
C	-1.83110100	-1.23877000	-0.30657100
C	-1.79666700	0.99001900	-0.90559600
C	-3.14112200	-1.39791200	-0.74686200
C	-3.10509900	0.94525800	-1.37568400
C	-3.75457500	-0.27716300	-1.28658700
O	0.59876100	0.38748700	1.57079400
C	-0.49425900	0.63866900	2.46483400
O	-0.87738200	1.82950800	2.51508300
O	-0.88018800	-0.35628100	3.11886500
C	3.62364900	0.76214100	-0.19813900
H	4.59512300	0.38441100	-0.53886100
H	3.70958700	1.85361300	-0.11318100
H	3.41611500	0.35948200	0.79804100
C	2.81388600	1.01776400	-2.55760200
H	3.04006800	2.08662200	-2.45772500
H	3.69165400	0.53270800	-3.00361500
H	1.97123400	0.91833700	-3.24633900
C	3.34251900	-2.04487200	-1.00164900
H	3.00823300	-3.08938000	-1.02743100
H	4.08335800	-1.91486300	-1.80047500
H	3.83703800	-1.86928600	-0.04138800
C	1.37835100	-1.53789000	-2.46836400
H	2.02738200	-1.54520800	-3.35219100
H	0.98696500	-2.55111100	-2.32355200
H	0.53131500	-0.87450300	-2.66497400

F	-1.27284000	-2.37323100	0.24453300
F	-1.20373200	2.23242300	-0.98584700
K	0.61074500	3.07726400	0.85519700
K	0.58093500	-2.28174200	2.25813500
F	-5.03304700	-0.37722900	-1.73247100
H	-3.59463700	1.82406100	-1.77846400
H	-3.65811800	-2.34640100	-0.66173700

21-ts

C	-0.08195000	2.71444500	-0.46642300
C	0.43722900	2.39517200	1.00472600
O	0.53324100	0.94986600	1.01157600
O	0.31133500	1.53454400	-1.20787800
B	0.54114700	0.51559000	-0.30726400
C	-1.58923500	-0.77025800	-0.30856700
C	-2.60253800	-0.44491800	-1.20462400
C	-2.12431800	-1.28718800	0.85599300
C	-3.98125200	-0.55007500	-0.99317600
C	-3.46570400	-1.44767500	1.21043900
C	-4.37890800	-1.04903000	0.24175500
O	1.29012200	-0.63620200	-0.68013100
C	2.61152100	-0.82072700	-0.39982700
O	3.38419700	0.16065100	-0.28885200
O	2.94861100	-2.05481900	-0.29626700
C	1.84970100	2.93346500	1.28473000
H	1.86634900	4.02953300	1.31526600
H	2.18040300	2.55795900	2.26008800
H	2.56158600	2.58034600	0.53357100
C	-0.50921100	2.82614200	2.12742400
H	-0.08485900	2.53056100	3.09365400
H	-0.64112700	3.91546800	2.13339400
H	-1.49058700	2.35542200	2.03418000
C	0.58589000	3.92166000	-1.13131200
H	0.18990900	4.03873600	-2.14614800
H	0.37524700	4.84424400	-0.57596400
H	1.66880000	3.79415400	-1.20512900
C	-1.60649100	2.86570400	-0.56539900
H	-1.94325600	3.79645200	-0.09331900
H	-1.89033100	2.88963100	-1.62243800
H	-2.13024400	2.02842300	-0.10051000
F	-2.25232500	0.03868700	-2.44603000
F	-1.21594400	-1.78386100	1.82199800
K	5.41185200	-1.32333500	0.04637900
K	0.33280300	-2.93652900	-0.13529200
F	-5.71320100	-1.17021600	0.50612600
H	-4.70703700	-0.26036800	-1.74575100

H	-3.78424600	-1.85520000	2.16388800

22

C	2.25218800	-0.89522500	-0.86253000
C	2.48956800	0.63543900	-0.57535400
O	1.16020000	1.11848100	-0.35874100
O	1.14472400	-1.19122600	-0.00995600
B	0.28684700	0.01648800	0.13792600
C	-1.11692400	-0.06926400	-0.75556900
C	-1.80386300	-1.25647900	-1.02440400
C	-1.75363700	1.02907900	-1.34029500
C	-2.94838200	-1.39023300	-1.80138300
C	-2.89573000	0.99668600	-2.13134800
C	-3.49737300	-0.23980400	-2.36867100
O	-0.01611700	0.19127700	1.58189900
C	-1.30266200	0.28871100	2.20720700
O	-1.75758900	1.45071400	2.30981700
O	-1.77188700	-0.79499500	2.62235800
C	3.32066900	0.87009200	0.70271000
H	4.36856100	0.57150500	0.57714700
H	3.31203800	1.94146900	0.94330800
H	2.89704200	0.32764000	1.55343900
C	3.11570200	1.41535500	-1.73646800
H	3.24422400	2.46735400	-1.45278300
H	4.10518300	1.01781000	-1.99616100
H	2.48101800	1.38491100	-2.62562100
C	3.42303600	-1.80949400	-0.48475300
H	3.16877400	-2.85069700	-0.71849900
H	4.32748400	-1.55440100	-1.05108100
H	3.65577600	-1.74708200	0.58275100
C	1.85159200	-1.16823700	-2.32543700
H	2.69677200	-1.03894000	-3.01217100
H	1.49906600	-2.20252500	-2.40768400
H	1.03909600	-0.50985000	-2.64584700
F	-1.33257300	-2.43567500	-0.47407400
F	-1.23165200	2.29164500	-1.12067800
K	-0.00630100	2.94623200	1.20178400
K	-0.04347300	-2.55004200	1.91336700
H	-3.29907100	1.91973300	-2.53486600
H	-3.39296100	-2.36995500	-1.94271700
H	-4.39327600	-0.30451300	-2.97918700

23-ts

C	-0.59147600	2.61627100	-0.46004900
C	0.00057900	2.36578000	0.99684600
O	0.25220100	0.93934100	1.00736800
O	-0.09819700	1.47827000	-1.20697700

B	0.26379200	0.49739200	-0.30836600
C	-1.74745200	-1.00132000	-0.23540400
C	-2.80497500	-0.78552200	-1.11370300
C	-2.20863300	-1.55742900	0.94379500
C	-4.15897000	-1.02440700	-0.86650600
C	-3.52106700	-1.84069300	1.31949000
C	-4.51672400	-1.55039500	0.38014900
O	1.10946600	-0.57930400	-0.69576300
C	2.44701300	-0.63432800	-0.43715400
O	3.12550400	0.41767400	-0.35800100
O	2.90136200	-1.82854000	-0.31893200
C	1.35426500	3.05398100	1.23548400
H	1.25461500	4.14568900	1.26699000
H	1.75127700	2.71807700	2.20047500
H	2.07856000	2.77789800	0.46420500
C	-0.95521000	2.69894100	2.14466900
H	-0.47672000	2.45045400	3.09882200
H	-1.19899000	3.76876500	2.15519500
H	-1.88440100	2.12857300	2.07692800
C	-0.07429400	3.88143700	-1.15170300
H	-0.50630200	3.94387600	-2.15667400
H	-0.36957600	4.78204500	-0.59876600
H	1.01389300	3.87103300	-1.25328300
C	-2.12573700	2.60479900	-0.51458400
H	-2.54519400	3.49523000	-0.03094200
H	-2.44061700	2.59727400	-1.56303000
H	-2.54333000	1.71629300	-0.03753500
F	-2.52126100	-0.28090000	-2.36845300
F	-1.22902800	-1.95230500	1.89674800
K	5.28756600	-0.86133200	-0.02872800
K	0.37623900	-2.94657200	-0.07568600
H	-4.90485900	-0.80447800	-1.62562500
H	-3.75278800	-2.26662400	2.29185100
H	-5.56085200	-1.74425300	0.61288100
24			
C	2.18119800	-0.24902100	-1.26275800
C	2.51853400	0.69289500	-0.04181300
O	1.22026900	1.06100500	0.43738300
O	0.99098700	-0.90424000	-0.82391200
B	0.22114700	0.00113200	0.07864200
C	-1.08655300	0.69968500	-0.63069400
C	-2.06563000	0.00913600	-1.34170900
C	-1.30101600	2.09219000	-0.57973400
C	-3.18122700	0.57430300	-1.94566500
C	-2.40720500	2.71892200	-1.16278700

C	-3.35811500	1.95630600	-1.84612500
O	-0.14081500	-0.79753800	1.28714600
C	-1.41267700	-1.00632100	1.91013000
O	-1.81757800	-0.07250500	2.64390400
O	-1.91982600	-2.12931800	1.69742800
C	3.26781800	-0.05061800	1.08245400
H	4.29149700	-0.31767700	0.79383200
H	3.33676900	0.60400600	1.96181600
H	2.73269100	-0.95872100	1.37591600
C	3.29051100	1.96460000	-0.41056600
H	3.47716800	2.56199000	0.49090800
H	4.26442700	1.72571100	-0.85653400
H	2.72769600	2.58420300	-1.11345200
C	3.24701100	-1.30946800	-1.56346400
H	2.93337800	-1.91319600	-2.42393700
H	4.20996900	-0.84813600	-1.81602500
H	3.39895300	-1.98184900	-0.71355700
C	1.87991000	0.53848700	-2.55295700
H	2.78526700	0.98677700	-2.97996600
H	1.45758600	-0.14961000	-3.29393300
H	1.14673100	1.33046300	-2.37711800
F	-1.93712100	-1.36487700	-1.49995700
K	0.11457500	1.53679600	2.78957400
K	-0.39628400	-3.07701600	-0.14963800
H	-0.54652100	2.70590900	-0.09102000
H	-2.52233400	3.79812700	-1.09185100
H	-4.22426900	2.42671800	-2.30419100
H	-3.88783800	-0.05809600	-2.47473700

25-ts

C	-0.62447200	2.55692500	-0.46082000
C	0.10154600	2.27489700	0.93015400
O	0.44578400	0.86481400	0.84070600
O	-0.13537100	1.48258300	-1.30755400
B	0.34387000	0.48770000	-0.49773100
C	-1.91798300	-1.03698700	-0.38376900
C	-2.49417700	-1.02403500	-1.67864900
C	-2.83241500	-1.43107500	0.57082300
C	-3.83231800	-1.35450000	-1.93950900
C	-4.17391000	-1.77120200	0.41441900
C	-4.68237600	-1.72465400	-0.88805300
O	1.07728200	-0.62041400	-0.93820800
C	2.40433000	-0.76867300	-0.59486400
O	3.22641900	0.10767400	-0.95236300
O	2.68041500	-1.84030300	0.04147000
C	1.42810900	3.03180700	1.09780000

H	1.26903500	4.11176700	1.19707800
H	1.92465900	2.67525000	2.00762400
H	2.10081000	2.84818800	0.25440900
C	-0.77712300	2.48280300	2.16413800
H	-0.20312300	2.24268800	3.06691600
H	-1.10309600	3.52723000	2.24146600
H	-1.66036700	1.84056000	2.14262900
C	-0.23161400	3.88048900	-1.12308900
H	-0.75069000	3.96857300	-2.08344600
H	-0.52646100	4.73345200	-0.49928600
H	0.84260900	3.93850000	-1.31605000
C	-2.15381300	2.45479300	-0.39431800
H	-2.57985800	3.28023500	0.18841500
H	-2.55418000	2.50996300	-1.41193800
H	-2.47645700	1.50369200	0.03263800
F	-2.36203000	-1.53926300	1.93042900
K	5.20223600	-1.37534500	-0.34319200
K	0.17786600	-2.04870600	1.22920100
H	-1.87302700	-0.72840100	-2.52680400
H	-4.21736000	-1.32165100	-2.95836500
H	-5.72364900	-1.97795600	-1.07553200
H	-4.79078300	-2.05861000	1.26288500

26

C	-2.10667900	-1.24804700	-0.95217600
C	-2.22453600	-1.33643100	0.62094100
O	-0.93698200	-0.88960200	1.05381100
O	-1.26170300	-0.10886200	-1.13652100
B	-0.35211100	0.04960000	0.04651600
C	1.21077400	-0.35049600	-0.23406000
C	2.07417700	0.44090900	-1.02053700
C	1.75792200	-1.54481700	0.27559400
C	3.39408300	0.07063500	-1.29416100
C	3.07890700	-1.94281000	0.02601300
C	3.87100700	-1.12093700	-0.76215700
O	-0.51954300	1.46349200	0.52555000
C	0.42506500	2.52042800	0.64193200
O	1.11007600	2.53173200	1.68977700
O	0.40650600	3.34808300	-0.30426100
C	-3.29864100	-0.38796000	1.19093700
H	-4.31574400	-0.71554200	0.94375400
H	-3.21153200	-0.36971000	2.28422200
H	-3.15429600	0.63495200	0.83108200
C	-2.46661700	-2.75043700	1.16122400
H	-2.53455700	-2.72327000	2.25583600
H	-3.40725700	-3.16898100	0.78094600

H	-1.65170500	-3.42750300	0.89143600
C	-3.43663700	-0.99916400	-1.67502200
H	-3.26422600	-0.94042600	-2.75691400
H	-4.14700900	-1.81596300	-1.49735300
H	-3.90692500	-0.06529600	-1.34951200
C	-1.42704300	-2.48323000	-1.57287200
H	-2.07034700	-3.37057300	-1.53224700
H	-1.20383300	-2.27020600	-2.62441100
H	-0.48200800	-2.71165100	-1.07398800
K	0.53050600	0.37485100	2.90416900
K	-1.43635500	2.42257800	-1.81179000
H	3.48418800	-2.87063400	0.42045900
H	4.04885700	0.69473300	-1.89540200
H	1.72690800	1.39270000	-1.41491200
H	1.12348700	-2.19930600	0.87048700
F	5.16001700	-1.49300800	-1.02022500

27-ts

C	-0.45211200	2.61635100	-0.76955600
C	0.17186100	2.50828700	0.69199400
O	0.54912300	1.11016900	0.78927700
O	0.13014300	1.47413200	-1.45086400
B	0.57829100	0.59693200	-0.48869700
C	-1.66393800	-1.02537100	-0.13635900
C	-2.67254500	-1.26542800	-1.10426100
C	-2.15766200	-0.99726200	1.19204500
C	-4.03722900	-1.44876200	-0.80865900
C	-3.50866200	-1.17343700	1.54368200
C	-4.42354400	-1.39755300	0.52319800
O	1.37806800	-0.50392800	-0.85788200
C	2.61560600	-0.77923000	-0.33904000
O	3.38959600	0.15571700	-0.03187800
O	2.87449100	-2.03087100	-0.25088300
C	1.46446300	3.32017600	0.87248500
H	1.27256800	4.39934000	0.84605600
H	1.90039400	3.07172000	1.84642000
H	2.20395600	3.06948600	0.10618600
C	-0.80266000	2.82700900	1.82673400
H	-0.29603000	2.69313900	2.78948700
H	-1.14687300	3.86705100	1.76776300
H	-1.67208900	2.16644700	1.80733900
C	-0.04577500	3.87432400	-1.54236800
H	-0.48843400	3.84068800	-2.54390900
H	-0.41255900	4.77843800	-1.04072100
H	1.03860600	3.95140200	-1.65651000
C	-1.97841700	2.46521700	-0.80806400

H	-2.47508700	3.32805200	-0.34856900
H	-2.29808400	2.40358300	-1.85415800
H	-2.30498300	1.55134100	-0.30891500
K	5.19068900	-1.44307800	0.76705700
K	0.30508400	-2.86782000	-0.75739100
H	-4.78404700	-1.61584600	-1.58272100
H	-3.85118500	-1.13486900	2.57627100
H	-1.46299700	-0.79878700	2.01325800
H	-2.40712700	-1.28090500	-2.16741600
F	-5.75053800	-1.57283900	0.84186900

28

C	-2.59640000	-1.20318400	-0.35307100
C	-2.79583400	-0.48706500	1.04172800
O	-1.52667900	0.07929200	1.27191000
O	-1.71079200	-0.34550600	-1.02649500
B	-0.94434400	0.49788200	-0.05378700
C	0.69080200	0.08292100	0.00501800
C	1.36716800	-0.72112500	-0.91550400
C	1.48846900	0.53253200	1.06024600
C	2.71985600	-1.04701500	-0.81232100
C	2.84315800	0.23361000	1.20071500
C	3.46921000	-0.56569500	0.25343200
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O	-1.01218500	3.84392500	-1.38602600
O	0.49065400	2.20154300	-1.83548900
C	-3.85752900	0.63740800	0.97698200
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H	-3.82002600	1.20059300	1.91830700
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C	-3.14214500	-1.42864800	2.20799100
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C	-1.94105000	-2.59970100	-0.20371500
H	-2.62491400	-3.34645300	0.22954500
H	-1.63191400	-2.94341200	-1.19822700
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F	3.33030000	-1.83816600	-1.74267900
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F	0.97073400	1.32440800	2.03347800
29-ts			
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C	-2.62142500	-1.08127600	0.86676200
O	-1.71118400	-0.02536800	1.15269300
O	-1.73768700	-0.23876500	-1.14817400
B	-1.28353300	0.56673800	-0.07050900
C	1.01945200	0.05342700	0.00505600
C	1.78095400	-0.12407800	-1.13435700
C	1.76034600	0.14496700	1.16826600
C	3.17376900	-0.20188000	-1.15482700
C	3.15281700	0.07625500	1.22821600
C	3.86715500	-0.09736700	0.04692100
O	-1.04793100	1.92028400	-0.21960500
C	-2.13246400	2.86548000	-0.32801800
O	-3.29300200	2.38397500	-0.28667000
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C	-4.04774900	-0.52136200	1.04301900
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H	-2.61004900	-1.85638700	2.88253600
H	-3.05034700	-3.07710500	1.66506600
H	-1.35159400	-2.56331700	1.85913600
C	-3.49951700	-1.82370100	-1.49604100
H	-3.16935300	-2.03790000	-2.52095200
H	-4.00660500	-2.71805600	-1.10433400
H	-4.21302400	-0.99652800	-1.53730000
C	-1.21512100	-2.55828200	-0.77314900
H	-1.60046700	-3.53956600	-0.45937200
H	-0.90943800	-2.62164900	-1.82444200
H	-0.32536000	-2.31441600	-0.18708400
F	1.18458100	-0.25682600	-2.37187400
F	3.89216600	-0.38472500	-2.31071200
F	5.23204200	-0.17074100	0.06770100
F	3.85165600	0.16588400	2.40680200
F	1.14503200	0.30504400	2.39172600
30			
C	-1.65964000	-0.64237800	-0.15132900
C	-1.19571600	0.81906300	0.23147700
O	-0.45551700	-1.21579200	-0.68159800
O	0.18906400	0.62403300	0.54803400
B	0.64278300	-0.51073900	-0.14208700

O	1.89331500	-0.93621500	-0.26181800
C	3.11636100	-0.01039400	-0.03371000
O	3.86114000	-0.45826300	0.83581300
O	3.11509400	0.95579000	-0.79936800
C	-1.26608000	1.80260700	-0.95038500
H	-2.30105700	2.05759200	-1.21276000
H	-0.73872700	2.72083600	-0.67068100
H	-0.76666300	1.39365300	-1.83460400
C	-1.89938100	1.42654300	1.44791700
H	-1.48845600	2.42338800	1.64504700
H	-2.97857100	1.52973300	1.27190500
H	-1.74542000	0.81938300	2.34403200
C	-2.75503700	-0.71627900	-1.21871700
H	-2.99040900	-1.76625100	-1.43021800
H	-3.67491800	-0.22207500	-0.87838400
H	-2.43233400	-0.25103000	-2.15395800
C	-2.07437400	-1.47941700	1.07260900
H	-3.02741500	-1.14146300	1.49926100
H	-2.18439600	-2.52471400	0.76212900
H	-1.30712500	-1.44024600	1.85298400

31

C	-1.20366400	0.37401300	0.00006500
C	-1.15470000	-1.01887200	0.00022700
C	0.00000000	-1.76188400	0.00001000
C	1.15470100	-1.01887300	-0.00019300
C	1.20366400	0.37401300	-0.00003600
C	0.00000000	1.07647500	0.00001200
F	2.37562900	1.08460400	0.00006600
F	0.00000000	2.43947900	-0.00000600
F	-2.37562900	1.08460400	-0.00006600
F	-2.40160600	-1.64596700	-0.00013800
F	2.40160500	-1.64596700	0.00008800

32-ts

C	2.15407200	-1.31467300	-0.23889700
C	0.85791200	-1.08848800	0.22299700
C	0.35956300	0.16798600	0.50722400
C	1.23236200	1.21344000	0.29821400
C	2.54056200	1.05949100	-0.15818000
C	3.00307500	-0.22577800	-0.42648600
C	-1.45152300	0.43034700	1.60914200
H	-1.17504000	1.49028400	1.76167300
C	-2.41693600	0.26099600	0.44882400
C	-3.15807800	-0.91997800	0.31828400
C	-2.64315700	1.30625900	-0.45743600
C	-4.09085200	-1.06243600	-0.71243200

H	-2.98075900	-1.71309800	1.03933800
C	-3.57940500	1.17155200	-1.48560400
H	-2.06506700	2.22420600	-0.35920000
C	-4.30710000	-0.01778300	-1.61965200
H	-4.65423700	-1.98940300	-0.80895800
H	-3.74145500	1.99110800	-2.18404900
H	-5.03515600	-0.12769200	-2.42145400
F	0.83007000	2.51485800	0.53023500
F	3.37716100	2.11717000	-0.35042600
F	4.27046100	-0.41695900	-0.87193700
F	2.61772800	-2.56342500	-0.51954700
F	0.07524900	-2.20178500	0.37371500
O	-1.48590900	-0.35122000	2.58478800

33

C	-1.84919400	1.43657800	0.03808500
C	-0.59573400	0.90880200	0.33214900
C	-0.33167200	-0.46615300	0.34194700
C	-1.41702000	-1.28084500	0.01492600
C	-2.68849900	-0.78784100	-0.27526000
C	-2.90985400	0.58353600	-0.25965700
C	1.00728900	-1.06771000	0.94136100
H	0.98035600	-2.13985700	0.61835500
C	2.22795600	-0.48587200	0.17343000
C	3.24404100	0.13810400	0.90332300
C	2.38652000	-0.63012400	-1.21190300
C	4.39141700	0.61938000	0.26325900
H	3.08985600	0.22604500	1.97615000
C	3.52900400	-0.14965400	-1.86015600
H	1.60624500	-1.12568900	-1.79081600
C	4.53976200	0.47987500	-1.12187400
H	5.17414100	1.10587300	0.84469800
H	3.63324700	-0.26556900	-2.93849500
H	5.43183200	0.85428900	-1.62174600
F	-1.27284100	-2.63213400	-0.04697000
F	-3.70870900	-1.62575000	-0.58356700
F	-4.13713500	1.08587900	-0.53171300
F	-2.05588000	2.77557000	0.02574400
F	0.38163200	1.80028300	0.60083800
O	1.00208000	-0.88477000	2.25688600

34-ts

C	-2.43523700	-2.35826100	-0.70621800
C	-2.70331900	-2.04640400	0.83127500
O	-2.64685300	-1.09213300	-1.32598500
O	-2.43337500	-0.64792800	0.93246900
B	-2.52030600	-0.07952200	-0.35814800

O	-2.89482800	1.22202000	-0.60021000
C	-4.29070300	1.60469500	-0.56335800
O	-4.47713700	2.81156300	-0.81115400
O	-5.10008700	0.68492200	-0.29272500
C	-4.17685500	-2.24566600	1.24003700
H	-4.48513800	-3.30018100	1.18750700
H	-4.29614700	-1.90223100	2.27560000
H	-4.82780200	-1.62494300	0.61568000
C	-1.78964200	-2.80318000	1.80321600
H	-2.02607600	-2.50030800	2.83126800
H	-1.93850500	-3.89021400	1.72504800
H	-0.73597300	-2.57688700	1.62226600
C	-3.41563000	-3.36483200	-1.32662000
H	-3.17937800	-3.48578200	-2.39164800
H	-3.33520600	-4.35038000	-0.84487200
H	-4.44783700	-3.01263900	-1.24869200
C	-0.99075400	-2.80225300	-1.00422600
H	-0.74907500	-3.76994900	-0.54176600
H	-0.87641600	-2.90057300	-2.09168400
H	-0.29354700	-2.02755600	-0.67256500
C	3.86698700	-0.32370100	-1.21896900
C	2.70959100	0.38579900	-0.91382900
C	1.91518000	0.09655300	0.20551600
C	2.38236200	-0.94149400	1.01339200
C	3.53182800	-1.67936200	0.72954900
C	4.27960300	-1.37223700	-0.39884800
C	0.49185000	0.74570400	0.39579100
H	0.15322400	0.40522300	1.40223400
C	0.62465500	2.28484500	0.52883200
C	-0.35396400	3.09308300	-0.06484100
C	1.63700000	2.89349400	1.28600400
C	-0.30942100	4.48296700	0.09271400
H	-1.16082700	2.61058200	-0.61152800
C	1.69114100	4.28419000	1.43492300
H	2.39756400	2.27583700	1.76537800
C	0.71390500	5.08721900	0.83374100
H	-1.09209800	5.09045000	-0.35803300
H	2.49266100	4.73854300	2.01850600
H	0.74582900	6.17048200	0.95057600
F	1.72614600	-1.27848800	2.15539200
F	3.93986100	-2.68398900	1.54758900
F	5.39826600	-2.07967800	-0.69947600
F	4.61702400	-0.00355300	-2.30395700
F	2.38968500	1.39438000	-1.74544200
O	-0.27947300	0.29444700	-0.60464200

35

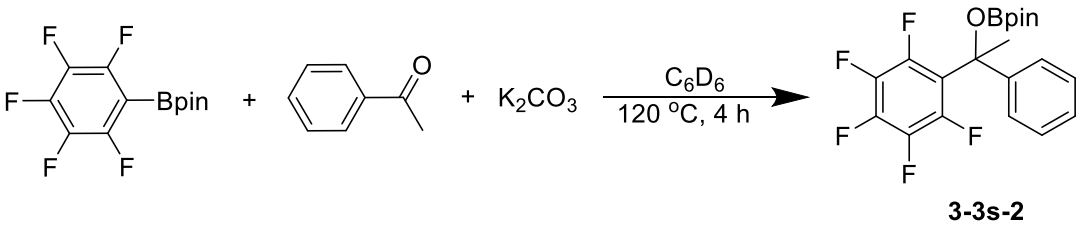
C	3.17789600	0.05272200	-1.53301500
C	2.83728200	1.27642100	-0.57184700
O	2.74973800	-1.07358400	-0.80513600
O	1.74129200	0.79911600	0.18003800
B	1.70472300	-0.69858700	0.15506000
O	1.70023300	-1.36718100	1.42563100
C	2.69738400	-1.47131500	2.41721300
O	2.31754000	-2.09144200	3.44404800
O	3.82471800	-0.96157900	2.18115200
C	3.99231500	1.62117000	0.39199900
H	4.87645400	2.01254800	-0.13661900
H	3.63878300	2.39671600	1.08608700
H	4.25050100	0.73834000	0.98892600
C	2.41261600	2.55883700	-1.31425100
H	2.16712000	3.33423900	-0.57610900
H	3.22199900	2.94437900	-1.95341900
H	1.52545100	2.39354200	-1.93436400
C	4.67610100	-0.11024500	-1.84256200
H	4.81770100	-0.98075000	-2.49853000
H	5.08698500	0.77414500	-2.35377500
H	5.23746500	-0.28742900	-0.92133000
C	2.39743900	0.10596100	-2.86998800
H	2.72241600	0.93324400	-3.51959400
H	2.56610400	-0.83917300	-3.40339900
H	1.32303200	0.19302100	-2.68385200
C	-2.34071200	2.18533100	-0.97670400
C	-1.83368600	0.89091700	-0.91661700
C	-1.44417600	0.28834300	0.28400700
C	-1.61443700	1.05756700	1.43595700
C	-2.11914100	2.35828900	1.40621000
C	-2.47923000	2.92756900	0.19211700
C	-0.76484100	-1.10603600	0.31167900
H	-0.47889100	-1.30652200	1.35629400
C	-1.75524500	-2.19836200	-0.11164300
C	-1.34095800	-3.18899300	-1.01122700
C	-3.05028500	-2.27727300	0.42235500
C	-2.20402200	-4.22751100	-1.37427100
H	-0.33151500	-3.11425300	-1.40376600
C	-3.91628700	-3.31438400	0.06209500
H	-3.38479500	-1.52303800	1.13290900
C	-3.49700600	-4.29667900	-0.84269000
H	-1.86335400	-4.98976500	-2.07389300
H	-4.91697600	-3.35707600	0.49072900
H	-4.16814900	-5.10680800	-1.12501300

F	-1.31612900	0.55325900	2.64806000
F	-2.27607200	3.06988700	2.54694000
F	-2.97822200	4.18587400	0.14523000
F	-2.71629800	2.73175200	-2.15876700
F	-1.74802300	0.22031600	-2.08151600
O	0.35556800	-1.10110500	-0.48811000

3.7.7 Investigation of the Reaction Mechanism

(a) Reactivity test of acetophenone with pentafluorophenyl-Bpin and K_2CO_3

A mixture of acetophenone (0.04 mmol, 4.8 mg), pentafluorophenyl-Bpin (0.04 mmol, 6.7 mg) and K_2CO_3 (0.04 mmol, 5.5 mg, 1 equiv.) was dissolved in 0.7 mL C_6D_6 in a Young's tap NMR tube. The ^1H and ^{11}B NMR spectra of the mixture were recorded immediately. Then, the mixture was heated at 120 °C for 4 h. They subsequently were studied by ^1H and ^{11}B NMR spectra, which revealed that the formation of product **3-3s-2** was observed.



3-3s-2

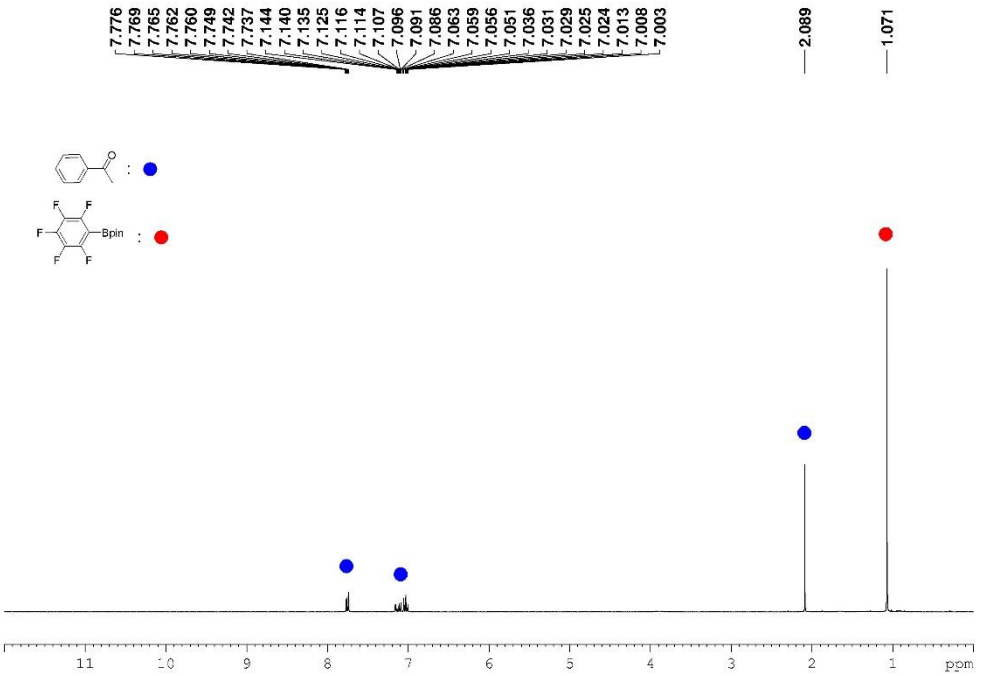


Figure 3-16. ^{1}H NMR spectrum at 0 min (300 MHz, C_6D_6).

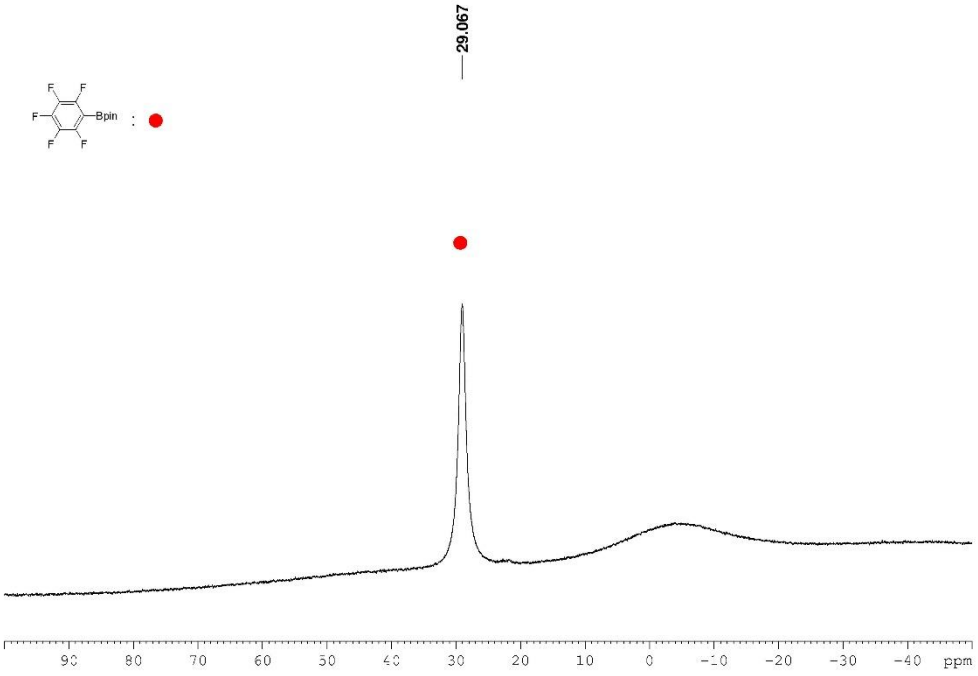


Figure 3-17. ^{11}B NMR spectrum at 0 min (96 MHz, C_6D_6).

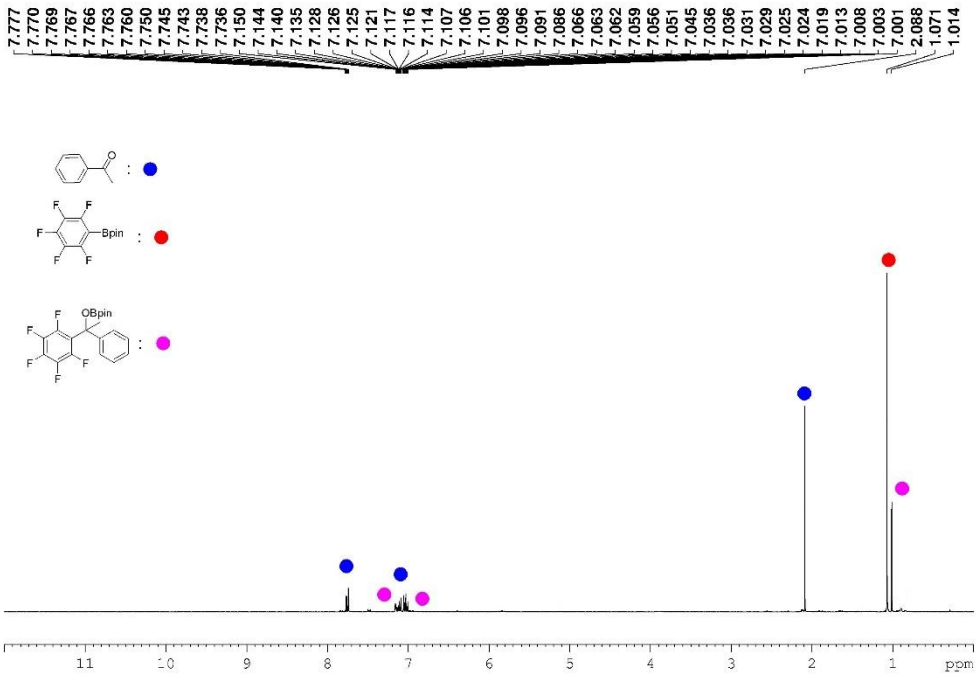


Figure 3-18. ^{1}H NMR spectrum after 4 h heating (300 MHz, C_6D_6).

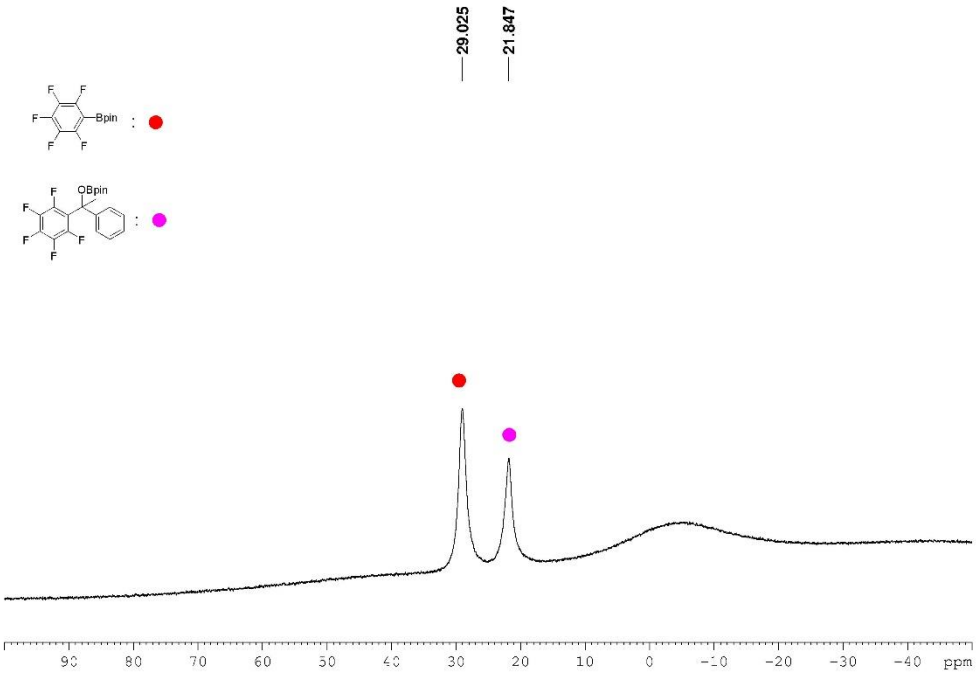
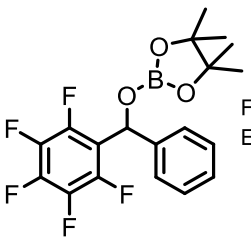
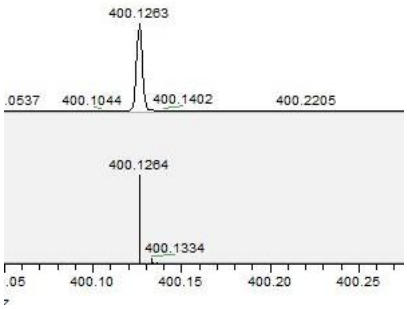


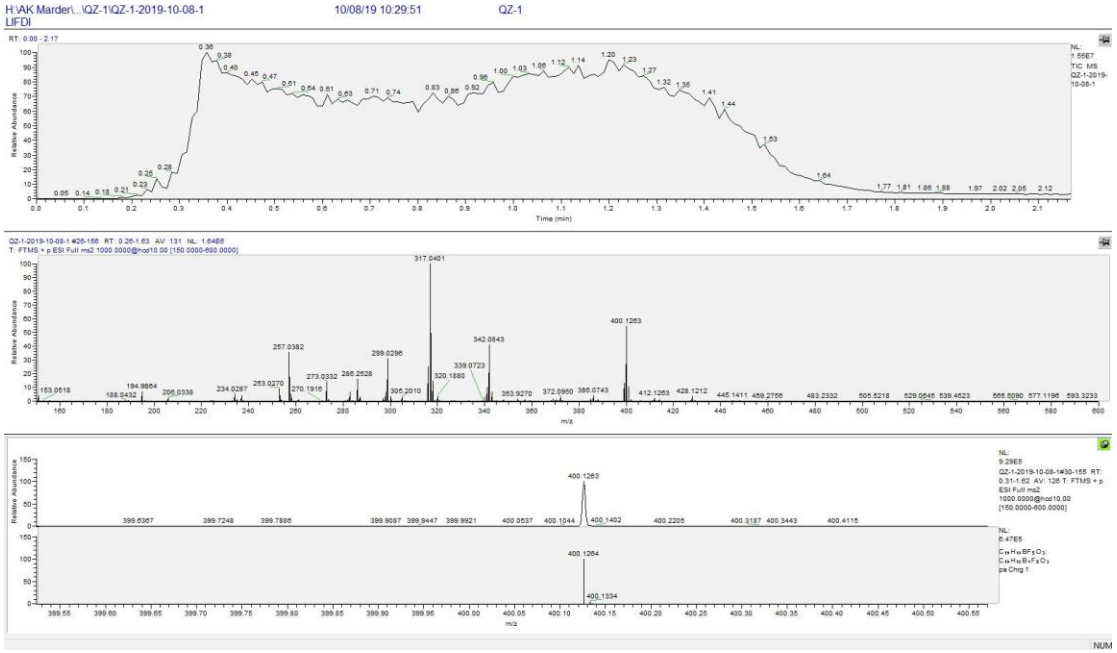
Figure 3-19. ^{11}B NMR spectrum after 4 h heating (96 MHz, C_6D_6).

(b) HRMS data of intermediate 3-D



Formula: $C_{19}H_{18}BF_5O_3$
Exact Mass: 400.1269
Found: 400.1263




H:\AK Marder\..\QZ-1\QZ-1-2019-10-08-1
LIFDI
10/08/19 10:29:51
QZ-1
Relative Abundance
Time (min)
m/z
317.0401
400.1263
342.0843
299.0296
257.0382
339.0723
320.1680
273.0332
286.2528
253.0270
270.1916
305.2910
234.0287
194.9864
188.0432
153.0618
206.0336
400.1264
400.1334

3.7 References

[1] a) C. Bolm, J. P. Hildebrand, K. Muniz, N. Hermanns, *Angew. Chem. Int. Ed*. **2001**, *40*, 3284-3308; *Angew. Chem.* **2001**, *113*, 3382-3407; b) L. Pu, H. B. Yu, *Chem. Rev.* **2001**, *101*, 757-824; c) K. Fagnou, M. Lautens, *Chem. Rev*. **2003**, *103*, 169-196; d) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829-2844; e) P. Knochel, S. Perrone, N. Grenouillat, 9.04-Zinc and Cadmium. In Comprehensive Organometallic Chemistry III, Vol. 9 (Eds.: R. H. Crabtree, D. M. P. Mingos, P. Knochel), Elsevier, Oxford, **2007**, pp. 81-143.

[2] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, 39, 4414-4435; *Angew. Chem.* **2000**, *112*, 4584-4606; b) P. Knochel, A. Gavryushin, A. Krasovskiy, H. Leuser, 9.03-Magnesium. In Comprehensive Organometallic Chemistry III, Vol. 9 (Eds.: R. H. Crabtree, D. M. P. Mingos, P. Knochel), Elsevier, Oxford, **2007**, pp. 31-79; c) Y. Muramatsu, T. Harada, *Chem. Eur. J.* **2008**, *14*, 10560-10563.

[3] a) P.-Y. Wu, H.-L. Wu, B.-J. Uang, *J. Org. Chem.* **2006**, *71*, 833-835; b) J. Shannon, D. Bernier, D. Rawson, S. Woodward, *Chem. Commun.* **2007**, 3945-3947; c) G. Lu, F. Y. Kwong, J. W. Ruan, Y. M. Li, A. S. C. Chan, *Chem. Eur. J.* **2006**, *12*, 4115-4120; d) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev*. **2006**, *35*, 454-470; e) K. Soai, S. Niwa, *Chem. Rev*. **1992**, *92*, 833-856.

[4] M. Gray, M. Tinkl, V. Snieckus, 11.01-Lithium. In Comprehensive Organometallic Chemistry II, Vol. 11 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, A. McKillop), Elsevier, Oxford, **1995**, pp. 1-92.

[5] a) T. Hanamoto, K. Yamada, *J. Org. Chem*. **2009**, *74*, 7559-7561; b) S. Oi, M. Moro, Y. Inoue, *Organometallics*. **2001**, *20*, 1036-1037; c) T. Fujii, T. Koike, A. Mori, K. Osakada, *Synlett* **2002**, 298-300; d) R. Lerebours, C. Wolf, *J. Am. Chem. Soc.* **2006**, *128*, 13052-13053.

[6] S. Oi, M. Moro, Y. Inoue, *Chem. Commun.* **1997**, 1621-1622.

[7] a) T. Imamoto, T. Kusumoto, M. Yokoyama, *J. Chem. Soc. Chem. Commun*. **1982**, 1042-1044; b) H.-J. Liu, K.-S. Shia, X. Shang, B.-Y. Zhu, *Tetrahedron.* **1999**, *55*, 3803-3830; c) G. Bartoli, M. Bosco, E. Di Martino, E. Marcantoni, L. Sambri, *Eur. J. Org. Chem*. **2001**, 2901-2909; d) G. Bartoli, E. Marcantoni, M. Marcolini, L. Sambri, *Chem. Rev*. **2010**, *110*, 6104-6143. e) A. Music, D. Didie, *Synlett*. **2019**, *30*, 1843-1849; l) A. Music, C. Hoarau, N. Hilgert, F. Zischka, D. Didier, *Angew. Chem. Int. Ed*. **2019**, *58*, 1188-1192; *Angew. Chem*. **2019**, *131*, 1200-1204.

[8] a) K. Yoshida, T. Hayashi, Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**; b) A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178-184; c) N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457-2483. For potassium organotrifluoroborates, see: d) S. Darses, J.-P. Genet, *Chem. Rev*. **2008**, *108*, 288-325; e) S. Darses, J.-P. Genet, *Eur. J. Org. Chem*. **2003**, 4313-4327; f) M. Pucheault, S. Darses, J.-P. Genet, *Chem. Commun.* **2005**, 4714-4716.

[9] M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem. Int. Ed.* **1998**, *37*, 3279-3280; *Angew. Chem.* **1998**, *110*, 3475-3477.

[10] For selected references for Rh, see: a) H. Tajuddin, L. Shukla, A. C. Maxwell, T. B. Marder, P. G. Steel, *Org. Lett.* **2010**, *12*, 5700-5703; b) T. Focken, J. Rudolph, C. Bolm, *Synthesis* **2005**, 429-436; c) M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450-4452; d) R. Huang, K. H. Shaughnessy, *Chem. Commun.* **2005**, 4484-4486; e) R. A. Batey, A. N. Thadani, D. V. Smil, *Org. Lett.* **1999**, *1*, 1683-1686; f) P. M. P. Gois, A. F. Trindade, L. F. Veiros, V. André, M. T. Duarte, C. A. M. Afonso, S. Caddick, F. G. N. Cloke, *Angew. Chem. Int. Ed.* **2007**, *46*, 5750-5753; *Angew. Chem*. **2007**, *119*, 5852-5855; g) C. S. Marques, D. Peixoto, A. J. Burke, *RSC Adv.* **2015**, *5*, 20108-20114; h) R. Jana, J. A. Tunge, *J. Org. Chem.* **2011**, 76, 8376-8385; i) S. Morikawa, K. Michigami, H. Amii, *Org. Lett.* **2010**, *12*, 2520-2523; j) A. F. Trindade, V. Andre, M. T. Duarte, L. F. Veiros, P. M. P. Gois, C. A. M. Afonso, *Tetrahedron*. **2010**, *66*, 8494-8502; k) J. R. White, G. J. Price, P. K. Plucinski, C. G. Frost, *Tetrahedron Lett*. **2009**, *50*, 7365-7368; l) Y. Kuang, Y. Wang, *Eur. J. Org. Chem.* **2014**, 1163-1166.

[11] For selected references for Pd, see: a) T. Yamamoto, T. Ohta, Y. Ito, *Org. Lett.* **2005**, *7*, 4153-4155; b) S. Lin, X. Lu, *J. Org. Chem*. **2007**, *72*, 9757-9760; c) M. Kuriyama, R. Shimazawa, R. Shirai, *J. Org. Chem*. **2008**, *73*, 1597-1600; d) H. Zhao, M. Cheng, T. Zhang, M. Cai, *J. Organometal. Chem.* **2015**, *777*, 50-56; e) T. Yamamoto, T. Furusawa, A. Zhumagazin, T. Yamakawa, Y. Oe, T. Ohta, *Tetrahedron* **2015**, *71*, 19-26; f) T. Yamamoto, A. Zhumagazin, T. Furusawa, *Adv. Synth. Catal*. **2014**, *356*, 3525-3529.

[12] Y. X. Liao, C. H. Xing, P. He, Q. S. Hu, *Org. Lett.* **2008**, *10*, 2509-2512.

[13] For selected references for Ni, see: a) G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Chem. Commun*. **2005**, 1459-1461; b) T. Arao, K. Kondo, T. Aoyama, *Tetrahedron Lett*. **2007**, *48*, 4115-4117; c) J. Bouffard, K. Itami, *Org Lett.* **2009**, *11*, 4410-4413.

[14] For selected references for Cu, see: a) H. Zheng, Q. Zhang, J. Chen, M. Liu, S.

Cheng, J. Ding, H. Wu, W. Su, *J. Org. Chem*. **2009**, *74*, 943-945; b) R. Shintani, K. Takatsu, T. Hayashi, *Chem. Commun.* **2010**, *46*, 6822-6824; c) H. Zheng, J. Ding, J. Chen, M. Liu, W. Gao, H. Wu, *Synlett* **2011**, 1626-1630.

[15] T. Zou, S. S. Pi, J. H. Li, *Org. Lett*. **2009**, *11*, 453-456.

[16] J. Karthikeyan, M. Jeganmohan, C. H. Cheng, *Chem. Eur. J.* **2010**, *16*, 8989-8992.

[17] a) Y. Yamamoto, K. Kurihara, N. Miyaura, *Angew. Chem. Int. Ed*. **2009**, *48*, 4414-4416; *Angew. Chem.* **2009**, *121*, 4478-4480; b) H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880-7882.

[18] a) S. T. Chen, J. M. Fang, *J. Org. Chem.* **1997**, *62*, 4349-4357; b) M. D. Vu, M. Das, X. W. Liu, *ACS Catal.* **2019**, *9*, 9009-9014; c) Y.-L. Liu, X.-Y. Lin, *Adv. Synth. Catal.* **2019**, *361*, 876-918.

[19] K. Ishihara, M. Hatano, *Synthesis* **2008**, *11*, 1647-1675.

[20] a) R. McDaniel, A. Thamchaipenet, C. Gustafsson, H. Fu, M. Betlach, M. Betlach, G. Ashley, *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 1846-1851; b) M. C. Cuquerella, V. Lhiaubet-Vallet, J. Cadet, M. A. Miranda, *Acc. Chem. Res*. **2012**, *45*, 1558-1570; c) P. V. Kamat, *Chem. Rev*. **1993**, *93*, 267-300; d) L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem. Int. Ed*. **2008**, *47*, 3043-3045; *Angew. Chem.* **2008**, *120*, 3085-3088; e) W.-J. Gong, D.-X. Liu, F.-L. Li, J. Gao, H.-X. Li, J.-P. Lang, *Tetrahedron*. **2015**, *71*, 1269-1275; f) J. Wang, B. P. Cary, P. D. Beyer, S. H. Gellman, D. J. Weix, *Angew. Chem. Int. Ed.* **2019**, *58*, 12081-12085; *Angew. Chem.* **2019**, *131*, 12209-12213; g) F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241-8245.

[21] a) X. Zhang, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2017**, *139*, 11353-11356; b) R. A. Swyka, W. Zhang, J. Richardson, J. C. Ruble, M. J. Krische, *J. Am. Chem. Soc*. **2019**, *141*, 1828-1832; c) J. L. Schwarz, F. Schäfers, A. Tlahuext-Aca, L. Lückemeier, F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 12705-12709; d) T. Verheyen, L. van Turnhout, J. K. Vandavasi, E. S. Isbrandt, W. M. De Borggraeve, S. G. Newman, *J. Am. Chem. Soc.* **2019**, *141*, 6869-6874; e) R. A. Swyka, W. G. Shuler, B. J. Spinello, W. Zhang, C. Lan, M. J. Krische, *J. Am. Chem. Soc.* **2019**, *141*, 6864-6868; f) P. Fan, Y. Lan, C. Zhang, C. Wang, *J. Am. Chem. Soc*. **2020**, *142*, 2180-2186; g) C. Lei, D. Zhu, V. I. T. Tangcueco, J. S. Zhou, *Org. Lett*. **2019**, *21*, 5817-5822; f) T. Wakaki, T. Togo, D. Yoshidome, Y. Kuninobu, M. Kanai, *ACS Catal*. **2018**, *8*, 3123-3128.

[22] L. Wang, T. Wang, G. Cheng, X. Li, J. Wei, B. Guo, C. Zheng, G. Chen, C. Ran, C. Zheng, *ACS Catal.* **2020**, *10*, 7543-7551.

[23] a) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015**, *115*, 931-972; b) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827-856; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330; e) Y. Sakamoto, T. Suzuki, M. Kobayashi, Y. Gao, Y. Fukai, Y. Inoue, F. Sato, S. Tokito, *J. Am. Chem. Soc.* **2004**, *126*, 8138-8140; f) Y. Sakamoto, T. Suzuki, A. Miura, H. Fujikawa, S. Tokito, Y. Taga, *J. Am. Chem. Soc*. **2000**, *122*, 1832-1833; g) Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder, *Adv. Synth. Catal.* **2021**. DOI: 10.1002/adsc.202001291.

[24] M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett*. **1999**, *40*, 7449-7453.

[25] S. Brogan, N. B. Carter, H. W. Lam, *Synlett* **2010**, 615-617.

[26] G. F. Du, F. Xing, C. Z. Gu, B. Dai, L. He, *RSC Adv*. **2015**, *5*, 35513-35517.

[27] X. J. Jia, J. Wang, X. Ding, J. Yang, Z. Y. Huang, *J. Org. Chem.* **2015**, *80*, 10874-10882.

[28] a) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc*. **2016**, *138*, 5250-5253; b) Y.-M. Tian, X.-N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen, T. B. Marder, *J. Am. Chem. Soc*. **2018**, *140*, 17612-17623; c)Y. P. Budiman, S. Lorenzen, Z. Liu, U. Radius, T. B. Marder, *Chem. Eur. J.* **2021**, *27*, 3869–3874; d) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem* **2019**, *11*, 5387-5396; e) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius, T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 6036-6050; f) Z. Liu, Y. P. Budiman, Y.-M. Tian, A. Friedrich, M. Huang, S. A. Westcott, U. Radius, T. B. Marder, *Chem. Eur. J.* **2020**, *26*, 17267-17274.

[29] a) S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Y. Mo, D. Qiu, M. S. Cheung, L. Dang, J. B. Wang, U. Radius, Z. Y. Lin, C. Kleeberg, T. B. Marder, *Chem. Eur. J.* **2015**, *21*, 7082-7098; b) A. F. Eichhorn, S. Fuchs, M. Flock, T. B. Marder, U. Radius, *Angew. Chem. Int. Ed*. **2017**, *56*, 10209-10213; *Angew. Chem*. **2017**, *129*, 10343-10347.

[30] a) T. Dahl, *Acta Chem. Scand.* **1988**, *42*, 1-7; b) J. H. Williams, *Acc. Chem. Res.* **1993**, *26*, 593-598; c) G. W. Coates, A. R. Dunn, L. M. Henling, D. A. Dougherty, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1997,** *36*, 248-251; *Angew. Chem.* **1997**, *109*, 290-293; d) J. C. Collings, K. P. Roscoe, R. L. Thomas, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, T. B. Marder, *New J. Chem*. **2001**, *25*, 1410-1417.

[31] a) C. Dai, P. Nguyen, T. B. Marder, A. J. Scott, W. Clegg, C. Viney, *Chem. Commun*.

1999, 2493-2494; b) J. C. Collings, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *Cryst. Eng.* **2002**, *5*, 37-46; c) J. C. Collings, K. P. Roscoe, E. G. Robins, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, S. J. Clark, T. B. Marder, *New J. Chem*. **2002**, *26*, 1740-1746; d) C. E. Smith, P. S. Smith, R. L. Thomas, E. G. Robins, J. C. Collings, C. Y. Dai, A. J. Scott, S. Borwick, A. S. Batsanov, S. W. Watt, S. J. Clark, C. Viney, J. A. K. Howard, W. Clegg, T. B. Marder, *J. Mater. Chem*. **2004**, *14*, 413-420; e) J. C. Collings, P. S. Smith, D. S. Yufit, A. S. Batsanov, J. A. K. Howard, T. B. Marder, *CrystEngComm*, **2004**, *6*, 25-28; f) S. W. Watt, C. Dai, A. J. Scott, J. M. Burke, R. L. Thomas, J. C. Collings, C. Viney, W. Clegg, T. B. Marder, *Angew. Chem. Int. Ed*. **2004**, *43*, 3061-3063; *Angew. Chem.* **2004**, *116*, 3123-3125; g) A. Friedrich, I. E. Collings, K. F. Dziubek, S. Fanetti, K. Radacki, J. Ruiz-Fuertes, J. Pellicer-Porres, M. Hanfland, D. Sieh, R. Bini, S. J. Clark, T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 18907-18923.

[32] M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120-126.

[33] a) J. W. Steed, *CrystEngComm* **2003**, *5*, 169-179; b) K. M. Anderson, A. E. Goeta, K. S. B. Hancock, J. W. Steed, *Chem. Commun.* **2006**, 2138-2140; c) G. R. Desiraju, *CrystEngComm.* **2007**, *9*, 91-92.

[34] C. P. Brock, L. L. Duncan, *Chem. Mater.* **1994**, *6*, 1307-1312.

[35] B. Moulton, M. J. Zaworotko, *Chem. Rev.* **2001**, *101*, 1629-1658.

[36] a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc*. **2002**, *124*, 390-391; b) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, J. F. A Hartwig, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem* **2019**, *11*, 5387-5396.

[37] G.-F. Du, F. Xing, C.-Z. Gu, B. Dai, L. He, *RSC Adv*. **2015**, *5*, 35513-35517.

[38] M.-T. Meng, K. Cheng, *J. Org. Chem.* **2018**, *83*, 3275-3284.

[39] S. Chang, J. Wang, L. Dong, D. Wang, B. Feng, Y. Shi, *RSC Adv*. **2017**, *7*, 51928-51934.

[40] P. Lei, Y. Ling, M. Szostak, *J. Org. Chem.* **2017**, *82*, 6638-6646.

[41] M.-Z. Li, C. Wang, H. Ge, *Org. Lett*. **2011**, *13*, 2062-2064.

[42] a) G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.* **2008**, *64*, 112-122; b) C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *J. Appl. Crystallogr*. **2011**, *44*, 1281-1284; c) G. M. Sheldrick, *Acta Crystallogr. Sect. C: Struct. Chem.* **2015**, *71*, 3-8; d) G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Adv.* **2015**, *71*, 3-8.

[43] B. Moulton, M. J. Zaworotko, *Chem. Rev.* **2001**, *101*, 1629-1658.

[44] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian 09, revision E.01; Gaussian, Inc.: Wallingford, CT, **2013**.

[45] A. D. Becke, *J. Chem. Phys*. **1993**, *98*, 5648-5652.

[46] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785-789.

[47] K. Fukui, *Acc. Chem. Res.* **2002**, *14*, 363-368.

[48] E. Canc ès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032-3041.

[49] M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett.* **1996**, *255*, 327-335.

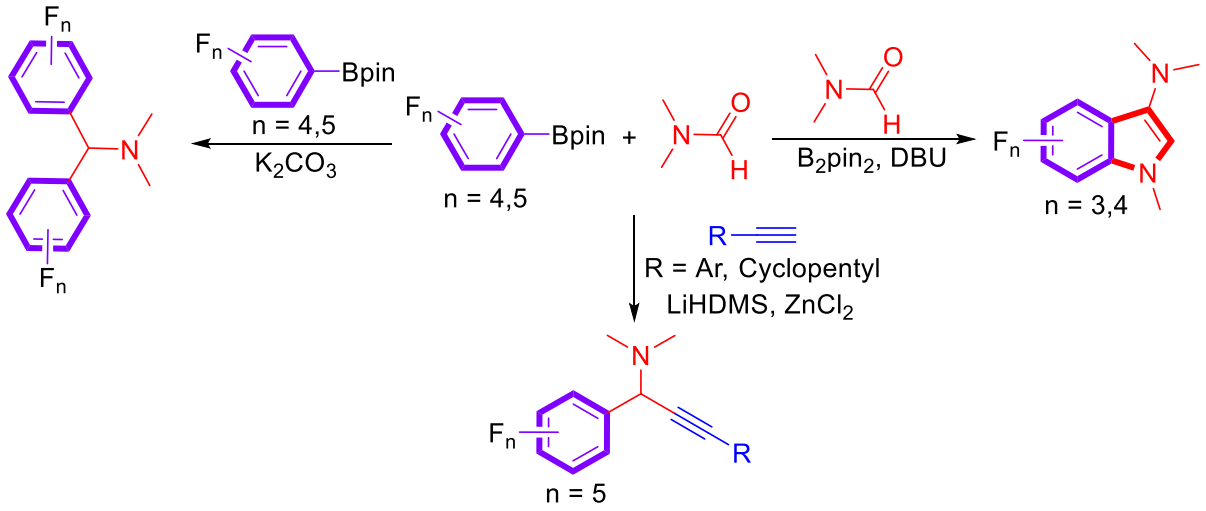
[50] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378-6396.

[51] Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157-167.

[52] C.Y. Legault, CYLView, Université de Sherbrooke, Canada, **2009**.

Chapter 4

Base-Controlled Reactions of Polyfluorophenylboronates with DMF



4. Base-Controlled Reactions of Polyfluorophenylboronates with DMF

4.1 Abstract

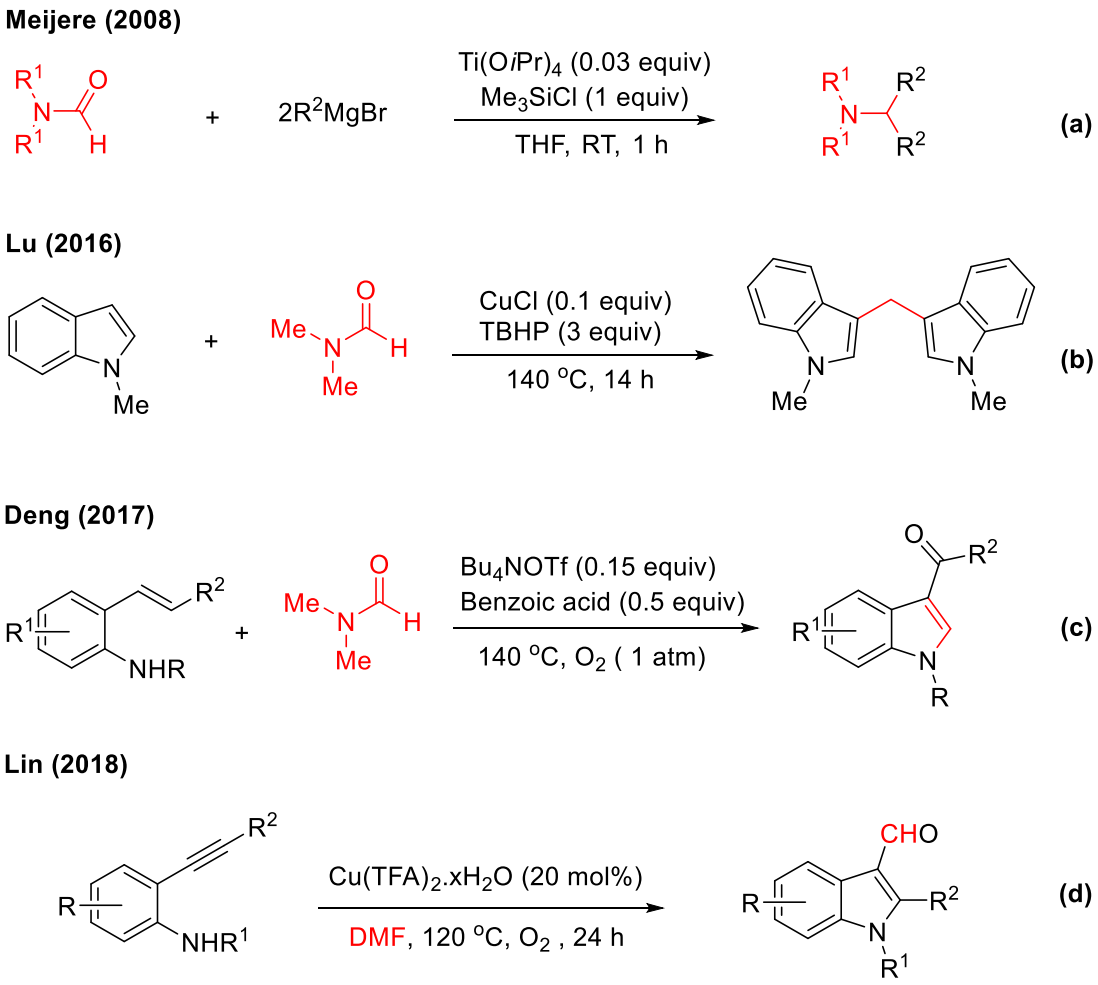
A novel protocol for the transition metal-free addition and annulation of polyfluoroarylboronates with DMF is reported, which provides 3-aminoindoles and tertiary amines. While exploring applications of this strategy in synthesis, propargylamines were generated in high yields.

4.2 Introduction

Indole heterocycles are present in numerous natural products, pharmaceuticals, and bioactive compounds. [1] Among numerous indole derivatives, 3-amino-indoles have many applications in medicinal chemistry as effective anticancer agents, compounds with analgesic properties, potent inhibitors of tubulin polymerization, and agents for the prevention of type II diabetes. [2] Due to their enormous importance, a variety of synthetic methodologies have been developed in recent years. For example, in 2010, Gevorgyan *et al*. [3] reported the copper-catalyzed three component coupling reaction *via* isomerization of 3-amino-indoline intermediates. Beller *et al*. [4] reported that these important compounds can be generated from a cascade cyclization reaction starting from arylhydrazines and propargylic amides. Miura *et al*.[5] used a copper catalyst system and Liu *et al*.[6] used a rhodium complex a precatalyst to obtain 3-amino-indole derivatives starting from *o*-alkynyl-anilines and electrophilic nitrogen sources. However, the reported examples all need transition metal complexes as a catalyst. The direct installation of an amino group into an indole skeleton offers another synthetic strategy for generating these compounds. In 2017, Wang *et al.* disclosed the direct introduction of a 3-amidation step using *N*-[(benzenesulfonyl)oxy]amides as an electrophilic nitrogen source.[7] Very recently, Moriyama *et al*. introduced the Cu-catalyzed oxidative 3-amination of indoles.[8] Although significant advances that have been achieved in this field, some inherent drawbacks of these methodologies are evident, such as the requirement for multisteps to prepare the starting materials and the use of a transition metal catalyst. In particular, transition metal-free reactions are highly desirable in the pharmaceutical industry, because even trace amounts of metal contamination in the final products are deleterious.[9] Propargyl amines are a versatile class of building blocks in organic synthesis and medicinal chemistry.[10] In

the last few decades, the synthesis of these important molecules has been extensively investigated and these efforts resulted in several highly efficient methodologies,[11] but the development of other efficient methods is still desirable.

Scheme 4-1. Previous reports on the use of DMF as a synthon.



Although typically having the role of solvents, DMF (*N,N*-dimethylformamide) has attracted considerable attention as a multi-purpose reagent in organic synthesis.[12] For example, DMF can be used as a versatile synthon to introduce C,[13] CH,[14] CH_3,[15] CHO,[16] CN,[17] CO,[18] NH_2,[19] and NMe_2[20] groups. In 2008, Meijere and co-workers disclosed the synthesis of tertiary alkylamines by the addition of Grignard reagents to *N,N*-dialkylformamides, a reaction mediated by $Ti(OiPr)_4$ and Me_3SiCl (Scheme 4-1a).[21] Utilization of DMF as a reagent to synthesize indole derivatives has also been widely studied. In 2016, Lu and co-workers reported a Cu-catalyzed protocol for the synthesis of

3,3'-diindolylmethane (DIM) and its derivatives, using DMF as a methyating agent (Scheme 4-1b).[22] Recently, Deng and co-workers reported a facile protocol for synthesizing 3-acylindoles, using DMF as a one-carbon synthon (Scheme 4-1c).[23] The cyclization of internal alkynes for the synthesis of C3-formylated indoles using DMF as the formyl precursor under Cu(II)-catalysis was reported by Lin and co-workers (Scheme 4-1d).[24] The construction of indole derivatives from DMF still relies mainly on transition metal catalysts, and the activation of DMF under transition-metal-free conditions would represent a useful advance.

Multi-fluorinated arenes exhibit markedly altered properties compared to the parent nonfluorinated molecules and are present in numerous, pharmaceuticals, agrochemicals, and organic materials.[25] Indeed, up to 30% of pharmaceuticals currently contain at least one fluorine atom.[26] Fluorinated arenes are not naturally occurring, and methods for the synthesis of fluorine-containing compounds remain limited.[27] A potential route to partially fluorinated arene compounds involves the selective and controlled C-F transformation of commercially-available polyfluoroarenes. The divergence of such transformations has been expanded with the aid of transition metal catalysis, including complexes based on Pd and Ni.[28] In 2006, Radius *et al*.[29a] described the Ni-catalyzed selective C-F activation of perfluorinated arenes for the synthesis of perfluorinated biaryls. Marder and Radius *et al*.[29b] expanded their work and disclosed NHC Ni-catalyzed Suzuki−Miyaura cross-coupling reactions between aryl boronate esters and perfluorobenzenes. Recently, Zhang *et al*.[30] demonstrated the Pd-catalyzed direct C−F bond arylation of polyfluoroarenes and Pd-catalyzed *ortho*-selective C-F hydrodefluorination of polyfluoroarenes. In 2011, Chatani *et al*.[31] developed the Ni-catalyzed Suzuki-Miyaura reaction of aryl fluorides while Ackermann *et al*.[32a] used a Ni complex and Xiong *et al*.[32b] used a Cu catalyst system to achieve C-F alkylation. Subsequently, Lu *et al*.[33a] and Huang *et al*.[33b] reported hydrogenolysis of aryl C−F bonds using rhodium and ruthenium precatalysts. Mao and Walsh *et al*.[34] then disclosed a domino reaction of 2-fluorotoluenes and nitriles to synthesize indoles, which facilitated intramolecular nucleophilic aromatic substitution reactions (S_NAr). Despite the advances that have been made in this field, further development of new complementary methods for the activation of inert C-F bonds without transition metals would be desirable.

We have been developing the C-F borylation of fluoroarenes using an NHC ligated Ni complex as a precatalyst for generating fluorinated arylboronic acid pinacol esters (Ar_F-Bpin) in good to excellent yields.[35a,b] We have also reported optimized conditions for the Suzuki-Miyaura cross-coupling reaction of Ar_F-Bpin with aryl iodides or bromides using a combination of CuI and 1,10-phenanthroline as a catalyst precursor to generate cross-coupling products in moderate to excellent yields.[35c] Furthermore, we reported the palladium-catalyzed homocoupling of fluorinated arylboronates,[35d] and the copper-catalyzed oxidative cross-coupling of electron-deficient polyfluorophenyl boronate esters with terminal alkynes.[35e] As a continuation of our studies on fluorine-containing organoboronates,[35f] herein we report base-controlled reactions of polyfluorophenylboronates with DMF.

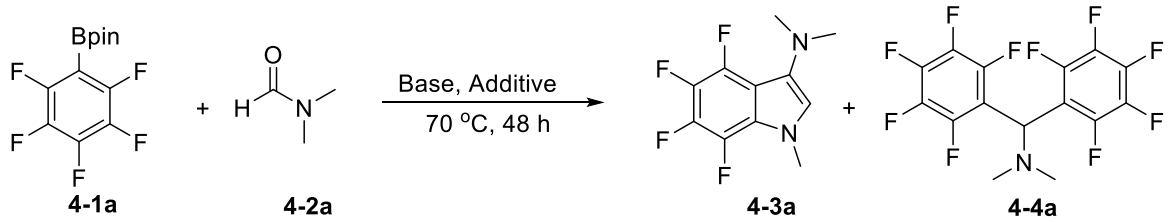
4.3 Results and Discussion

4.3.1 Optimization of Reaction Conditions

We began our research by selecting pentafluorophenyl-Bpin (**4-1a**) and DMF (**4-2a**) as model substrates. No reaction occurred when heating the mixture in the presence of KOMe as a base (Table 4-1, entry 1). However, 20% of the desired product **4-4a** was obtained when AcOK was employed as the base (Table 4-1, entry 2). Encouraged by this result, several bases were subsequently explored to enhance the yield of **4-4a** (Table 4-1, entries 3-5). These experiments revealed that the employment of K_2CO_3 as the base led to significantly increased yields of **4-4a** up to 92% (Table 4-1, entry 5). Interestingly, using B_2pin_2 as an additive gave rise to compound **4-3a** in 12% yield (Table 4-1, entry 6). Moreover, the ^{19}F NMR spectrum of **4-3a** clearly indicated that one fluorine atom was lost during the reaction. The structure of compound **4-3a** was unambiguously confirmed by single-crystal X-ray diffraction *vide infra*. Encouraged by this result, we briefly screened the use of bases to enhance the yield of compound **4-3a** (Table 4-1, entries 7-13). The experimental results revealed that the employment of DBU as the base significantly increased the yield of **4-3a** to 48% (Table 4-1, entry 13). Further experiments demonstrated that the reaction temperature had a significant impact on the reaction performance (Table 4-1, entry 14) as the target product was furnished in higher yields (83%) at 90 °C. In addition, reaction optimization also revealed poor performance when reactions were conducted under aerobic conditions (Table 4-1, entry 15). However, with

DBU as the base, no reaction took place when B_2pin_2 was absent (Table 4-1, entry 16), indicating that B_2pin_2 is an important additive for this annulation reaction. Different solvents were then evaluated, giving a similar yield when toluene and THF were employed (Table 4-1, entries 17-18).

Table 4-1. Optimization of the reaction conditions[a]



Entry	Base	Additive	Yield **4-3a**(%)[b]	Yield **4-4a**(%)[b]
1	$KOCH_3$	-	0	0
2	AcOK	-	0	20
3	^{t}BuONa	-	0	72
4	K_3PO_4	-	0	81
5	K_2CO_3	-	0	92
6	K_2CO_3	B_2pin_2	12	68
7	AcOK	B_2pin_2	22	8
8	^{t}BuONa	B_2pin_2	10	5
9	K_3PO_4	B_2pin_2	14	25
10	NEt_3	B_2pin_2	7	78
11	*i*PrNEt	B_2pin_2	5	83
12	DABCO	B_2pin_2	32	36
13	DBU	B_2pin_2	48	21
14[c]	**DBU**	**B_2pin_2**	**83**	**0**
15[d]	DBU	B_2pin_2	11	0
16	DBU	-	0	0
17[e]	DBU	B_2pin_2	81	0
18[f]	DBU	B_2pin_2	80	0

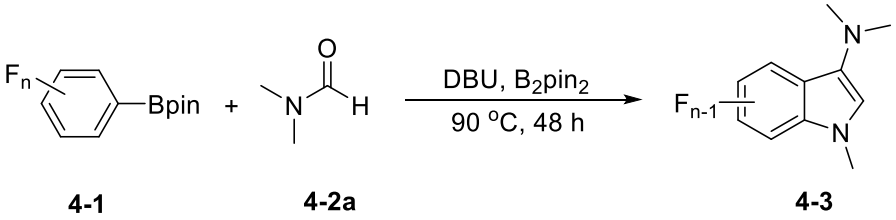
[a] Reaction conditions: **4-1a** (0.4 mmol), base (1.0 equiv), additive (0.5 equiv), **4-2a** (3 mL, anhydrous and degassed), 70 °C, 48 h, under argon. [b] The yields were determined by GC-MS of a diluted and filtered aliquot of the reaction mixture using *n*-dodecane as the internal standard (average of two runs). [c] 90 °C. [d] The reaction was performed in air. [e] Degassed and alumina-dried (solvent purification system) toluene (2 mL). [f] Degassed

and alumina-dried dried (Solvent Purification System) THF (2 mL). DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

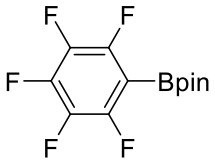
4.3.2 Investigation of Reaction Scope

After the optimal conditions (Table 4-1, entry 14) were established, we focused our attention on investigating the scope and limitations of the present annulation reaction (Scheme 4-2). We first examined a variety of fluorophenyl boronate esters derived from the structural motif of **4-1**. With the highly electron-withdrawing CF_3-substituent, excellent yields were observed (**4-3b**) under these conditions. When reactions were performed at 100 °C with a longer reaction time, trifluorophenylboronate ester **4-1c** smoothly underwent annulation to give the desired product **4-3c** in good yield 65%. A very low yield was observed when the 4-CH_3-tetrafluorophenyl boronate ester was used, which indicated that electron-donating groups on the aromatic ring have a negative effect on this reaction. Unfortunately, this protocol was found to be inefficient for 2,4,6-trifluorophenyl-Bpin and 2,6-difluorophenyl-Bpin.

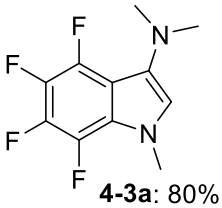
Scheme 4-2. Substrate scope of the annulation reaction.[a]



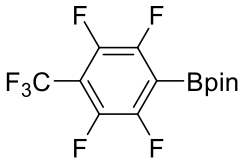
4-1 **4-2a** **4-3**



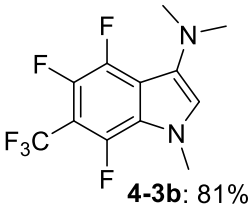
4-1a



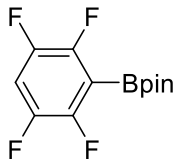
4-3a: 80%



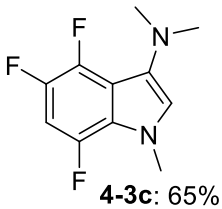
4-1b



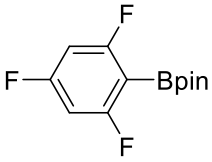
4-3b: 81%



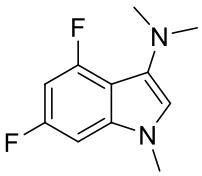
4-1c



4-3c: 65%[c]



4-1d



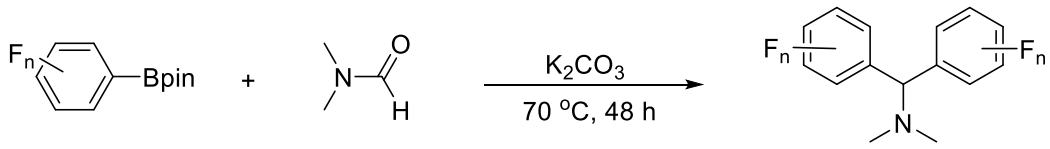
4-3d: 0%

[a] Conditions: **4-1a** (0.4 mmol), **4-2a** (3 mL, anhydrous and degassed), DBU (0.4 mmol), B_2pin_2 (0.2 mmol), 90 °C, 48 h, under argon. [b] Isolated yields. [c] 100 °C, 48 h.

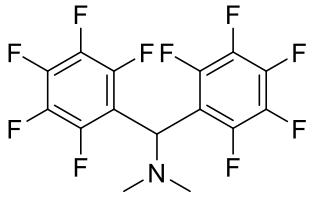
Encouraged by our early results in generating tertiary amines when reactions were carried out in the absence of B_2pin_2, we then focused on examining the reaction of other fluorophenylboronate esters with DMF (Scheme 4-3). After increasing the temperature, we found that a tetrafluorophenylboronate ester smoothly underwent a similar addition reaction to give the corresponding product **4-4b** in good yield. However, these reaction conditions were not suitable for the reactions of 2,5-difluorophenyl-Bpin and 2-fluorophenyl-Bpin with DMF. Surprisingly, reactions with these substrates resulted in the

formation of alcohols (**4-4c** and **4-4d**) when a strong base was used. Unfortunately, no reaction occurred when 4-fluorophenyl-Bpin and 4-cyanophenyl-Bpin were examined.

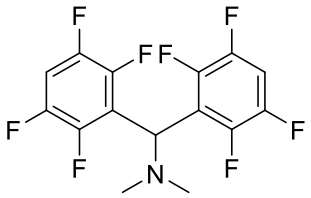
Scheme 4-3. Substrate scope of the addition reaction of fluorophenylBpin derivatives to DMF.[a]



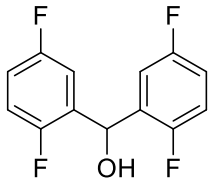
4-1, n = 1, 2, 4, 5 **4-2a** **4-4**



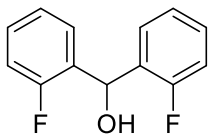
4-4a: 89%



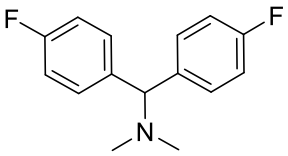
4-4b: 85%[c]



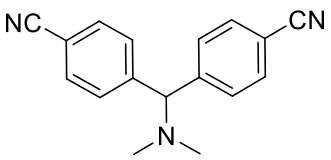
4-4c: 75%[d]



4-4d: 79%[d]



4-4e: ND

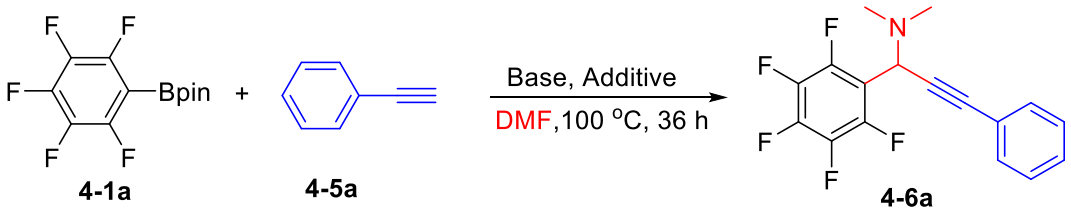


4-4f: ND

[a] Conditions: **4-1a** (0.4 mmol), **4-2a** (3 mL, anhydrous and degassed), K_2CO_3 (0.4 mmol), 70 °C, 36 h, under argon. [b] Isolated yields. [c] 100 °C, 48 h. [d] 100 °C, 48 h, $KOCH_3$ (0.4 mmol).

We then examined the three-component cross-coupling reaction of C_6F_5Bpin, phenyl acetylene and DMF, for the novel synthesis of propargylamines as shown in **Table 4-2**. Initially, the reaction was investigated in the presence of KOMe under an argon atmosphere in DMF to afford **4-6a** in 10% yield. Among the bases screened (Table 4-2, entries 1-7), LiHDMS was found to be optimal. Optimization of the Lewis acid additive showed a dramatic enhancement of the yield upon addition of 1 equiv of $ZnCl_2$ (Table 4-2, entry 8-10), whereas 0.5 equiv of $ZnCl_2$ provided a lower yield of **4-6a** (Table 4-2, entry 11). These experimental results indicate that $ZnCl_2$ play an important role in the reaction, either by C−H zincation of a terminal alkyne, or by Lewis acid activation of the DMF.[36]

Table 4-2. Optimization of the reaction conditions.[a]

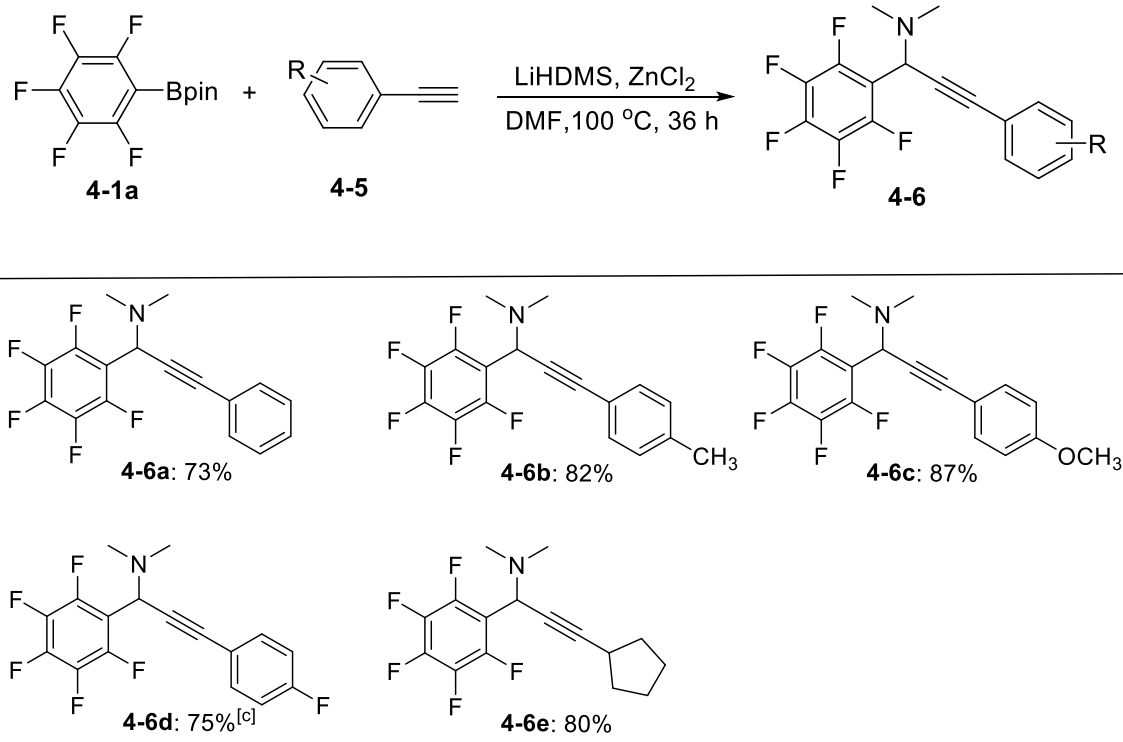


Entry	Base	Additive	Yield **4-6a**(%)[b]
1	$KOCH_3$	-	10
2	AcOK	-	5
3	^{t}BuONa	-	6
4	DBU	-	12
5	K_2CO_3	-	15
6	KHDMS	-	21
7	LiHDMS	-	25
8	LiHDMS	$MgCl_2$	31
9	LiHDMS	$AlCl_3$	18
10	LiHDMS	$ZnCl_2$	73
11[c]	LiHDMS	$ZnCl_2$	48

[a] Reaction conditions: **4-1a** (0.2 mmol), **4-5a** (0.2 mmol), base (1 equiv), additive (1 equiv), degassed and anhydrous DMF (3 mL), 100 °C, 36 h, under argon. [b] The yields were determined by GC-MS of a diluted and filtered aliquot of the reaction mixture using *n*-dodecane as the internal standard (average of two runs). [c] $ZnCl_2$ (0.5 equiv).

After the optimal conditions were established, we focused our attention on investigating the scope and limitations of this coupling reaction. As shown in Scheme 4-4, alkynes with different electron-donating substituents on the aromatic ring were first employed to react with pentafluorophenyl-Bpin under the standard conditions (**4-6b** and **4-6c**), providing the desired products in excellent yields. With an electron-withdrawing F-substituent, a moderate yield was observed (**4-6d**). Importantly, an aliphatic alkyne gave the desired products in good yield (**4-6e**). Unfortunately, phenyl-Bpin, 4-CH_3-phenyl-Bpin, 4-CN-phenyl-Bpin 2,4,6-trifluorophenyl-Bpin, 2,6-difluorophenyl-Bpin, and 3-fluorophenyl-Bpin all failed to provide any product, indicating the importance of the number of fluorine atom in the arylboronate ester.

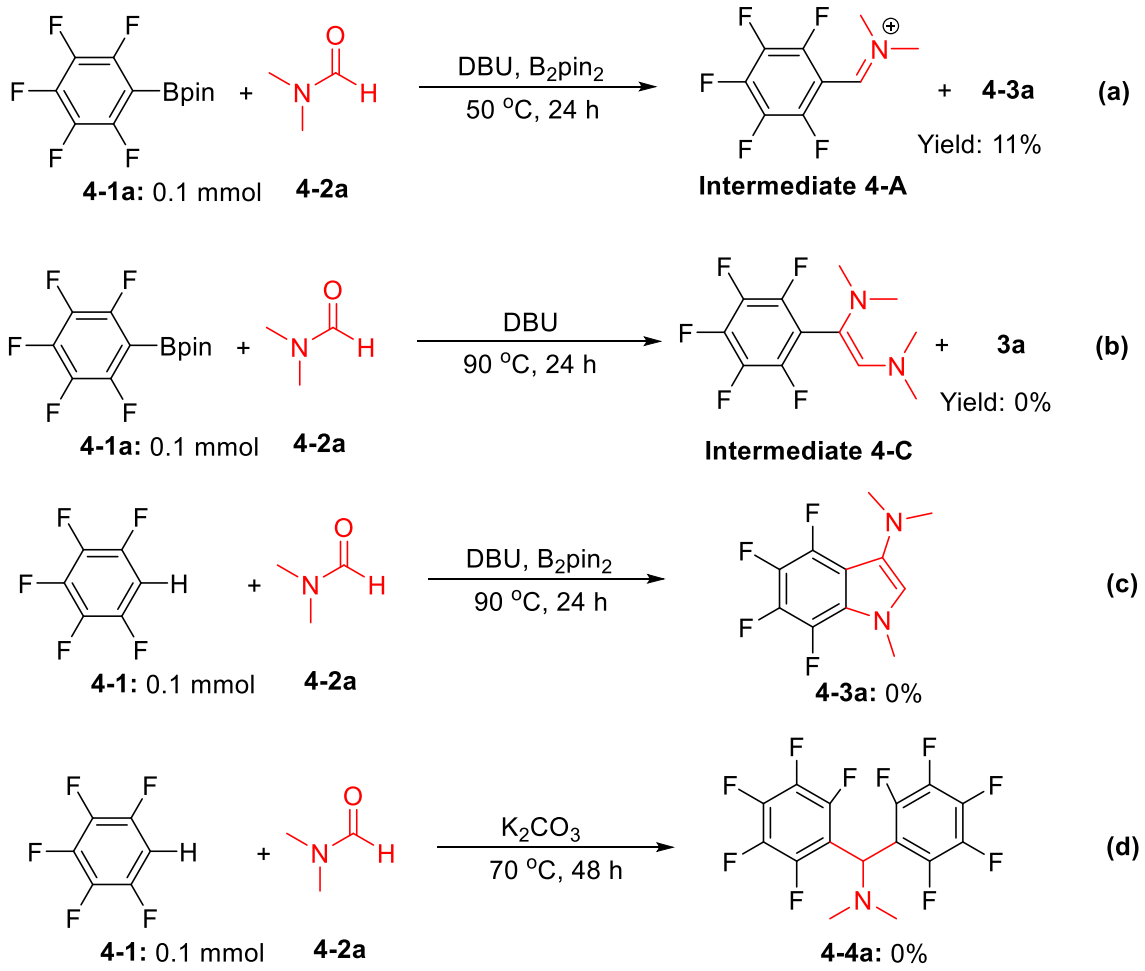
Scheme 4-4. Scope of the reaction with respect to the different terminal alkyne substrates **4-5**.[a]



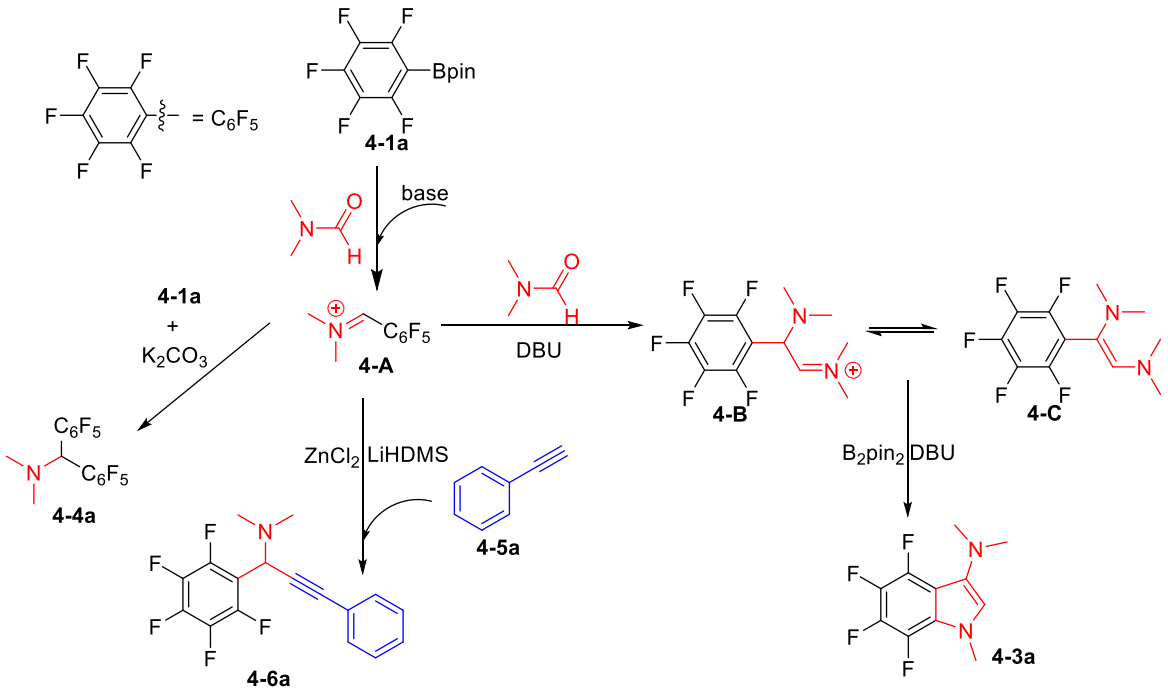
[a] Reaction conditions: **4-1a** (0.2 mmol), **4-5** (0.2 mmol), LiHDMS (1.0 equiv), $ZnCl_2$ (1 equiv), degassed and anhydrous DMF (3 mL), 100 °C, 36 h, under argon. [b] Isolated yields. [c] 80 °C.

4.4 Preliminary mechanistic studies

To gain further insight into the aforementioned reactions, several mechanistic studies were conducted. First, the reaction of **4-1a** and **4-2a** at 50 °C was examined, the yield of **4-3a** dropped dramatically and imminium intermediates **4-A** was detected by HRMS (Scheme 4-5a). Interestingly, the reaction is completely inhibited in the absence of B_2pin_2, and amine intermediate **4-C** was also detected by HRMS, indicating that B_2pin_2 plays a crucial role in the outcome of the reaction (Scheme 4-5b). (see section 4.7.6). If the reaction of **4-2a** with pentafluorobenzene **4-1** under standard conditions was attempted, **3a** and **4a** were not detected (Schemes 4-5c and 4-5d), indicating that the C-Bpin moiety is essential and deprotonation of the fluoroarene or nucleophilic attack at the fluoroarene by the base is not a plausible pathway.



Scheme 4-5. Preliminary mechanistic studies.



Scheme 4-6. Proposed mechanism of annulation and addition reaction of polyfluorophenylboronates with DMF.

Based on previous reports,[21,37] and the aforementioned observations, a plausible mechanism is depicted in Scheme 4-6. The first step would involve the addition of DMF to pentafluorophenyl-Bpin leading to the formation of an immonium intermediate **4-A** and $OBpin^-$. The immonium salt **4-A** would undergo addition of the second molecule of the Ar_F^- anion to generate compound **4-4a**. Attack of the deprotonated alkyne to immonium intermediate **4-A** would leads to propargylamine compound **4-6a**. When DBU was used as a base, coordination of the oxygen atom of DMF to the Bpin moiety would afford a *tert*-amine anion.[37f] The anion would subsequently undergo nucleophilic attack at the imminium intermediates **4-A** carbon atom to obtain reversible intermediates **4-B** and **4-C**. Finally, the desired product **4-3a** would be generated and $[B_2pin_2.F]^-$ also would be afforded.[37h-i]

4.5 Crystal and Molecular Structures of Products

The structures of **4-3a** and **4-4c** were unambiguously confirmed by single crystal X-ray diffraction studies (Figure 4-1). Compound **4-3a** crystallizes in the triclinic space group $P\bar{1}$, and there is one molecule in its asymmetric unit. Two molecules of **4-3a** stack in an *anti*-fashion with π···π stacking interactions between the fluorinated moiety and the indole moiety, parallel to the $\vec{a},\vec{c}$-plane (Figure 4-2). Such arene-fluoroarene interactions, are well known to form highly ordered π-stacks of alternating arene and perfluoroarene molecules in co-crystals of arenes and perfluoroarenes, and can be applied as a supramolecular synthon in crystal engineering.[38] Compound **4-4a** crystallizes in the monoclinic space group $P2_1/c$. The N atom adopts a distorted pyramidal geometry, as expected for a tertiary amine. Among the intermolecular interactions are C-F···C, C-H···π(C) and F···F interactions (Figure 4-3). No significant π-stacking interaction was found between the pentafluorophenyl rings. Compound **4-4c**, on the other hand, crystallizes in the trigonal space group $R\bar{3}$. The alcohol -OH group is involved in O-H···O intermolecular hydrogen bonding. Six molecules exist as hydrogen bonded hexamers forming 12 membered (O-H···O) hexagonal rings of graph set notation $\boldsymbol{R}_6^6(12)$,[39] which adopt chair conformation, as shown in Figure 4-4. This pattern of hydrogen bonding is

different from what we observed in a similar series of chiral secondary alcohols.[40]

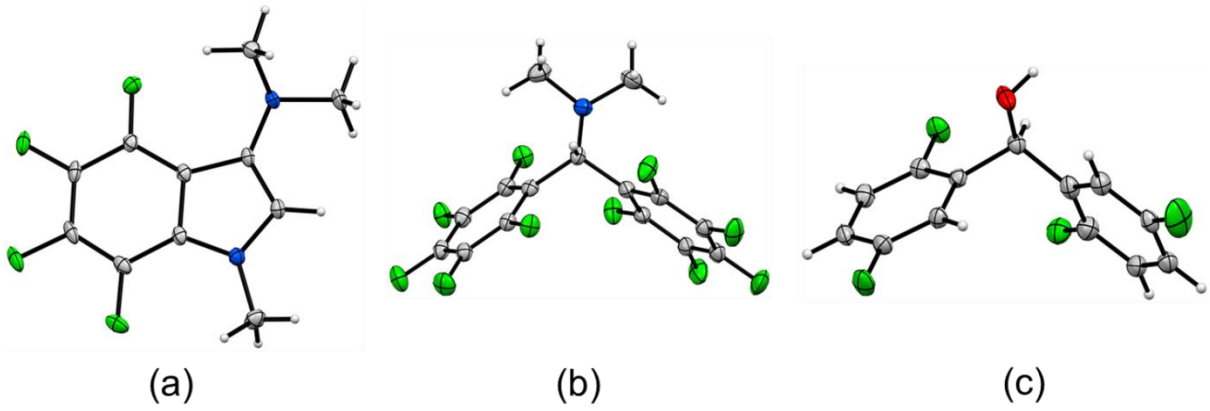


Figure 4-1. Molecular structures of compounds **4-3a**, **4-4a**, and **4-4c** in the solid state at 100 K. Atomic displacement ellipsoids are drawn with 50% probability. Color code: grey – carbon, red – oxygen, blue – nitrogen, green – fluorine, and white – hydrogen.

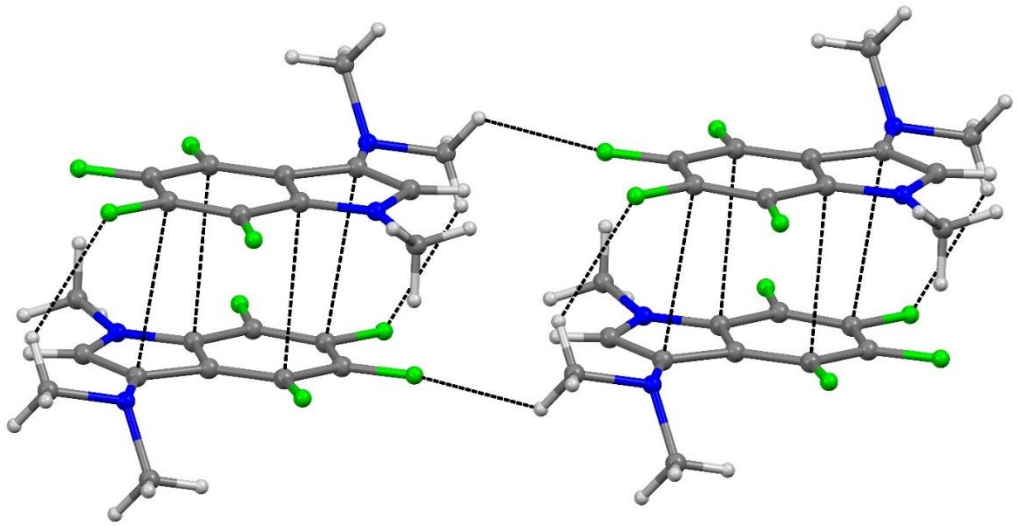


Figure 4-2: Molecules of **4-3a** stack in anti-fashion. The fluorinated moiety interacts with the indole moiety of another molecules, and there exist intermolecular weak C-H ··F interactions as well.

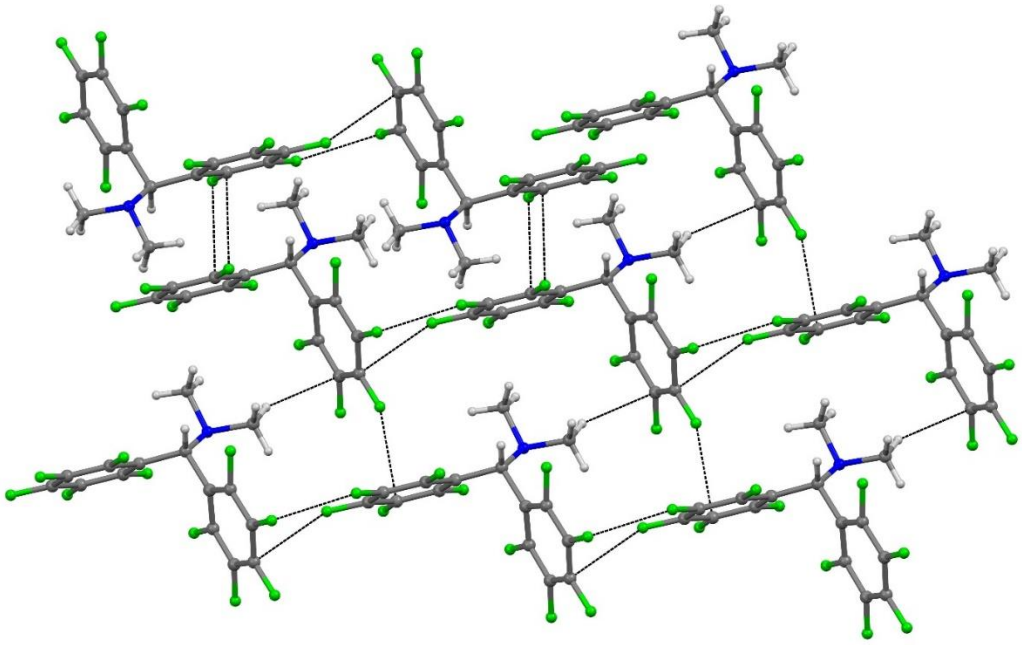


Figure 4-3: Various weak interactions present in the crystal structure of **4-4a**.

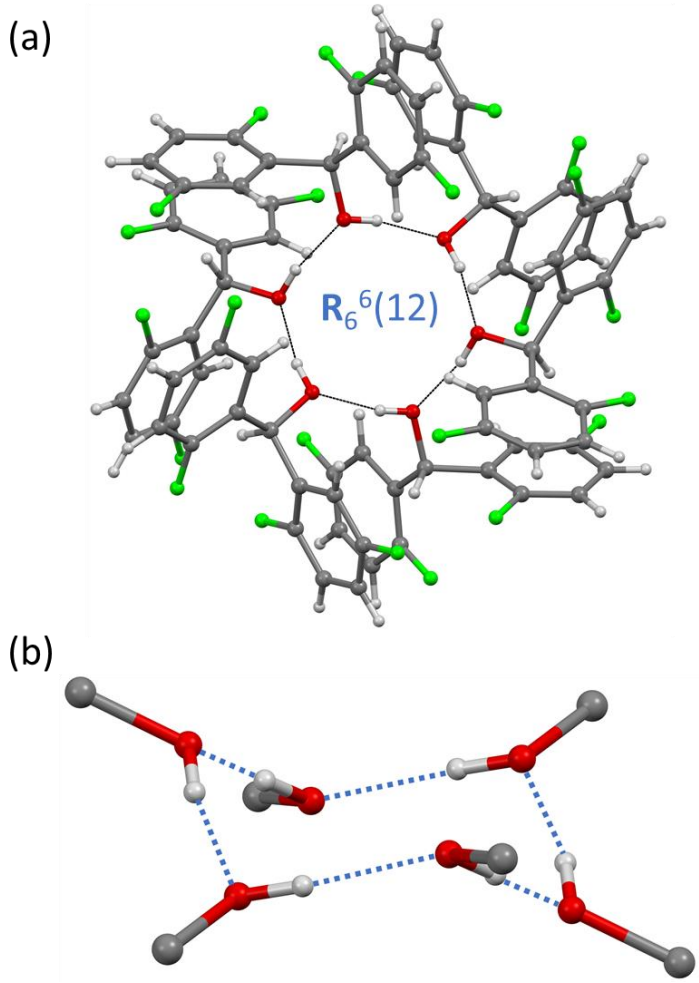


Figure 4-4: Pattern of hydrogen bonding in **4-4c** is shown. The -OH groups of six different moleculecules form 12 membered hexagonal ring via O-H ··O hydrogen bonding interaction (b); and the ring adopts a chair conformation (b).

4.6 Conclusions

We have demonstrated simple conditions for the addition and annulation of DMF with polyfluorophenylboronate compounds. This strategy has the advantages of a transition metal-free catalyst system and the use simple substrates to furnish 3-aminoindoles. The method also introduces the use of polyfluoropenyl-Bpin compounds instead of Grignard reagents for polyfluorophenylation of DMF to synthesize propargylamines. Further mechanistic studies and applications of the above protocols are underway in our laboratory and will be reported in due course.

4.7 Detailed Experiments and Characterization Data

4.7.1 General Information

All NMR spectra were recorded on a Bruker AC–500 spectrometer (500 MHz for ^{1}H NMR, 125 MHz for $^{13}C\{^{1}H\}$ NMR, and 470 MHz for ^{19}F NMR) with $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm and ^{1}H NMR spectra were referenced via residual proton resonances of $CDCl_3$ (7.26 ppm), $^{13}C\{^{1}H\}$ spectra were referenced to $CDCl_3$ (77.16 ppm) and ^{19}F spectra are referenced to external $CFCl_3$. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. GCMS analyses were performed on an Agilent Technologies GCMS system (GC 7890A, EI-MS 5975C). HRMS were measured on a Thermo Scientific Exactive Plus equipped with an Orbitrap. ESI measurements were conducted using a HESI source with an aux-gas temperature of 50 °C. Measurements were conducted using an APCI source with a corona needle; aux-gas temperature was 400 °C. Chemical yields referred to pure isolated product. Automated flash chromatography was performed on silica gel (Biotage SNAP cartridge KP-Sil), obtained from Biotage, using a Biotage® Isolera Four Flash system. Unless otherwise stated, all reagents were commercially purchased and used without further purification. The degassed and dry solvents were used. B_2pin_2 was kindly provided by AllyChem Co. Ltd. (Dalian, China).

4.7.2 Borylation of Polyfluoroarenes

Pentafluorophenyl-Bpin, 2,3,5,6-tetrafluorophenyl-Bpin, 2,3,4,6-tetrafluorophenyl-Bpin and 2,4,6-trifluorophenyl-Bpin used were prepared according to the literature

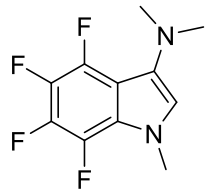
procedures.[41] In an argon filled glovebox, a solution of $[(COD)Ir(OMe)]_2$ (0.5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2 mol%), bispinacolatodiboron (B_2pin_2) (0.5 equiv.) and pentafluoroarene (1 equiv.) in hexane (dry and degassed) was stirred at room temperature in a sealed reaction vessel for 48h. The volatile materials were removed *in vacuo* to give the crude product, together with unreacted starting arene. The residue was then purified by flash chromatography on silica gel to provide the corresponding product (~90 %).

4.7.3 General Procedures

In an argon filled glovebox, a sealable reaction tube with a cap equipped with a magnetic stir bar was charged with polyfluorophenyl boronate esters **1** (0.4 mmol), B_2pin_2 (0.2 mmol) and DBU (0.4 mmol, degassed) in DMF (3 mL, anhydrous and degassed) at room temperature. The sealed reaction vessel was placed in an oil bath at 90 ℃ for 48 h. After the reaction was completed, it was cooled to room temperature. The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: *n*-pentane and EtOAc) to give the desired product.

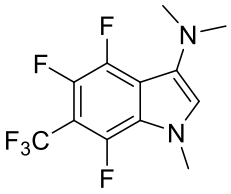
NOTE: 3-aminoindole derivatives (4-3) and tertiary amine derivatives (4-4) are not very stable under air. We stored them in an argon filled glovebox.

4.7.4 Characterization Data

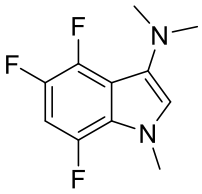


(**4-3a**): 78.7 mg, 80% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.50 (s, 1H), 3.85 (d, *J* = 2 Hz, 3H), 2.75 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 139.5 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.1 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 135.1 (dm, $^1J_{F\text{-}C}$ = 248 Hz), 134.0 (dm, $^1J_{F\text{-}C}$ = 233 Hz), 132.8, 120.8 (m), 118.6, 109.3 (m), 45.6 (d, $^4J_{F\text{-}C}$ = 4 Hz), 35.4 (d, $J_{F\text{-}C}$ = 6 Hz). $^{13}C\{^{19}F\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 139.4, 137.0, 135.1, 134.4, 132.8, 120.8 (d, *J* = 3 Hz), 118.6 (d, *J* = 183 Hz), 109.3 (d, *J* = 8 Hz), 45.6 (qd, *J* = 5 Hz, 129 Hz), 35.4 (qd, *J* = 3 Hz, 139 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -149.3 (t, *J*

= 21 Hz, 1F), -165.7 (t, *J* = 16 Hz, 1F), -166.2 (t, *J* = 19 Hz, 1F), -171.4 (td, *J* = 5 Hz, 24 Hz, 1F). HRMS (ESI): calcd. for $[C_{11}H_{10}F_4N_2]^+$: 246.0780, found: 246.0775.

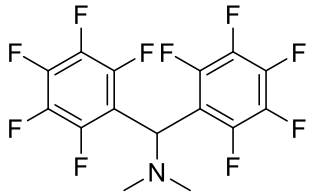


(**4-3b**): 95.9 mg, 81% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.66 (s, 1H), 3.91 (d, *J* = 3 Hz, 3H), 2.77 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 142.7 (dm, $^1J_{F\text{-}C}$ = 251 Hz), 139.8 (dm, $^1J_{F\text{-}C}$ = 249 Hz), 139.7 (dm, $^1J_{F\text{-}C}$ = 248 Hz), 132.9 (m), 124.6 (q, $^1J_{F\text{-}C}$ = 272 Hz), 121.7, 121.3 (t, $J_{F\text{-}C}$ = 11 Hz), 116.6 (m), 101.2 (m), 45.6 (d, $^4J_{F\text{-}C}$ = 4 Hz), 35.8 (d, $J_{F\text{-}C}$ = 8 Hz). $^{13}C\{^{19}F\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 142.8, 139.8, 139.7, 133.0, 122.4, 121.8 (dm, *J* = 147 Hz), 121.0, 116.6 (d, *J* = 9 Hz), 101.2, 45.6 (qd, *J* = 4 Hz, 138 Hz), 35.8 (qd, *J* = 3 Hz, 140 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -54.7 (dd, *J* = 19 Hz, 24Hz, 3F), -139.9 (t, *J* = 24 Hz, 1F), -149.6 (t, *J* = 23 Hz, 1F), -154.2 (td, *J* = 8 Hz, 24Hz, 1F). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ (ppm) = -54.7 (dd, *J* = 23 Hz, 24Hz, 3F), -139.9 (tt, *J* = 8 Hz, 41 Hz, 1F), -149.6 (t, *J* = 19 Hz, 1F), -154.2 (td, *J* = 8 Hz, 23Hz, 1F). HRMS (ESI): calcd. for $[C_{12}H_{10}F_6N_2]^+$ $[M+H]^+$: 297.0812, found: 297.0821.

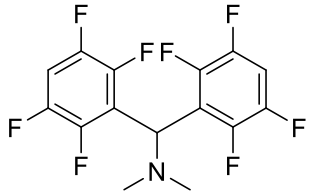


(**4-3c**): 59.2 mg, 65% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.75 (td, *J* = 5 Hz, 15 Hz, 1H), 6.53 (s, 1H), 3.85 (d, *J* = 2 Hz, 3H), 2.77 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.6 (dm, $^1J_{F\text{-}C}$ = 240 Hz), 142.1 (dm, $^1J_{F\text{-}C}$ = 241 Hz), 139.3 (dm, $^1J_{F\text{-}C}$ = 242 Hz), 132.8, 122.1 (m), 119.2, 114.9 (m), 98.3 (t, $^2J_{F\text{-}C}$ = 25 Hz), 45.7 (d, $^4J_{F\text{-}C}$ = 4 Hz), 35.4 (d, $J_{F\text{-}C}$ = 6 Hz). $^{13}C\{^{19}F\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 144.5 (d, *J* = 6 Hz), 142.1 (d, *J* = 8 Hz), 139.3 (d, *J* = 8 Hz), 132.5, 122.1, 119.2 (d, *J* = 186 Hz), 115.0, 98.3 (d, *J* = 165 Hz), 45.7 (q, *J* = 136 Hz), 35.4 (q, *J* = 139 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.2 (q, *J* = 10 Hz, 1F), -150.7 (dd, *J* = 9 Hz, 14 Hz, 1F),

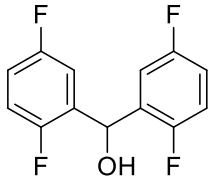
-152.1 (td, J = 5 Hz, 24 Hz, 1F). HRMS (ESI): calcd. for $[C_{11}H_{11}F_3N_2]^+$ $[M+H]^+$: 229.0946, found: 229.0947.



(**4-4a**): 143.8 mg, 92% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.14 (s, 1H), 2.33 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.2 (dm, $^1J_{F-C}$ = 250 Hz), 143.1 (dm, $^1J_{F-C}$ = 248 Hz), 137.7 (dm, $^1J_{F-C}$ = 250 Hz), 112.6, 57.9, 44.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.2 (d, J = 12 Hz, 4F), -153.3 (s, 2F), -161.1 (t, J = 14 Hz, 4F). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ (ppm) = -139.2 (d, J = 15 Hz, 4F), -153.5 (t, J = 23 Hz, 2F), -161.2 (q, J = 11 Hz, 4F). HRMS (ESI): calcd. for $[C_{15}H_7F_{10}N]$ $[M+H]^+$: 392.0488, found: 392.0492.

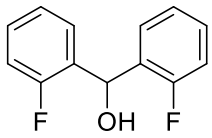


(**4-4b**): 120.7 mg, 85% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.09-7.02 (m, 2H), 5.25 (s, 1H), 2.38 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 146.1 (dm, $^1J_{F-C}$ = 250 Hz), 144.7 (dm, $^1J_{F-C}$ = 248 Hz), 117.9 (m), 106.1 (m), 58.5, 44.5. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -138.1 (s, 4F), -139.8 (s, 4F). HRMS (ESI): calcd. for $[C_{15}H_9F_8N]^+$ $[M+H]^+$: 356.0675, found: 356.0680.

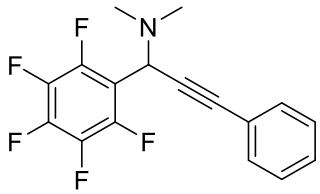


(**4-4c**): 77 mg, 75% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.17-7.13 (m, 2H), 7.03-6.95 (m, 4H), 6.33 (d, J = 4 Hz, 1H), 2.43 (d, J = 4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 158.8 (dd, $^1J_{F-C}$ = 250 Hz, J_{F-C} = 3 Hz), 155.7 (dd, $^1J_{F-C}$ = 249 Hz, J_{F-C} = 3 Hz), 130.6 (m), 116.7 (dm, $^2J_{F-C}$ = 22 Hz), 116.1 (dm, $^2J_{F-C}$ = 22 Hz), 114.6 (dm, $^2J_{F-C}$ = 25 Hz), 63.8 (m). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -117.7 – -

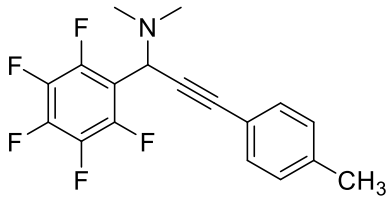
117.8 (m, 2F), -124.1 – -124.2 (m, 2F). HRMS (ESI): calcd. for $[C_{13}H_8F_4O]^+$ $[M\text{-}OH]^+$: 239.0472, found: 239.0478.



(**4-4d**): 70.0 mg, 79% yield, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.45 (td, *J* = 2 Hz, 8 Hz, 2H), 7.30-7.26 (m, 2H), 7.15 (td, *J* = 1 Hz, 8 Hz, 2H), 7.03 (td, *J* = 1 Hz, 10 Hz, 2H), 6.42 (s, 1H), 2.42 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 160.1 (d, $^1J_{F\text{-}C}$ = 248 Hz), 129.5 (m), 128.0 (m), 124.2 (t, $J_{F\text{-}C}$ = 2 Hz), 115.5 (dm, $^2J_{F\text{-}C}$ = 21 Hz), 64.6 (t, $^3J_{F\text{-}C}$ = 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -118.2 – -118.3 (m, 2F). HRMS (ESI): calcd. for $[C_{13}H_{10}F_2O]^+$ $[M\text{-}OH]^+$: 203.0665, found: 203.0667.

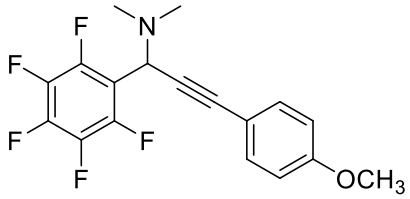


(**4-6a**): 50.7 mg, 78% yield, brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.47-7.46 (m, 2H), 7.34-7.32 (m, 3H), 5.06 (s, 1H), 2.40 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.3 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 141.0 (dm, $^1J_{F\text{-}C}$ = 250 Hz), 137.5 (dm, $^1J_{F\text{-}C}$ = 252 Hz), 131.8, 128.6, 128.3, 122.4, 111.8 (m), 86.0, 82.9, 52.0, 41.9. ^{13}C{^{19}F } NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.3 (d, *J* = 4 Hz), 140.9, 137.6, 131.8 (dt, *J* = 6 Hz, 164 Hz), 128.6 (dt, *J* = 8 Hz, 160 Hz), 128.3 (dd, *J* = 6 Hz, 160 Hz), 122.4 (d, *J* = 8 Hz), 111.8 (d, *J* = 7 Hz), 86.0 (d, *J* = 5 Hz), 82.9 (d, *J* = 11 Hz), 52.0 (dm, *J* = 135 Hz), 41.9 (qt, *J* = 5 Hz, 132 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.5 (d, *J* = 19 Hz, 2F), -154.1 (s, 1F), -161.7 (s, 2F). HRMS (ESI): calcd. for $[C_{17}H_{12}F_5N]^+$ $[M+H]^+$: 326.0955, found: 326.0963.

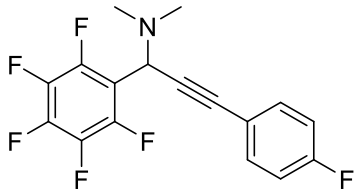


(**4-6b**): 55.6 mg, 82% yield, brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.35 (dd, *J* = 2 Hz, 6 Hz, 2H), 7.12 (dd, *J* = 1 Hz, 8 Hz, 2H), 5.05 (s, 1H), 3.03 (s, 3H), 2.39 (s, 6H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.3 (dm, $^{1}J_{F-C}$ = 250 Hz), 141.1 (dm, $^{1}J_{F-C}$ = 252 Hz), 138.7, 137.6 (dm, $^{1}J_{F-C}$ = 248 Hz), 131.7, 129.1, 119.4, 112.0 (m), 86.1, 82.2, 52.1, 41.9, 21.5. $^{13}C\{^{19}F\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.3 (d, *J* = 5 Hz), 140.9, 138.7 (m), 137.6, 131.7 (dd, *J* = 8 Hz, 160 Hz), 129.1 (dt, *J* = 6 Hz, 158 Hz), 119.4 (t, *J* = 8 Hz), 112.0 (d, *J* = 8 Hz), 86.0 (d, *J* = 5 Hz), 82.2 (d, *J* = 10 Hz), 52.1 (dm, *J* = 141 Hz), 41.9 (qt, *J* = 5 Hz, 134 Hz), 21.5 (qt, *J* = 4 Hz, 127 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.5 (d, *J* = 19 Hz, 2F), -154.3 (t, *J* = 19 Hz, 1F), -161.7 (t, *J* = 14 Hz, 2F). HRMS (ESI): calcd. for $[C_{18}H_{14}F_5N]^+$ $[M+H]^+$: 340.1114, found: 340.1119.

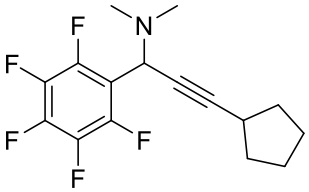


(**4-6c**): 61.7 mg, 87% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40 (dt, *J* = 2 Hz, 9 Hz, 2H), 6.84 (dt, *J* = 2 Hz, 9 Hz, 2H), 5.03 (s, 1H), 3.81 (s, 3H), 2.39 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 159.8, 145.3 (dm, $^{1}J_{F-C}$ = 250 Hz), 140.9 (dm, $^{1}J_{F-C}$ = 248 Hz), 137.5 (dm, $^{1}J_{F-C}$ = 250 Hz), 133.3, 114.5, 113.9, 112.1 (m), 85.9, 81.6, 55.3, 52.1, 41.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.5 (d, *J* = 19 Hz, 2F), -154.3 (t, *J* = 19 Hz, 1F), -161.8 (td, *J* = 9 Hz, 24 Hz, 2F). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ (ppm) = -139.6 (dm, *J* = 26 Hz, 2F), -154.3 (t, *J* = 23 Hz, 1F), -161.8 (q, *J* = 15 Hz, 2F). HRMS (ESI): calcd. for $[C_{18}H_{14}F_5NO]^+$ $[M+H]^+$: 356.1062, found: 356.1068.



(**4-6d**): 51.5 mg, 75% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.46-7.43 (m, 2H), 7.03-6.99 (m, 2H), 5.04 (s, 1H), 2.38 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 162.7 (d, $^{1}J_{F-C}$ = 250 Hz), 145.3 (dm, $^{1}J_{F-C}$ = 250 Hz), 141.1 (dm, $^{1}J_{F-C}$ = 248 Hz), 137.6 (dm, $^{1}J_{F-C}$ = 251 Hz), 133.7 (d, $^{3}J_{F-C}$ = 8 Hz), 118.4 (d, $^{4}J_{F-C}$ = 4 Hz), 115.6 (d, $^{2}J_{F-C}$ = 22 Hz), 111.7 (m), 84.9, 82.8, 51.9, 41.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -110.3 – -110.4 (m, 1F), -139.6 (d, *J* = 19 Hz, 2F), -154.0 (t, J_F = 21 Hz, 1F), -

161.6 (td, *J* = 9 Hz, 24 Hz, 2F) . HRMS (ESI): calcd. for $[C_{17}H_{11}F_6N]^+$ $[M+H]^+$: 344.0864, found: 344.0868.



(**4-6e**): (**6e**): 50.7 mg, 80% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.81 (s, 1H), 2.70-2.64 (m, 1H), 2.30 (s, 6H), 1.93-1.88 (m, 2H), 1.75-1.69 (m, 2H), 1.67-1.54 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.2 (dm, $^1J_{F-C}$ = 250 Hz), 140.7 (dm, $^1J_{F-C}$ = 250 Hz), 137.5 (dm, $^1J_{F-C}$ = 248 Hz), 112.4 (m), 90.9, 73.2, 51.6, 41.8, 33.7 (d, *J* = 7 Hz), 30.1, 24.9. $^{13}C\{^{19}F\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.3, 140.7 (d, *J* = 9 Hz), 137.5 (d, *J* = 18 Hz), 112.3 (d, *J* = 8 Hz), 91.0 (m), 73.2 (dd, *J* = 4 Hz, 10 Hz), 51.6 (dt, *J* = 6 Hz, 15 Hz), 41.8 (qt, *J* = 5 Hz, 134 Hz), 33.7 (t, *J* = 135 Hz), 30.1 (t, *J* = 123 Hz), 24.9 (t, *J* = 128 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ (ppm) = -139.6 (d, *J* = 19 Hz, 2F), -154.8 (t, *J* = 24 Hz, 1F), -162.1 (td, *J* = 7 Hz, 21 Hz, 2F). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ (ppm) = -139.7 (dm, *J* = 23 Hz, 2F), -154.8 (t, *J* = 23 Hz, 1F), -162.1 (q, *J* = 15 Hz, 2F). HRMS (ESI): calcd. for $[C_{16}H_{16}F_5N]^+$ $[M+H]^+$: 318.1268, found: 318.1276.

4.7.5 Single Crystal X-Ray Diffraction

Single crystals, suitable for X-ray diffraction, were selected, coated in fomblin oil, and mounted on microloop sample holders. Diffraction data were collected on Bruker X8 Apex II 4-circle diffractometers with CCD area detectors using Mo-Kα radiation monochromated by graphite or multi-layer focusing mirrors (**4-3a** and **4-4a**), and also with RIGAKU OXFORD DIFFRACTION XTALAB SYNERGY diffractometer with a semiconductor HPA-detector (HyPix-6000) and multi-layer mirror monochromated Cu-K_α radiation (**4-4c**). The crystals were cooled using an Oxford Cryostream low-temperature device. Diffraction data were collected at 100 K. The images were processed and corrected for Lorentz-polarization effects and absorption effects by employing the Bruker software packages or with CrysAlis^{Pro} software. The structure was solved using the intrinsic phasing method (SHELXT)[42] and expanded using Fourier techniques. All the non-hydrogen atoms were refined anisotropically with hydrogen atoms 'riding' in idealized positions, by full-matrix least squares against F^2 on all data, using SHELXL[43] software

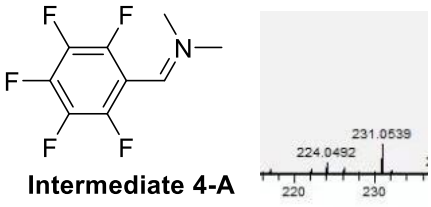
and the SHELXLE[44] graphical user interface. Diamond (Brandenburg, K. Diamond (version 4.4.0) and Mercury 4.0 (CCDC, UK) software were used for graphical representation. Crystal data and experimental details are listed in Table S1; full structural information has been deposited with the Cambridge Crystallographic Data Centre. CCDC-2084496 (**4-3a**), 2084497 (**4-4a**), and 2084498 (**4-4c**). While one of the difluorophenyl groups was found to be disordered in **4-4c**, the whole molecule of **4-4a** was found to be disordered in 75:25 ratio.

Table S1. Single-crystal X-ray diffraction data and structure refinements of 4-3a, 4-4a and 4-4c.

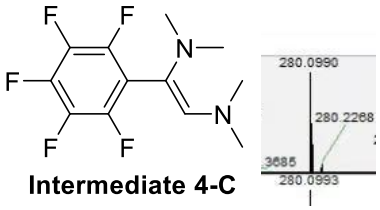
Compounds	**4-3a**	**4-4a**	**4-4c**
CCDC number	2084496	2084497	2084498
Empirical formula	$C_{11}H_{10}F_4N_2$	$C_{15}H_7F_{10}N$	$C_{13}H_8F_4O$
Formula weight (g mol^{-1})	246.21	391.22	256.19
Temperature (K)	100(2)	100(2)	100(2)
Radiation, λ (Å)	Mo-Kα 0.71073	Mo-Kα 0.71073	Cu-Kα 1.54184
Crystal colour, habit	Orange, block	Colourless, block	Colourless, block
Crystal size (mm^3)	0.462×0.37×0.238	0.28×0.80×0.97	0.13×0.21×0.23
Crystal system	Triclinic	Monoclinic	Trigonal
Space group	$P\ \bar{1}$	$P2_1/c$	$R\bar{3}$
Unit cell dimensions			
a (Å)	7.786(5)	9.891(4)	23.7773(2)
b (Å)	9.013(3)	21.203(9)	23.7773(2)
c (Å)	9.027(3)	7.406(4)	10.50543(12)
α (°)	93.99(2)	90	90
β (°)	112.842(16)	111.141(13)	90
γ (°)	113.666(14)	90	120
Volume (Å^3)	515.3(4)	1448.7(11)	5143.62(11)
Z	2	4	18
Calc. density (Mg m^{-3})	1.587	1.794	1.489
μ (mm^{-1})	0.147	0.196	1.214
F(000)	252	776	2340
θ range (°)	2.541 - 26.371	1.921 - 28.698	3.718 - 74.495
Reflections collected	13582	23000	11739
Independent reflections	2114	3682	2337
Minimum/maximum transmission	0.5197/0.7244	0.6728/0.7461	
Parameters / restraints	157 / 0	451 / 408	213 / 414
Goof on F^2	1.082	1.154	1.037
R_1 [$I>2\sigma(I)$]	0.0611	0.0554	0.0378

wR^2 (all data)	0.1693	0.2031	0.1019
Maximum/minimum residual electron density (e ·Å^{-3})	0.506 / –0.488	0.337 / –0.265	0.312 / –0.468

4.7.6 HRMS data of intermediate 4-A and 4-C



Intermediate 4-A



Intermediate 4-C

Chemical Formula: C9H7F5N

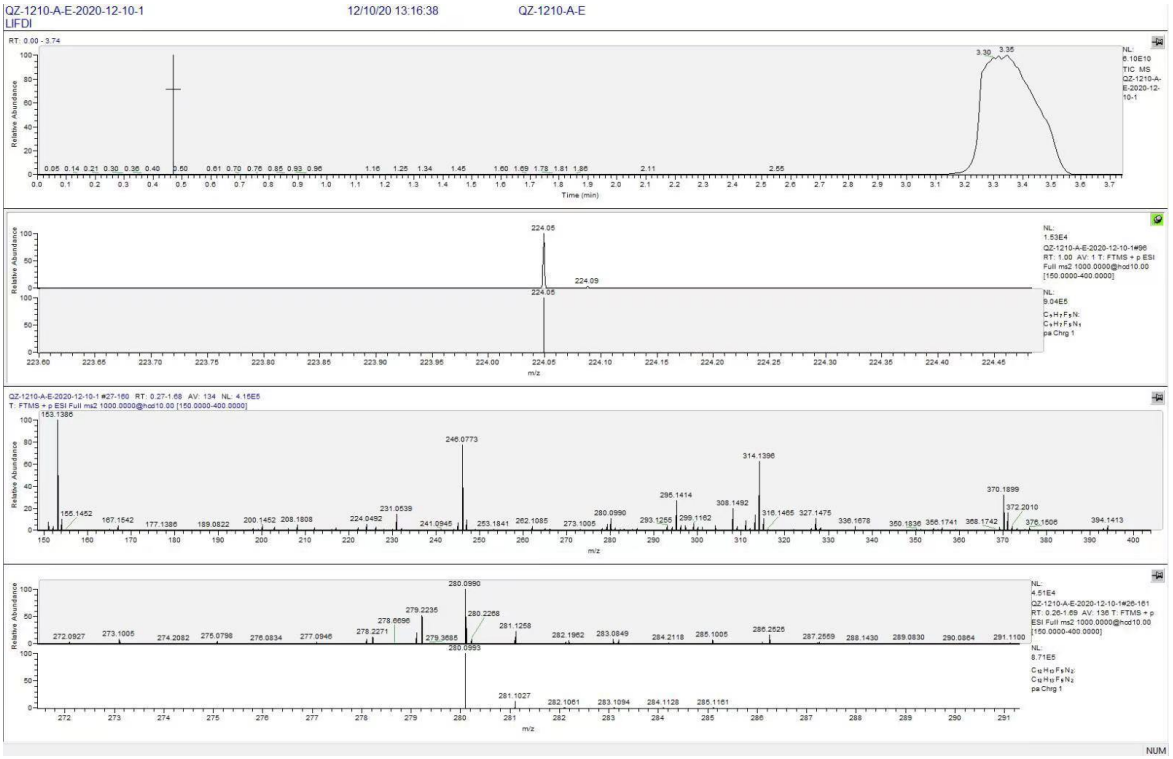
Exact Mass: 224.0499

Found: 224.0492

Chemical Formula: C12H13F5N2

Exact Mass: 280.0999

Found: 280.0990



4.8 References

[1] a) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489-4497; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195-7210; c) N. Kaushik, P. Attri, N. Kumar, C. Kim, A. Verma, E. Choi, *Molecules* **2013**, *18*, 6620-6662; d) J. Haynes-Smith, I. Diaz, K. L. Billingsley, *Org. Lett*. **2016**, *18*, 2008-2011; e) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875-2911; f) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644; *Angew. Chem.* **2009**, *121*, 9786-9824; g) J. Ni, Y. Jiang, Z. An, R. Yan, *Org. Lett*. **2018**, *20*, 1534-1537; h) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045-1075; i) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29-41; j) G. Bartoli, B. Giorgio, D. Renato, *Chem. Soc. Rev.* **2010**, *39*, 4449-4465; k) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873-2920; l) G. R. Humphrey, T. K. Jeffrey, *Chem. Rev*. **2006**, *106*, 2875-2911.

[2] a) R. H. Bahekar, M. R. Jain, A. Goel, D. N. Patel, V. M. Prajapati, A. A. Gupta, P. A. Jadav, P. R. Patel, *Bioorg. Med. Chem*. **2007**, *15*, 3248-3265; b) R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, N. Zonta, J. Balzarini, A. Brancale, H.-P. Hsieh, E. Hamel, *J. Med. Chem.* **2008**, *51*, 1464-1468; c) A. Kumar, S. Sharma, Archana, K. Bajaj, S. Sharma, H. Panwar, T. Singh, V. K. Srivastava, *Bioorg. Med. Chem*. **2003**, *11*, 5293-5299; d) E. Arzel, P. Rocca, P. Grellier, M. Labaeïd, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard, G. Quéguiner, *J. Med. Chem.* **2001**, *44*, 949-960.

[3] D. Chernyak, N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal*. **2010**, *352*, 961-966.

[4] a) A. Pews-Davtyan, A. Tillack, A. C. Schmole, S. Ortinau, M. J. Frech, A. Rolfs, M. A. Beller, *Org. Biomol. Chem.* **2010**, *8*, 1149-1153; b) A. Pews-Davtyan, M. Beller, *Org. Biomol. Chem.* **2011**, *9*, 6331-6334.

[5] N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem*. **2012**, *77*, 617-625.

[6] Z. Y. Hu, X. F. Tong, G. X. Liu, *Org. Lett.* **2016**, *18*, 2058-2061.

[7] G. X. Jr. Ortiz, B. N. Hemric, Q. Wang, *Org. Lett*. **2017**, *19*, 1314-1317.

[8] L. Watanabe, K. Moriyama, *Molecules* **2019**, *24*, 1147-1159.

[9] a) D. Nair, J. T. Scarpello, L. White, L. M. Freitas dos Santos, I. F. J. Vankelecom, A. G. Livingston, *Tetrahedron Lett*. **2001**, *42*, 8219-8222; b) C. Garrett, K. Prasad, *Adv. Synth. Catal*. **2004**, *346*, 889-900.

[10] a) K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev*. **2017**, *117*, 14091-

14200; b) S. Arshadi, E. Vessally, L. Edjlali, R. Hosseinzadeh-Khanmiri, R. Ghorbani-Kalhor, *J. Org. Chem.* **2017**, *13*, 625-638.

[11] a) S. Diethelm, E. M. Carreira, *J. Am. Chem. Soc*. **2015**, *137*, 6084-6096; b) W. Lin, S. M. Ma, *Org. Chem. Front.* **2014**, *1*, 338-346; c) Z.-H. Chen, Y.-Q. Zhang, Z.-M. Chen, Y.-Q. Tu, F.-M. Zhang, *Chem. Commun.* **2011**, *47*, 1836-1838; d) B. Jiang, Y.-G. Si, *Angew. Chem. Int. Ed.* **2003**, *43*, 216-218; *Angew. Chem.* **2003**, *116*, 218-220; e) C. Fischer, E. M. Carreira, *Org. Lett.* **2001**, *3*, 4319-4321; f) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268-269; g) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473-4476; h) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, *Org. Lett.* **2004**, *6*, 1001-1003; i) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*,1529-1532; j) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638-5639; k) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed*. **2003**, *42*, 5763-5766; *Angew. Chem.* **2003**, *115*, 5941-5944; l) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org.Lett*. **2006**, *8*, 2437-2440; m) W. Fan, S.-M. Ma, *Chem. Commun*. **2013**, *49*, 10175-10177; n) W. Lin, T. Cao, W. Fan, Y. Han, J. Kuang, H. Luo, B. Miao, X. Tang, Q. Yu, W. Yuan, J. Zhang, C. Zhu, S. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 277-281; *Angew*. *Chem*. **2014**, *126*, 281-285; o) C. Zhao, D. Seidel, *J. Am. Chem. Soc*. **2015**, *137*, 4650-4653; p) J. Li, M. Rudolph, F. Rominger, J. Xie, A. S. K. Hashmi, *Adv. Synth. Catal*. **2016**, *358*, 207-211.

[12] a) S. Ding, N. Jiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 9226-9237; *Angew. Chem*. **2012**, *124*, 9360; b) J. Muzart, *Tetrahedron* **2009**, *65*, 8313-8323; c) J. L. Bras, J. Muzart, *Molecules* **2018**, *23*, 1939-1969; d) M. M. Heravi, M. Ghavidel, L. Mohammadkhani, *RSC Adv*. **2018**, *8*, 27832-27862.

[13] a) M.-N. Zhao, R.-R. Hui, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Org. Lett*. **2014**, *16*, 3082-3085; b) Y. Weng, H. Zhou, C. Sun, Y. Xie, W. Su, *J. Org. Chem*. **2017**, *82*, 9047-9053; c) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu, Q. Zhang, *Chem. Commun*. **2013**, *49*, 6439-6441; d) X. Xu, M. Zhang, H. Jiang, J. Zheng, Y. Li, *Org. Lett*. **2014**, *16*, 3540-3543; e) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc*. **2015**, *137*, 4924-4927; f) D. N. Rao, S. Rasheed, P. Das, *Org. Lett*. **2016**, *18*, 3142-3145; g) W. Guo, J. Liao, D. Liu, J. Li, F. Ji, W. Wu, H. Jiang, *Angew. Chem. Int. Ed*. **2017**, *56*, 1289-1293; *Angew. Chem*. **2017**, *129*, 1309-1313.

[14] D. Zhao, T. Wang, J.-X. Li, *Chem. Commun*. **2014**, *50*, 6471-6474.

[15] H. M. Xia, F. L. Zhang, T. Ye, Y. F. Wang, *Angew. Chem. Int. Ed*. **2018**, *57*,11770-11775; *Angew. Chem.* **2018**, *130*, 11944-11949.

[16] Z. Tan, Z. Li, Y. Ma, J. Qin, C. Yu, *Eur. J. Org. Chem*. **2019**, 4538-4545.

[17] S. Ding, N. Jiao, *J. Am. Chem. Soc*. **2011**, *133*, 12374-12377.

[18] Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem*. **2002**, *67*, 6232–6235.

[19] A. Kodimuthali, A. Mungara, P. L. Prasunamba, M. Pal, *J. Braz. Chem. Soc*. **2010**, *21*, 1439-1445.

[20] a) W. Liu, C. Chen, H. Liu, *Beilstein J. Org. Chem*. **2015**, *11*,1721-1726; b) D. Xie, W. He, J. Xiao, Y. Wu, Y. Guo, Q. Liu, C. Guo, *RSC Adv*. **2019**, *9*, 7203-7209.

[21] O. Tomashenko, V. Sokolov, A. Tomashevskiy, H. Buchholz, U. Welz-Biermann, V. Chaplinski, A. Meijere, *Eur. J. Org. Chem*. **2008**, 5107-5111.

[22] F. Pu, Y. Li, Y. Song, J. Xiao, Z.-W. Liu, C. Wang, Z. Liu, J. Chen, J. Lu, *Adv. Synth. Catal*. **2016**, *358*, 539-542.

[23] J.-B. Wang, Y.-L. Li, J. Deng, *Adv. Synth. Catal*. **2017**, *359*, 3460-3467.

[24] B. Ganesan, G. C. Senadi, B. C. Guo, M. Y. Hung, W. Y. Lin, *RSC Adv*. **2018**, *8*, 40968-40973.

[25] a) J. R. Nitschke, T. D. Tilley, *J. Am. Chem. Soc*. **2001**, *123*, 10183-10190; b) P. Zacharias, M. C. Gather, M. Rojahn, O. Nuyken, K. Meerholz, *Angew. Chem. Int. Ed*. **2007**, *46*, 4388-4392; *Angew. Chem*. **2007**, *119*, 4467-4471; c) F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.* **2007**, 1003-1022; d) Y.-Y. Lai, Y.-J. Cheng, C.-S. Hsu, *Energy Environ. Sci*. **2014**, *7*, 1866-1883; e) M. de Candia, F. Liantonio, A. Carotti, R. De Cristofaro, C. Altomare, *J. Med. Chem.* **2009**, *52*, 1018-1028; f) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem*. **2015**, *58*, 8315-8359; g) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev*. **2011**, *40*, 3496-3508; h) M. Hird, *Chem. Soc. Rev*. **2007**, *36*, 2070-2095; i) B. Wiegmann, P. G. Jones, G. Wagenblast, C. Lennartz, I. Münster, S. Metz, W. Kowalsky, H.-H. Johannes, *Organometallics* **2012**, *31*, 5223-5226; j) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev*. **2016**, *116*, 422-518; k) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330; l) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; m) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev*. **2016**, *116*, 719-766.

[26] a) J. Wang, M. Sanchez-Rosello, J. Luis Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*. **2014**, *114*, 2432-2506; b) V. V. Grushin, *Acc. Chem. Res*. **2010**, *43*, 160-171.

[27] a) O. Eisenstein, J. Milani, R. N. Perutz, *Chem. Rev.* **2017**, *117*, 8710-8753; b) C. Liu,

B. Zhang, *Chem. Rec*. **2016**, *16*, 667-687; c) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev*. **2015**, *115*, 931-972; d) E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res*. **2011**, *44*, 333-348; e) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169; f) T. Furuya, J. E. M. N. Klein, T. Ritter, *Synthesis* **2010**, *2010*, 1804-1821; g) P. Kirsch, *Modern Fluoroorganic Chemistry*: *Synthesis*, *Reactivity*, *Applications*. Wiley-VCH, Weinheim, **2004**.

[28] Selected reviews on the synthesis of fluorinated molecules via metal-mediated or -catalyzed C-F cleavage: a) H. Amii, K. Uneyama, *Chem. Rev*. **2009**, *109*, 2119-2183; b) M. F. Kuehnel, D. Lentz, T. Braun, *Angew. Chem. Int. Ed*. **2013**, *52*, 3328-3348; *Angew. Chem*. **2013**, *125*, 3412-3433; c) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, *J. Fluorine Chem*. **2015**, *179*, 14-22; d) W. Chen, C. Bakewell, M. R. Crimmin, *Synthesis* **2017**, *49*, 810-821.

[29] a) T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc*. **2006**, *128*, 15964-15965; b) J. Zhou, J. H. J. Berthel, M. W. Kuntze-Fechner, A. Friedrich, T. B. Marder, U. Radius, *J. Org. Chem*. **2016**, *81*, 5789-5794.

[30] a) Z.-J. Luo, H.-Y. Zhao, X. Zhang, *Org. Lett*. **2018**, *20*, 2543-2546; b) Z. Chen, C.-Y. He, Z. Yin, L. Chen, Y. He, X. Zhang, *Angew. Chem. Int. Ed*. **2013**, *52*, 5813-5817; *Angew. Chem*. **2013**, *125*, 5925-5929.

[31] M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 19505-19511.

[32] a) V. Müller, D. Ghorai, L. Capdevila, A. M. Messinis, X. Ribas, L. Ackermann, *Org. Lett*. **2020**, *22*, 7034-7040; b) X. Li, B. Fu, Q. Zhang, X. Yuan, Q. Zhang, T. Xiong, *Angew. Chem. Int. Ed*. **2020**, *59*, 23056-23060; *Angew. Chem*. **2020**, *132*, 23256-23260.

[33] a) J. T. Moore, C. C. Lu, *J. Am. Chem. Soc.* **2020**, *142*, *27*, 11641–11646; b) H. Fang, Q. He, G. Liu, Z. Huang, *Org. Lett.* **2020**, *22*, 9298–9302.

[34] J. Mao, Z. Wang, X. Xu, G. Liu, R. Jiang, H. Guan, Z. Zheng, P. J. Walsh, *Angew. Chem. Int. Ed*. **2019**, *58*, 11033–11038; *Angew. Chem*. **2019**, *131*, 11149-11154.

[35] a) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc*. **2016**, *138*, 5250-5253; b) Y.-M. Tian, X.-N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen, T. B. Marder, *J. Am. Chem. Soc*. **2018**, *140*, 17612-17623; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem* **2019**, *11*, 5387-5396; d) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius, T. B. Marder, *J. Am.*

Chem. Soc. **2020**, *142*, 6036-6050; e) Z. Liu, Y. P. Budiman, Y.-M. Tian, A. Friedrich, M. Huang, S. A. Westcott, U. Radius, T. B. Marder, *Chem. Eur. J.* **2020**, *26*, 17267-17274; g) Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder, *Adv. Synth. Catal.* **2021**. 363, 2224-2255.

[36] M. Uzelac, K. Yuan, M. J. Ingleson, *Organometallics*. **2020**, *39*, 1332-1338.

[37] a) S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Y. Mo, D. Qiu, M. S. Cheung, L. Dang, J. B. Wang, U. Radius, Z. Y. Lin, C. Kleeberg, T. B. Marder, *Chem. Eur. J.* **2015**, *21*, 7082-7098; b) A. F. Eichhorn, S. Fuchs, M. Flock, T. B. Marder, U. Radius, *Angew. Chem. Int. Ed*. **2017**, *56*, 10209-10213; *Angew. Chem*. **2017**, *129*, 10343-10347; c) J. Wang, A. Zhong, J. Li, J. Yang, W. Yao, *Org. Lett.* **2020**, *22*, 8086-8090; d) J. Wang, A. Zhong, S. Wang , Y. Shao, W. Yao, *Org. Chem. Front.* **2020**, *7*, 3515-3520; e) P. Ye, Y. Shao, X. Ye, F. Zhang, R. Li, J. Sun, B. Xu, J. Chen, *Org. Lett*. **2020**, *22*, 1306-1310; f) F. Takahashi, K. Nogi, H. Yorimitsu, *Eur. J. Org. Chem.* **2020**, 3009-3012; g) D. R. Willcox, G. S. Nichol, S. P. Thomas, *ACS Catal*. **2021**, *11*, 3190-3197; h) S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radius, Z. Lin, C. Kleeberg, T. B. Marder, *Chem. Eur. J*. **2015**, *21*, 7082-7099; i) L. Kuehn, M. Stang, S. W ürtemberger-Pietsch, A. Friedrich, H. Schneider, U. Radius, T. B. Marder, *Faraday Discuss*. **2019**, *220*, 350-363.

[38] a) C. R. Patrick, G. S. Prosser, *Nature* **1960**, *187*, 1021-1021; b) G. W. Coates, A. R. Dunn, L. M. Henling, D. A. Dougherty, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1997,** *36*, 248-251; *Angew. Chem.* **1997**, *109*, 290-293; c) C. Dai, P. Nguyen, T. B. Marder, A. J. Scott, W. Clegg, C. Viney, *Chem. Commun.* **1999**, 2493-2494; d) J. C. Collings, K. P. Roscoe, R. Ll. Thomas, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, T. B. Marder, *New J. Chem*. **2001**, *25*, 1410-1417; e) J. C. Collings, K. P. Roscoe, E. G. Robins, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, S. J. Clark, T. B. Marder, *New J. Chem.* **2002**, *26*, 1740-1746; f) C. E. Smith, P. S. Smith, R. Ll. Thomas, E. G. Robins, J. C. Collings, C. Dai, A. J. Scott, S. Borwick, A. S. Batsanov, S. W. Watt, C. Viney, J. A. K. Howard, W. Clegg, S. J. Clark, T. B. Marder, *J. Mater. Chem.* **2004**, *14*, 413-420; f) A. Friedrich, I. E. Collings, K. F. Dziubek, S. Fanetti, K. Radacki, J. Ruiz-Fuertes, J. Pellicer-Porres, M. Hanfland, D. Sieh, R. Bini, S. J. Clark, T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 18907-18923.

[39] M. C. Etter, *Acc. Chem. Res*. **1990**, *23*, 120-126.

[40] a) C. P. Brock, L. L. Duncan, *Chem. Mater*. **1994**, *6*, 1307-1312; b) Z. Liu, G. K.

Kole, Y. P. Budiman, Y.-M. Tian, A. Friedrich, X. Luo, S. A. Westcott, U. Radius, T. B. Marder, *Angew. Chem. Int. Ed*. **2021**, DOI:10.1002/anie.202103686.

[41] a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc*. **2002**, *124*, 390-391; b) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058; *Angew. Chem.* **2002**, *114*, 3182-3184; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem*. **2019**, *11*, 5387-5396.

[42] G. M. Sheldrick, *Acta Crystallogr.*, **2015**, *A71*, 3-8.

[43] a) G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.* **2008**, *64*, 112-122; b) G. M. Sheldrick, *Acta Crystallogr. Sect. C: Struct. Chem.* **2015**, *C71*, 3-8. [8] B. Moulton, M. J. Zaworotko, *Chem. Rev.* **2001**, *101*, 1629-1658.

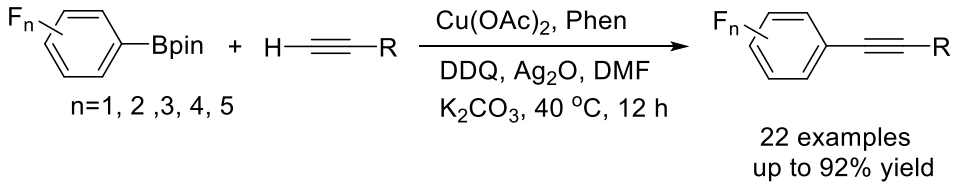
[44] C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *J. Appl. Crystallogr.* **2011**, *44*, 1281-1284.

5 Summary

It is generally acknowledged that polyfluoroarenes are important fluorinated structural units for various organic molecules, such as pharmaceuticals, agrochemicals, and organic materials. Polyfluorinated aryl alkynes and alcohols are also powerful building blocks in chemical synthesis because of their versatility to be transformed into various useful molecules and also their ubiquity in natural product synthesis. Efficient methods for the synthesis of polyfluorinated aryl alkynes and alcohols are presented in Chapter 2 and Chapter 3. In addition, 3-amino-indoles have found a broad applications in medicinal chemistry as effective anticancer agents, compounds with analgesic properties and can function as potent inhibitors of tubulin polymerization, and agents for the prevention of type II diabetes. A simple method for the synthesis of 3-amino-indoles via the annulation reaction of polyfluorophenylboronates with DMF is reported in Chapter 4.

Chapter 2

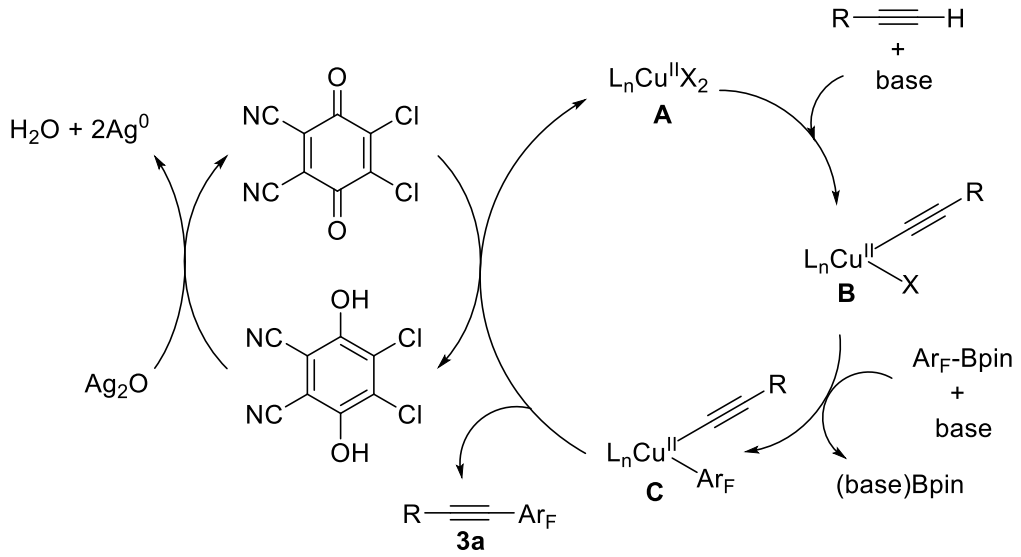
In Chapter 2, a mild process for the copper-catalyzed oxidative cross-coupling of electron-deficient polyfluorophenylboronate esters with terminal alkynes (Scheme S-1) is reported. This method displays good functional group tolerance and broad substrate scope, generating cross-coupled alkynyl(fluoro)arene products in moderate to excellent yields. This copper-catalyzed reaction was conducted on a gram scale to generate the corresponding product in good yield (72%).



Scheme S-1. Copper-catalyzed oxidative cross-coupling of terminal alkynes with polyfluorophenylboronate esters.

Based on previous reports and the aforementioned observations, a plausible catalytic cycle for this oxidative cross-coupling reaction is shown in Scheme S-2. The first step involves the addition of an alkynyl anion to Cu leading to the formation of alkynylcopper(II) species **B**. Subsequent transmetalation between Ar_FBpin and

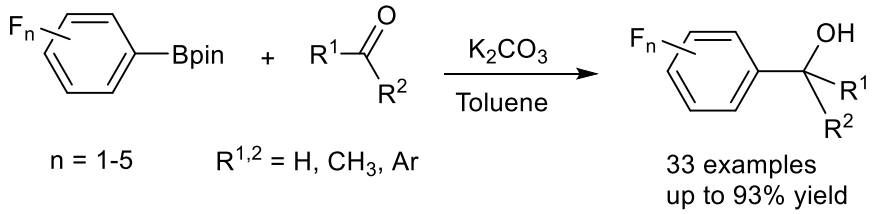
intermediate **B** occurs to form intermediate **C**. The desired product **3a** is generated by eductive elimination. Finally, the oxidation of Cu(0) to Cu(II) with DDQ and Ag_2O regenerates **A** to complete the catalytic cycle.



Scheme S-2. Proposed mechanism of copper(II)-catalyzed oxidative cross-coupling between terminal alkynes and polyfluorophenylboronate esters.

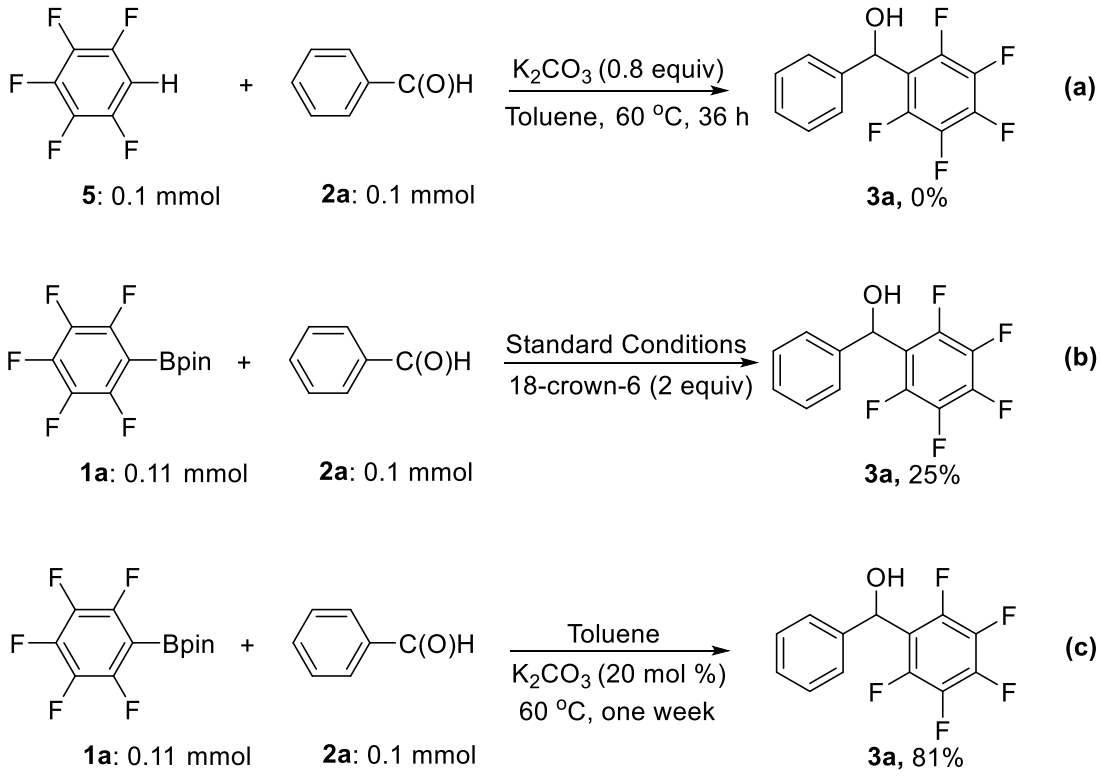
Chapter 3

In Chapter 3, A convenient and efficient protocol for the transition metal-free 1,2-addition of polyfluoroaryl boronate esters to aldehydes and ketones is reported, which provides secondary alcohols, tertiary alcohols, and ketones (Scheme S-3). The distinguishing features of this procedure include the employment of commercially available starting materials and the broad scope of the reaction with a wide variety of carbonyl compounds giving moderate to excellent yields.



Scheme S-3. Base-promoted 1,2-addition of polyfluorophenylboronates to aldehydes and ketones.

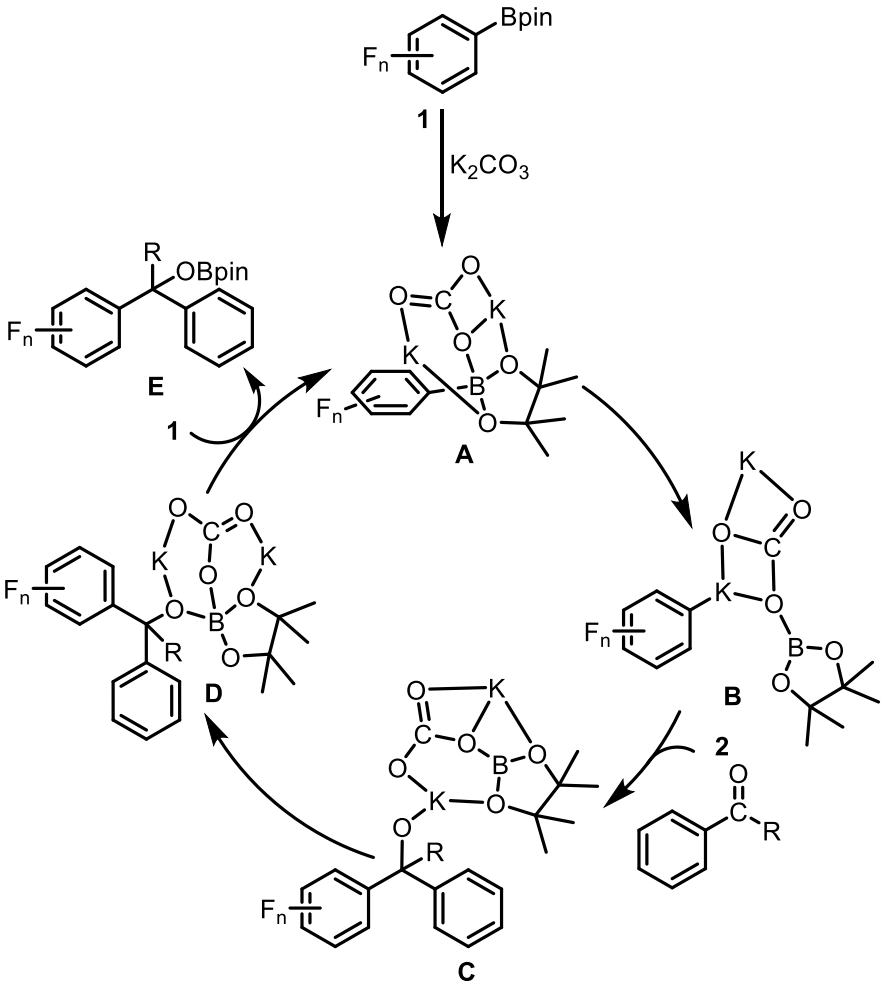
Control experiments were carried out to gain insight into the reaction mechanism. The reaction of **2a** with pentafluorobenzene **5** under standard conditions was examined, yet **3a** was not formed in any detectable amounts (Scheme S-4a), indicating that the C-Bpin moiety is essential and deprotonation of the fluoroarene or nucleophilic attack at the fluoroarene by the base is not a plausible pathway. Interestingly, for the standard reaction between **1a** and **2a**, the yield dropped dramatically if 18-crown-6 ether and K_2CO_3 were added (Scheme S-4b). This experimental result indicates that the presence of the potassium ion plays a crucial role for the outcome of the reaction. Furthermore, if the reaction of **1a** and **2a** was performed in the presence of only a catalytic amount of K_2CO_3 (20 mol%) (Scheme S-4c), reaction rates were reduced, and a week was required to produce **3a** in good yield. This finding again indicates that the potassium ion (or the base) plays an important role in the reaction. Substituting *ortho*-fluorines by *ortho*-chlorines, using either C_6Cl_5Bpin 2,6-dichlorophenyl-1-Bpin as substrates, did not yield any product as shown by *in situ* GCMS studies.



Scheme S-4. Control experiments.

Based on DFT calculations, a mechanism for the 1,2-addition of polyfluorophenylboronates to aryl aldehydes in the presence of K_2CO_3 as base is proposed, as shown in Scheme S-5. K_2CO_3 interacts with the Lewis-acidic Bpin moiety of

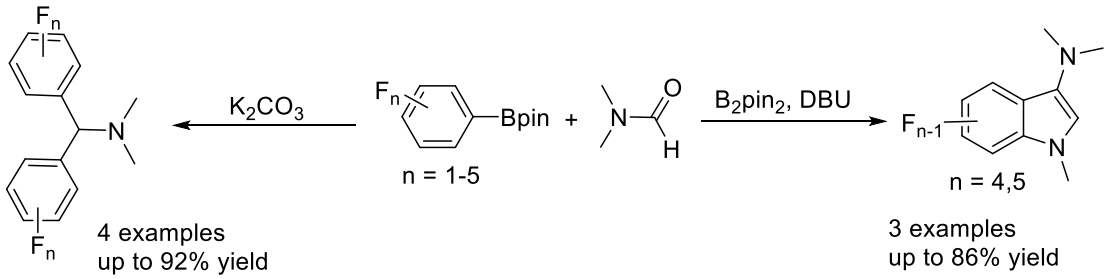
substrate **1** to generate base adduct **A**, which weakens the carbon-boron bond and ultimately cleaves the B–C bond along with attachment of a potassium cation to the aryl group. The resulting Ar_F^- anion adduct **B** undergoes nucleophilic attack at the aldehyde carbon atom of substrate **2** to generate methanolate **C**. The methanolate oxygen atom then attacks the electrophilic Bpin group to obtain compound **D**. Transfer of K_2CO_3 from intermediate **D** to the boron atom of the more Lewis-acidic polyfluorophenyl-Bpin **1** finally closes the cycle and regenerates complex **A**. Thus, the primary reaction product is the O-borylated addition product **E**, which was detected by HRMS and NMR spectroscopy for the perfluorinated derivative.



Scheme S-5. Proposed mechanism of the 1,2-addition of polyfluorophenylboronates to aldehydes and ketones.

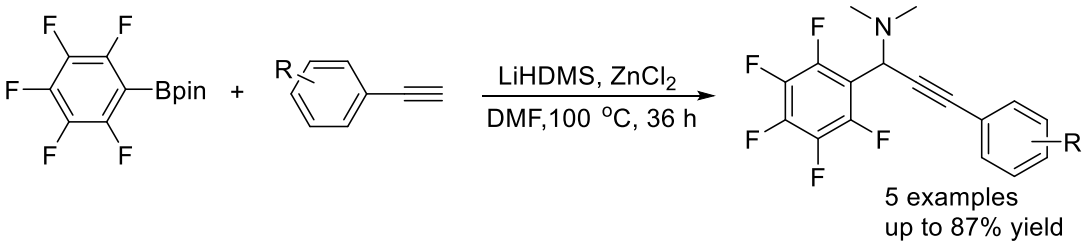
Chapter 4

Chapter 4 presents a novel protocol for the transition metal-free addition and annulation of polyfluoroarylboronate esters to DMF, which provides 3-aminoindoles and tertiary amines in moderate to excellent yields (Scheme S-6).



Scheme S-6. Annulation and addition reactions of polyfluorophenylboronates with DMF.

While exploring the application of this strategy in synthesis, perfluorophenylBpin reacted smoothly with ethynylarenes and DMF to afford propargylamines with moderate to excellent yields (Scheme S-7).



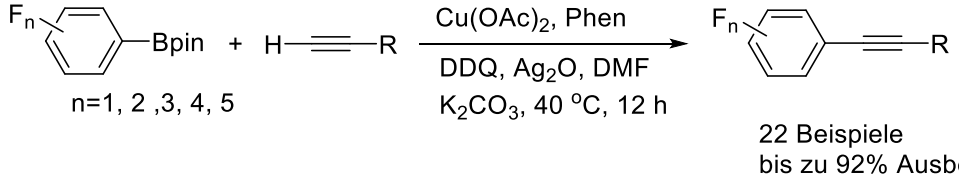
Scheme S-7. Three-component cross-coupling reaction for the synthesis of propargylamines.

6 Zusammenfassung

Polyfluorarene sind wichtige fluorierte Schlüsselstruktureinheiten für verschiedene organische Moleküle, wie z. B. Pharmazeutika, Agrochemikalien und organische Materialien. Auch polyfluorierte Arylalkine und -alkohole sind aufgrund ihrer vielseitigen Möglichkeiten, in verschiedene nützliche Moleküle umgewandelt zu werden als auch wegen ihrer Allgegenwart in der Naturstoffsynthese, leistungsfähige Bausteine. Effiziente Methoden zur Synthese polyfluorierter Arylalkine und -alkohole werden in Kapitel 2 und Kapitel 3 vorgestellt. Darüber hinaus haben 3-Amino-Indole eine breite Anwendung in der medizinischen Chemie als wirksame Antikrebsmittel, Verbindungen mit analgetischen Eigenschaften und als potente Inhibitoren der Tubulinpolymerisation sowie als Mittel zur Prävention von Typ-II-Diabetes gefunden. Eine einfache Methode zur Synthese von 3-Amino-Indolen über die Annulierungssreaktion von Polyfluorphenylboronaten mit DMF wird in Kapitel 4 berichtet.

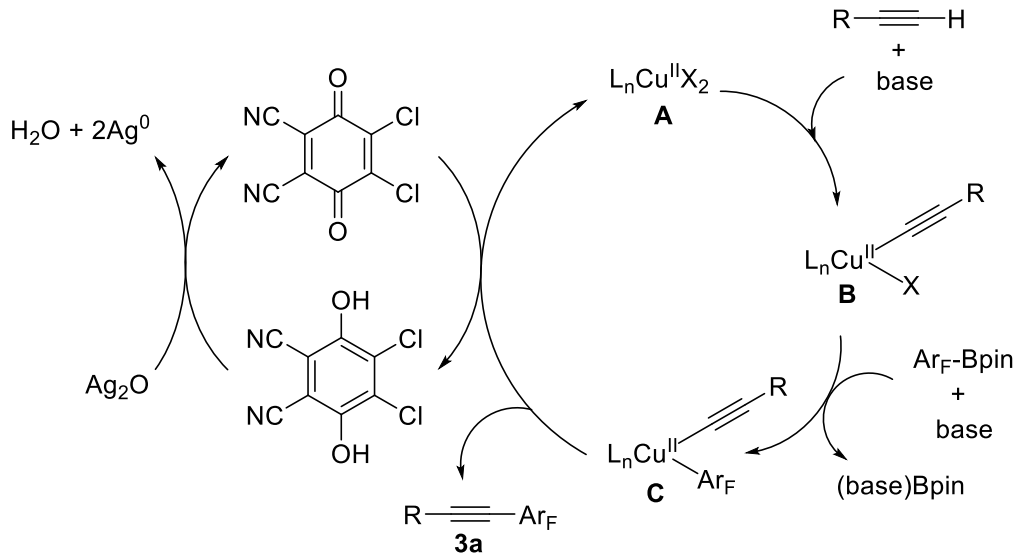
Kapitel 2

In Kapitel 2 wird über ein mildes Verfahren zur kupferkatalysierten oxidativen Kreuzkupplung von elektronenarmen Polyfluorphenylboronatestern mit terminalen Alkinen (Schema S-1) berichtet. Diese Methode zeichnet sich durch eine gute Toleranz gegenüber funktionellen Gruppen und eine große Bandbreite an Substraten aus und erzeugt kreuzgekoppelte Alkinyl(fluor)aren-Produkte in moderaten bis exzellenten Ausbeuten. Diese kupferkatalysierte Reaktion wurde im Gramm-Maßstab durchgeführt, und erzeugt das entsprechende Produkt in guter Ausbeute (72 %).



Schema S-1. Kupfer-katalysierte oxidative Kreuzkupplung terminaler Alkine mit Polyfluorphenylboronatestern.

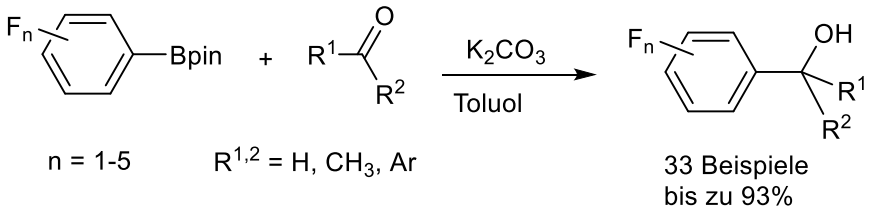
Basierend auf früheren Arbeiten und den oben erwähnten Beobachtungen ist ein plausibler katalytischer Zyklus für diese oxidative Kreuzkupplungsreaktion in Schema S-2 dargestellt. Der erste Schritt beinhaltet die Addition eines Alkinylanions, was zur Bildung des Alkinylkupfer(II)-Komplexes **B** führen sollte. Anschließend erfolgt eine Transmetallierung zwischen Ar_FBpin und dem Zwischenprodukt **B** zur Bildung des Zwischenproduktes **C**. Das gewünschte Produkt **3a** wirde dann daraus durch reduktive Eliminierung erzeugt. Durch eine Oxidation des dabei entstehenden Cu(0)-Komplexes mit DDQ und Ag_2O wird Komplex **A** regeneriert und der katalytische Zyklus schließt sich.



Schema S-2. Vorgeschlagener Mechanismus der Kupfer(II)-katalysierten oxidativen Kreuzkupplung terminaler Alkine und Polyfluorphenylboronatestern.

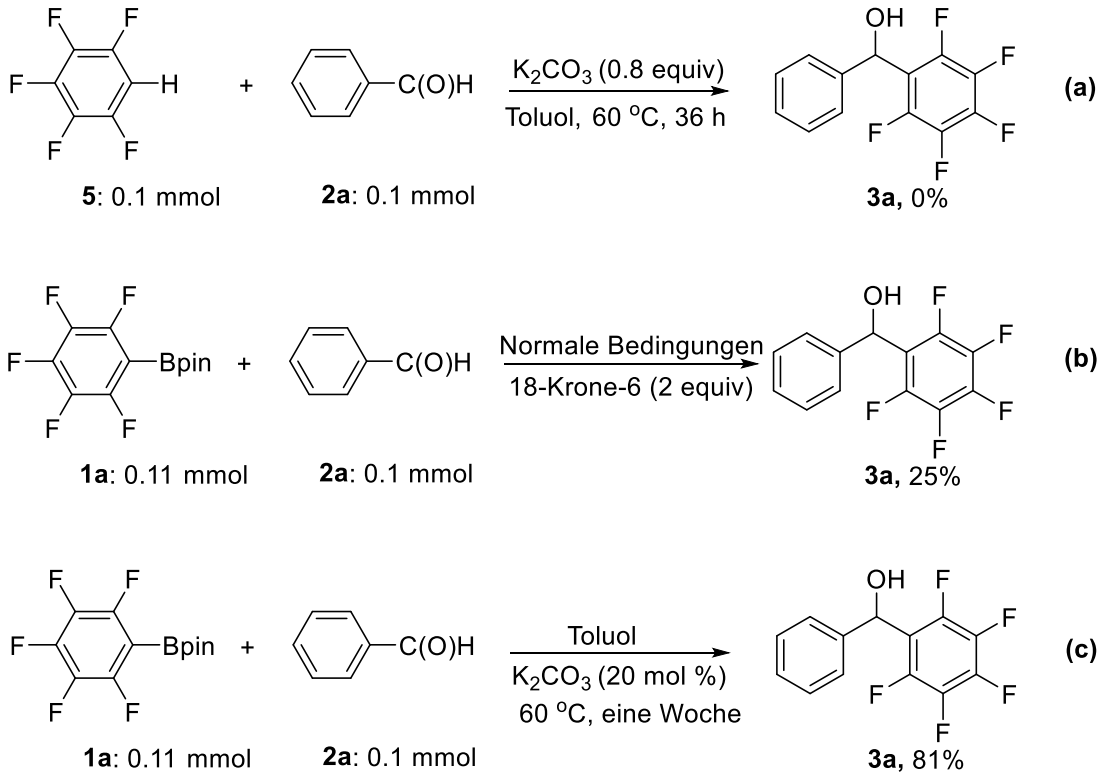
Kapitel 3

In Kapitel 3 wird ein praktisches und effizientes Protokoll für die übergangsmetallfreie 1,2-Addition von Polyfluorarylboronatestern an Aldehyde und Ketone vorgestellt, welches sekundäre Alkohole, tertiäre Alkohole und Ketone liefert (Schema S-3). Die besonderen Merkmale dieses Verfahrens sind die Verwendung kommerziell erhältlicher Ausgangsmaterialien und die große Bandbreite der Reaktion mit einer Vielzahl von Carbonylverbindungen, die mäßige bis exzellente Ausbeuten erbringen.



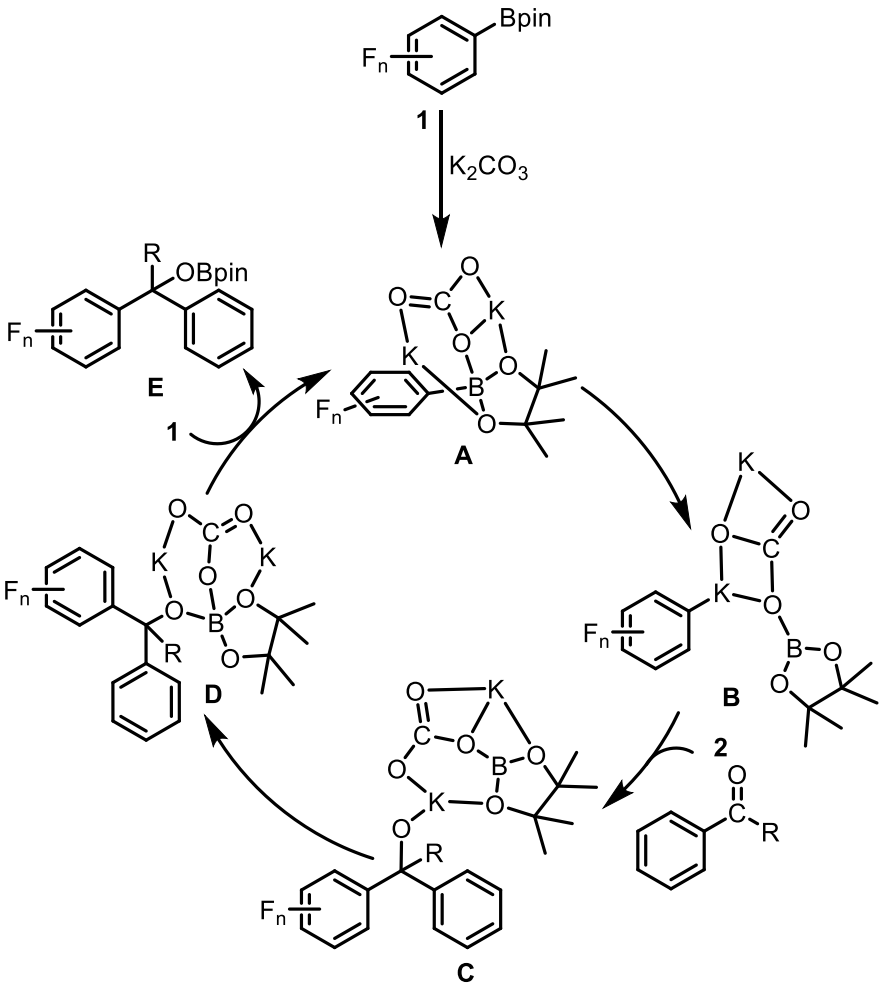
Schema S-3. Basen-unterstützte 1,2-Addition von Polyfluorphenylboronaten an Aldehyde und Ketone.

Um einen Einblick in den Reaktionsmechanismus zu erhalten, wurden Kontrollexperimente durchgeführt. Die Reaktion von **2a** mit Pentafluorbenzol **5** unter Standardbedingungen wurde untersucht, jedoch wurde **3a** nicht in nachweisbaren Mengen gebildet (Schema S-4a). Dies deudet darauf hin, dass der C-Bpin Anteil essenziell ist und eine Deprotonierung des Fluorarens oder ein nukleophiler Angriff am Fluoraren durch die Base kein plausibler Weg ist. Interessanterweise sank bei der Standardreaktion zwischen **1a** und **2a** die Ausbeute dramatisch, wenn 18-Kronen-6-Ether und K_2CO_3 zugesetzt wurden (Schema S-4b). Dieses experimentelle Ergebnis belegt, dass die Anwesenheit des Kalium-Ions eine entscheidende Rolle für den Ausgang der Reaktion spielt. Wenn die Reaktion von **1a** und **2a** in Gegenwart von nur einer katalytischen Menge K_2CO_3 (20 mol%) durchgeführt wurde (Schema S-4c), waren die Reaktionsgeschwindigkeiten geringer und es war eine Woche erforderlich, um **3a** in guter Ausbeute zu erlangen. Dieser Befund weist erneut darauf hin, dass das Kalium-Ion (oder die Base) eine wichtige Rolle bei der Reaktion spielt. Die Substitution von *ortho*-Fluorsubstituenten durch *ortho*-Chlorsubstituenten, wobei entweder C_6Cl_5Bpin oder 2,6-Dichlorphenyl-Bpin als Substrate verwendet wurden, lieferte kein Produkt, wie *in situ* GCMS-Studien zeigten.



Schema S-4. Kontrollexperimente.

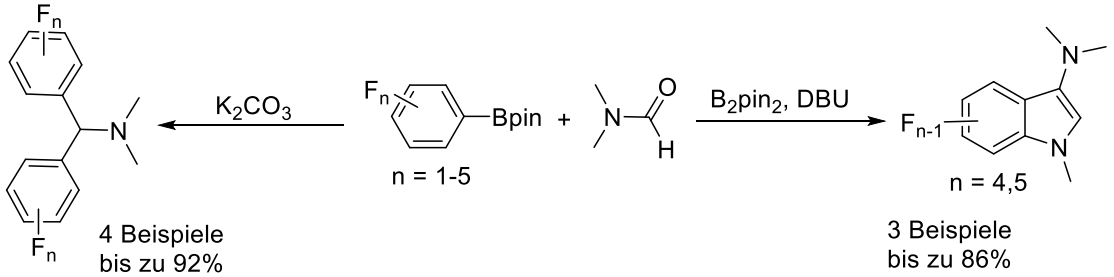
Ein Vorschlag zum Mechanismus der 1,2-Addition von Polyfluorphenylboronaten an Arylaldehyde in Gegenwart von K_2CO_3 als Base wird in Schema S-5 vorgeschlagen. Dabei wechselwirkt die Base K_2CO_3 mit der Lewis-sauren Bpin-Einheit des Substrats **1** unter Ausbildung des Basenadduktes **A**, in welchem die Kohlenstoff-Bor-Bindung geschwächt ist und schließlich die B-C Bindung gespalteen wird, wobei sich ein Kaliumkation an die Arylgruppe anlagert. Das resultierende Ar_F^- Anion im Addukt **B** greift nukleophil am Aldehyd-Kohlenstoffatom von Substrat **2** an, um Methanolat **C** zu erzeugen. Das Methanolat-Sauerstoffatom reagiert dann mit der elektrophilen Bpin-Gruppe, um Verbindung **D** zu erhalten. Die Übertragung von K_2CO_3 vom Zwischenprodukt **D** auf das Boratom des Lewis-acideren Polyfluorphenyl-Bpin **1** schließt schließlich den Zyklus und regeneriert den Komplex **A**. Das primäre Reaktionsprodukt ist also das O-borylierte Additionsprodukt **E**, das mittels HRMS und NMR-Spektroskopie für das perfluorierte Derivat nachgewiesen wurde.



Schema S-5. Vorgeschlagener Mechanismus der 1,2-Addition von Polyfluorphenylboronaten an Aldehyden und Ketonen.

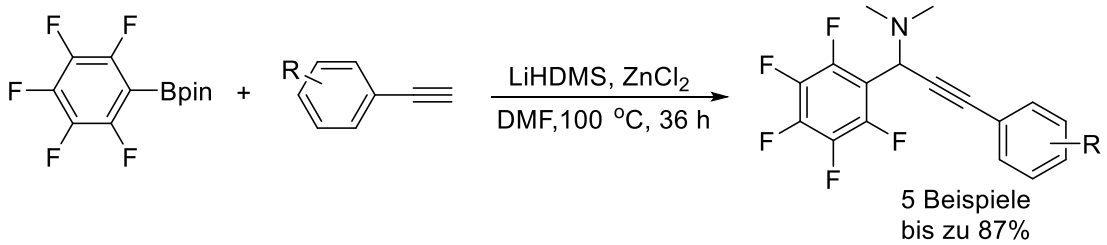
Kapitel 4

In Kapitel 4 wird ein neuartiges Protokoll für die übergangsmetallfreie Addition und Annulierungsreaktion von Polyfluorarylboronatestern an DMF vorgestellt, das 3-Aminoindole und tertiäre Amine in mäßigen bis ausgezeichneten Ausbeuten liefert(Schema S-6).



Schema S-6. Annulierungs- und Additionsreaktion von Polyfluorphenylboronaten mit DMF.

Bei der Erkundung der Anwendung dieser Strategie in der Synthese konnten Propargylamine mit mäßigen bis ausgezeichneten Ausbeuten hergestellt werden (Schema S-7).

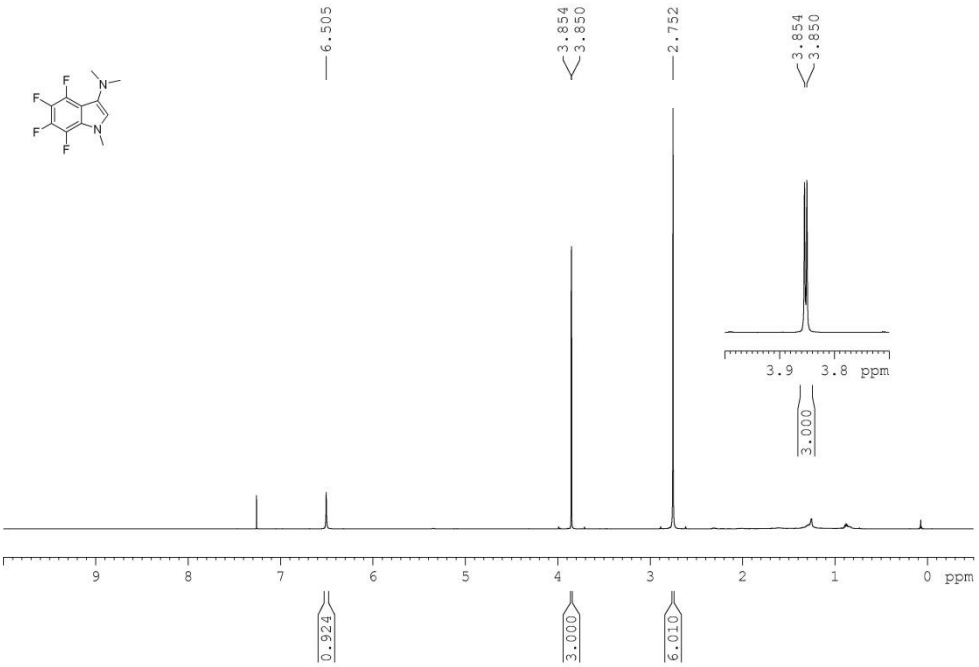


Schema S-7. Kreuzkupplungsreaktion für die Synthese von Propargylaminen.

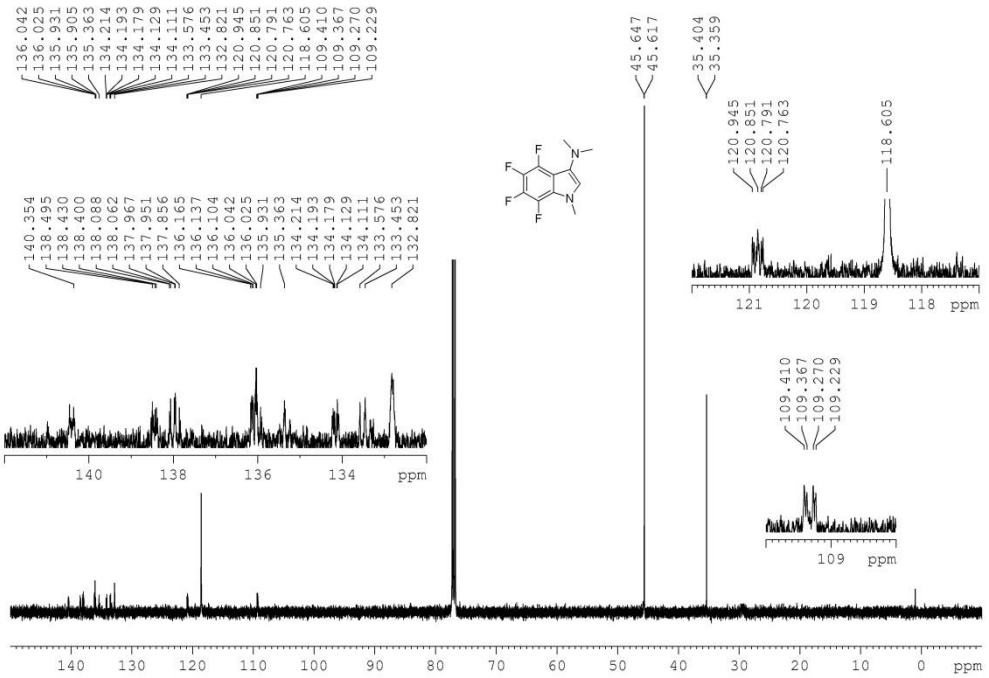
7. Appendix

7.1 NMR Spectra for Chapter 4

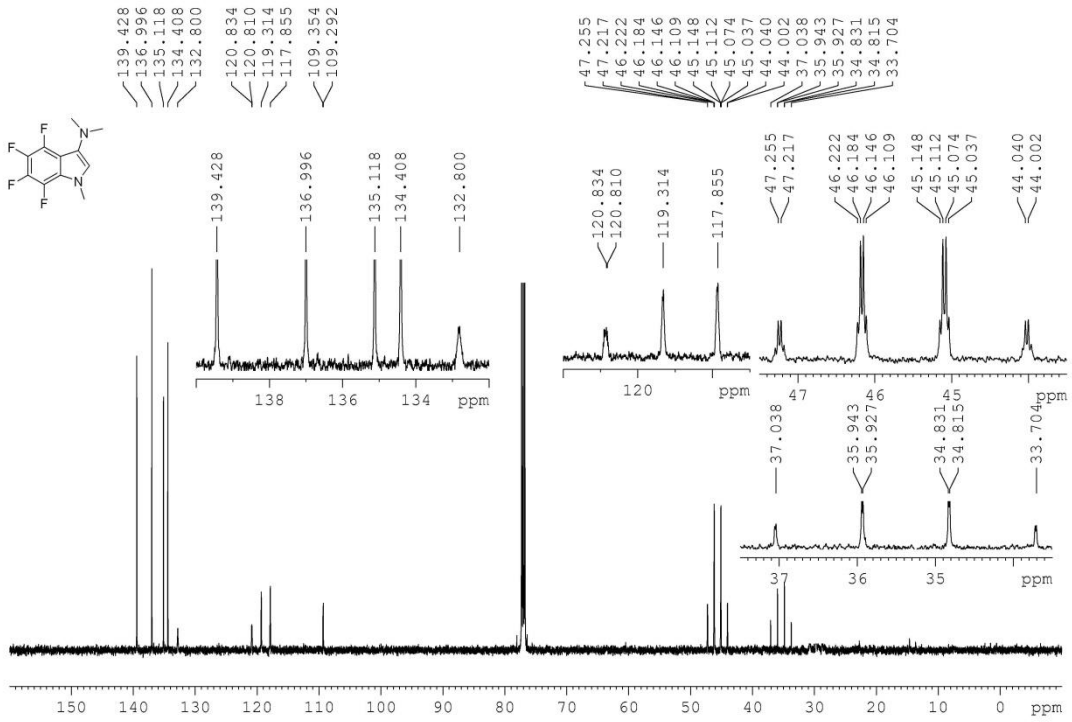
Compound 4-3a: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



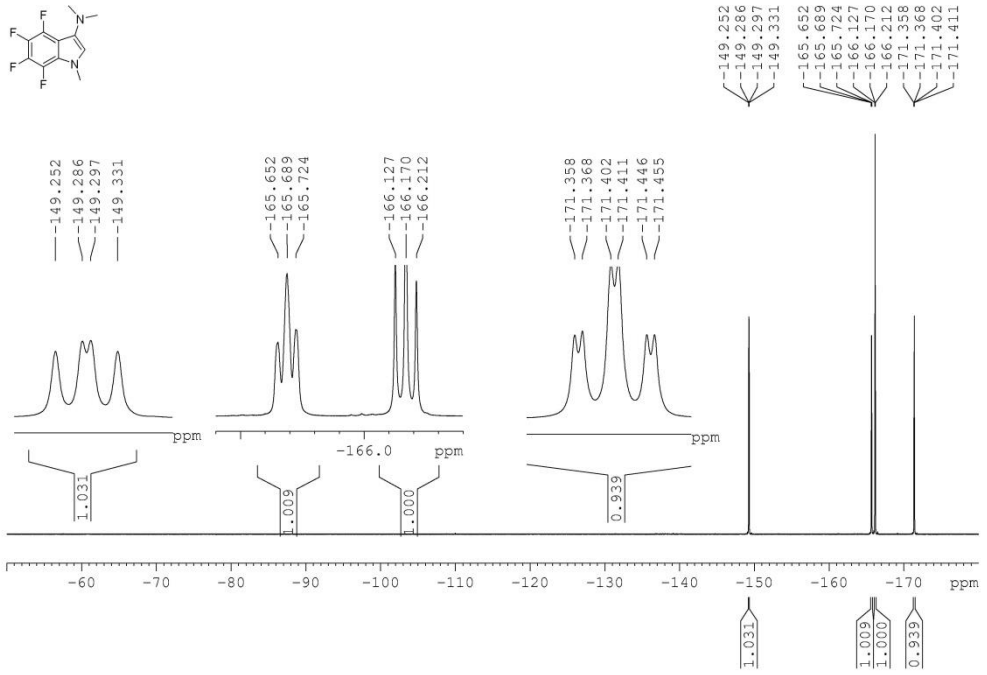
Compound 4-3a: ^{13}C{^{1}H} NMR spectrum (125 MHz, $CDCl_3$).



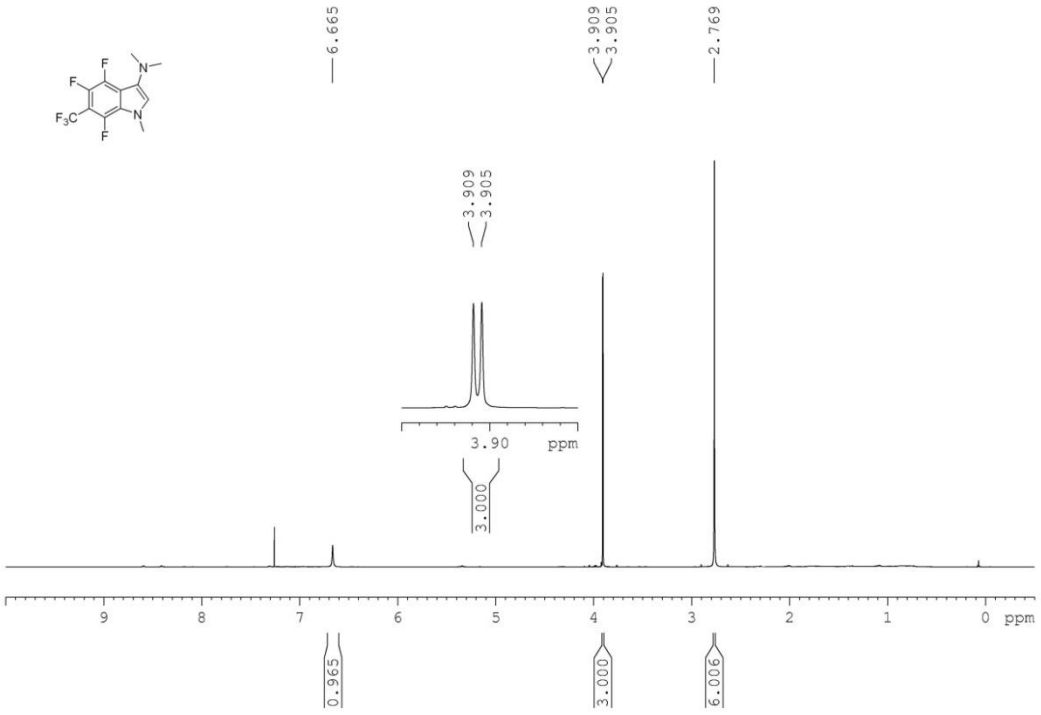
Compound 4-3a: $^{13}C\{^{19}F\}$ NMR spectrum (125 MHz, $CDCl_3$).



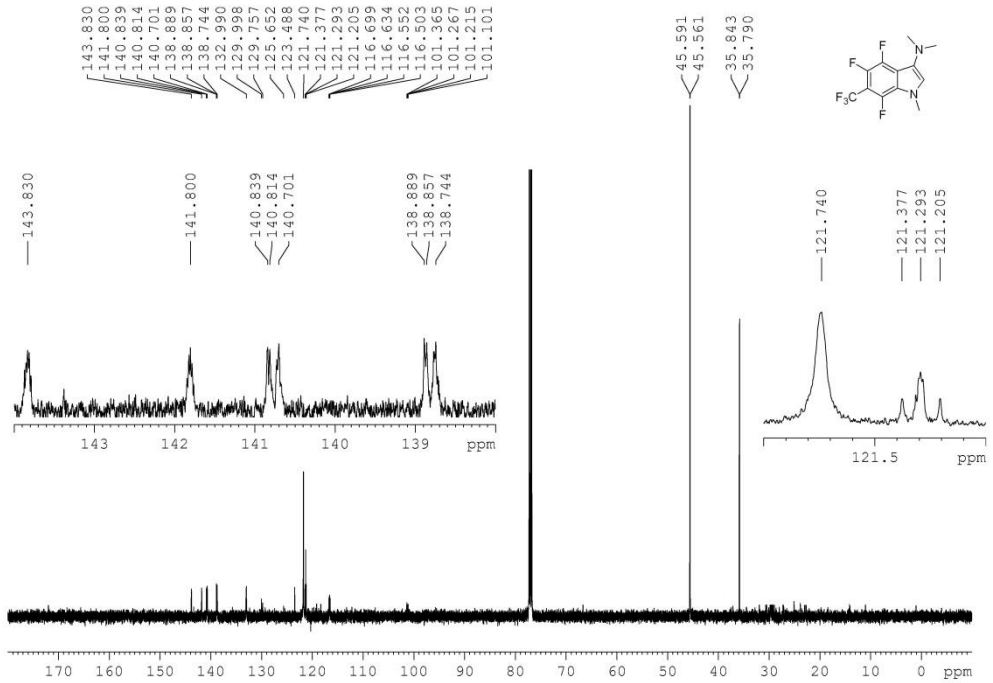
Compound 4-3a: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



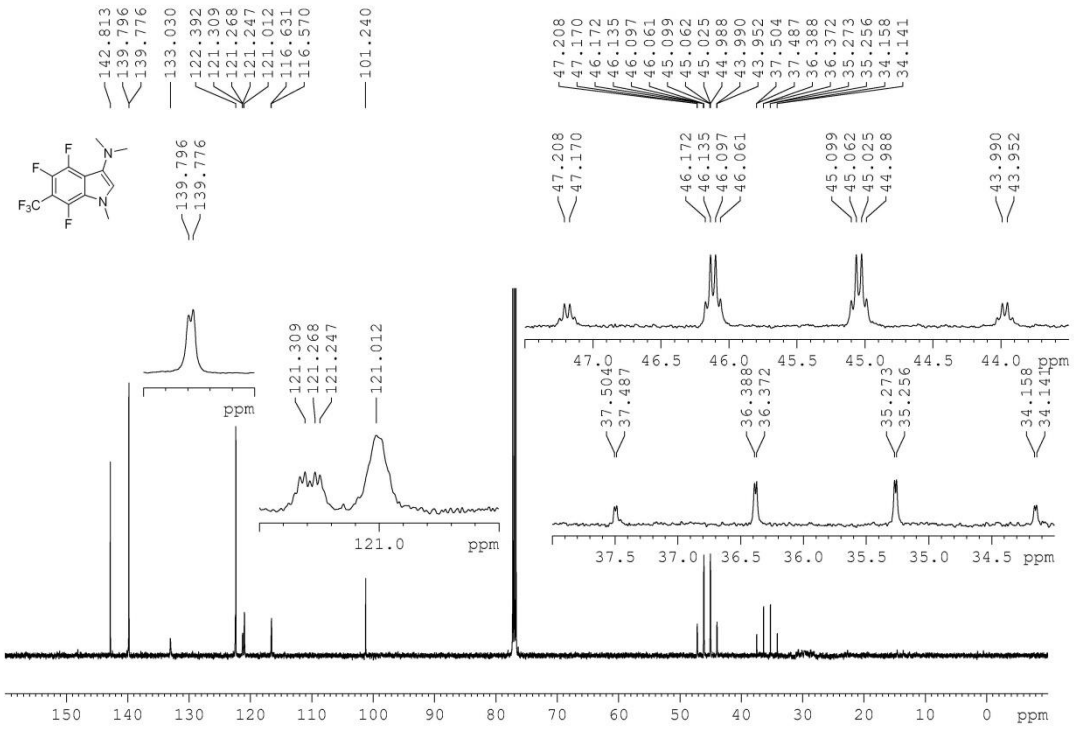
Compound 4-3b: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



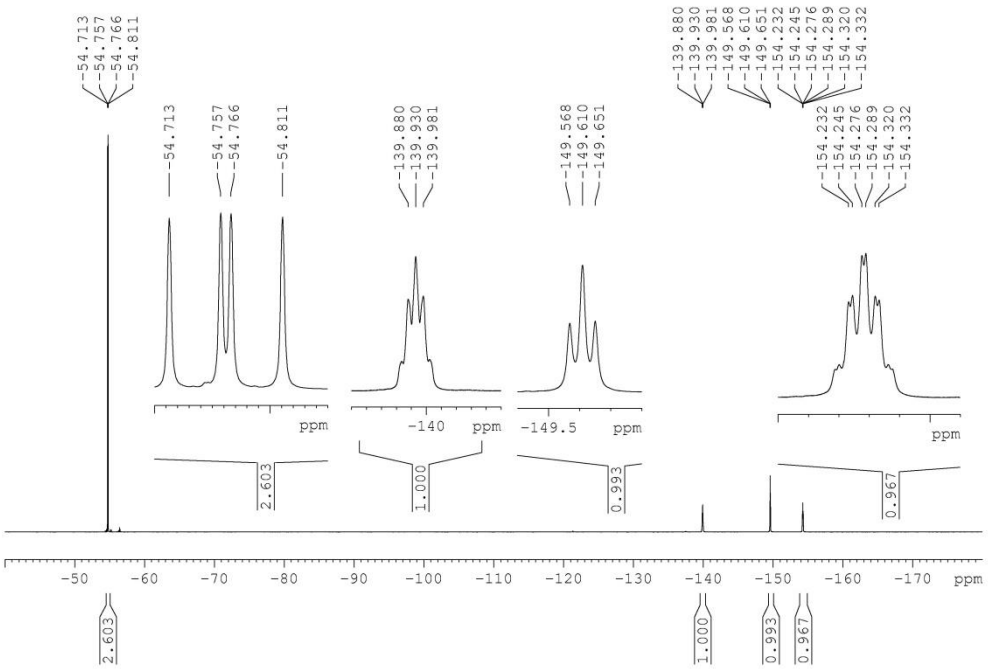
Compound 4-3b: ^{13}C{^{1}H} NMR spectrum (125 MHz, $CDCl_3$).



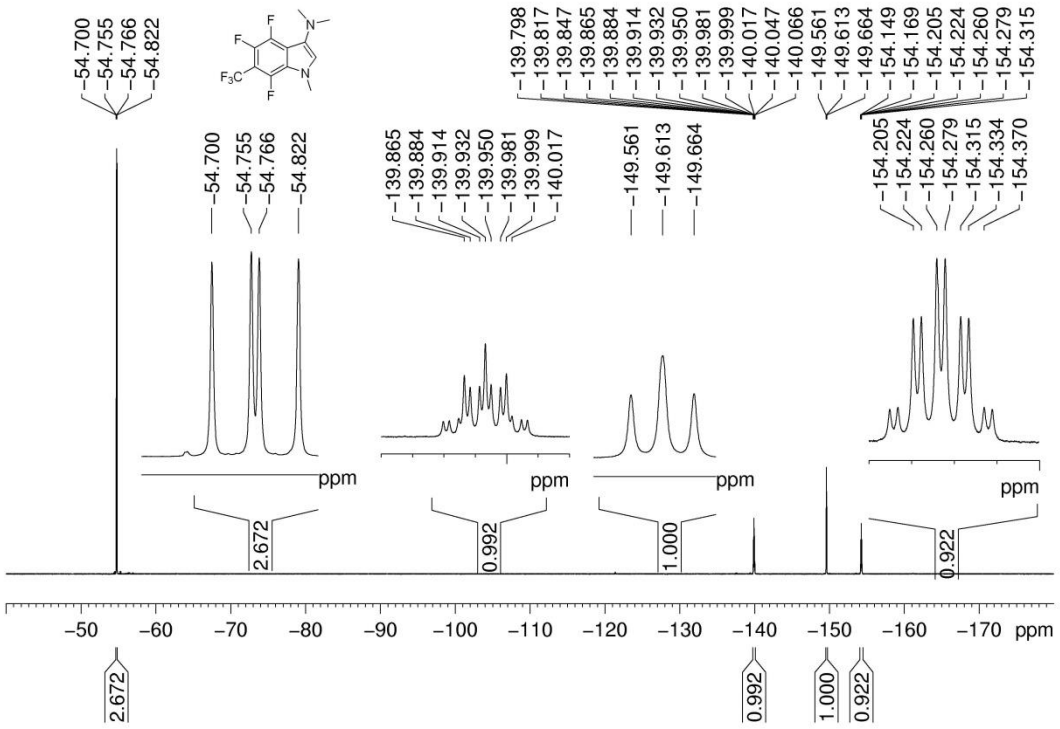
Compound 4-3b: $^{13}C\{^{19}F\}$ NMR spectrum (125 MHz, $CDCl_3$).



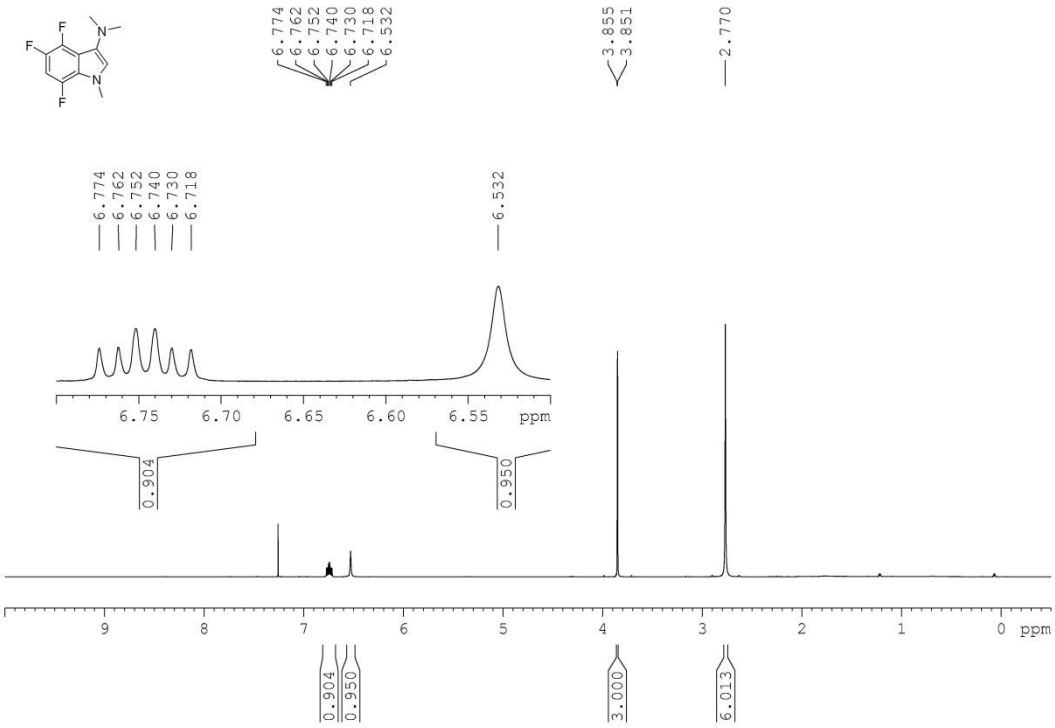
Compound 4-3b: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



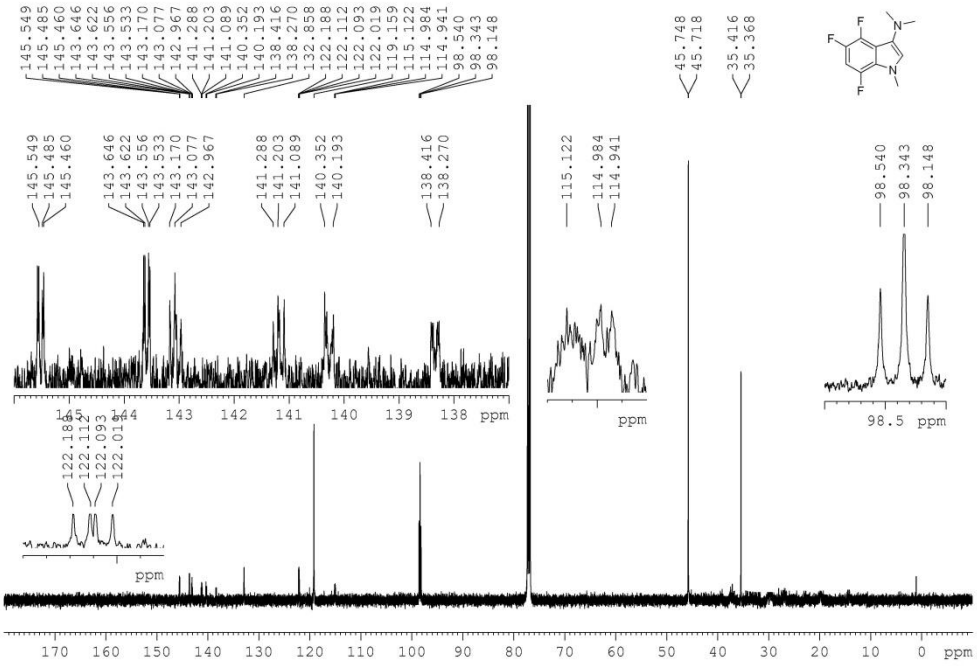
Compound 4-3b: $^{19}F\{^{1}H\}$ NMR spectrum (376 MHz, $CDCl_3$).



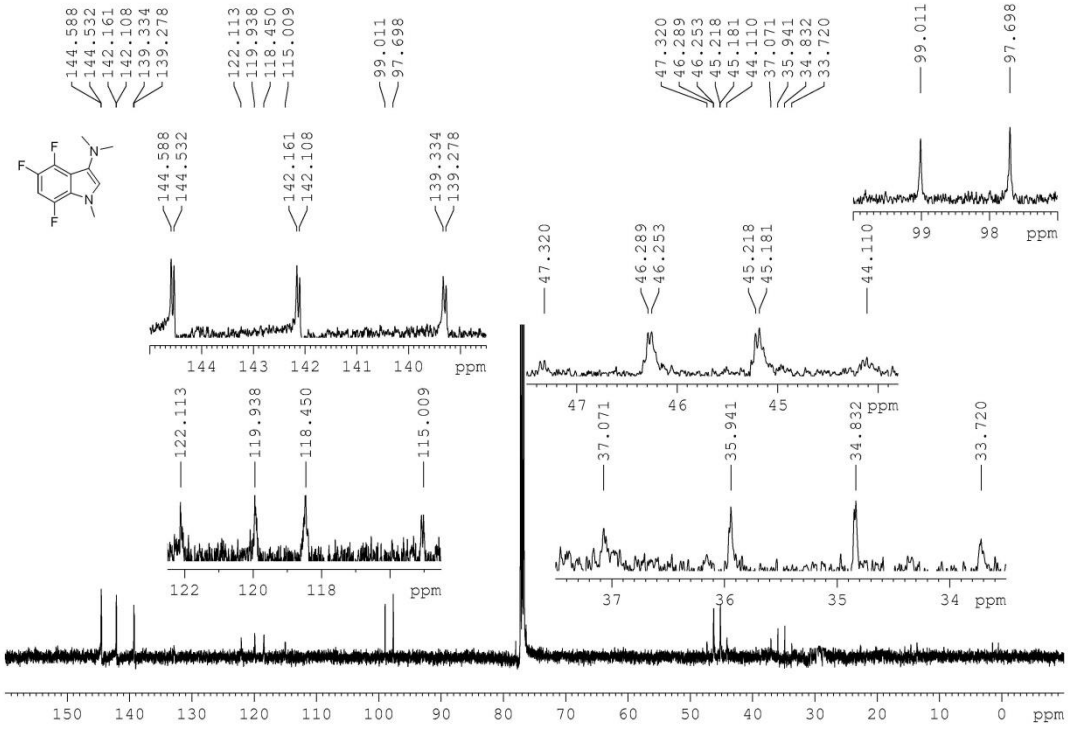
Compound 4-3c: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



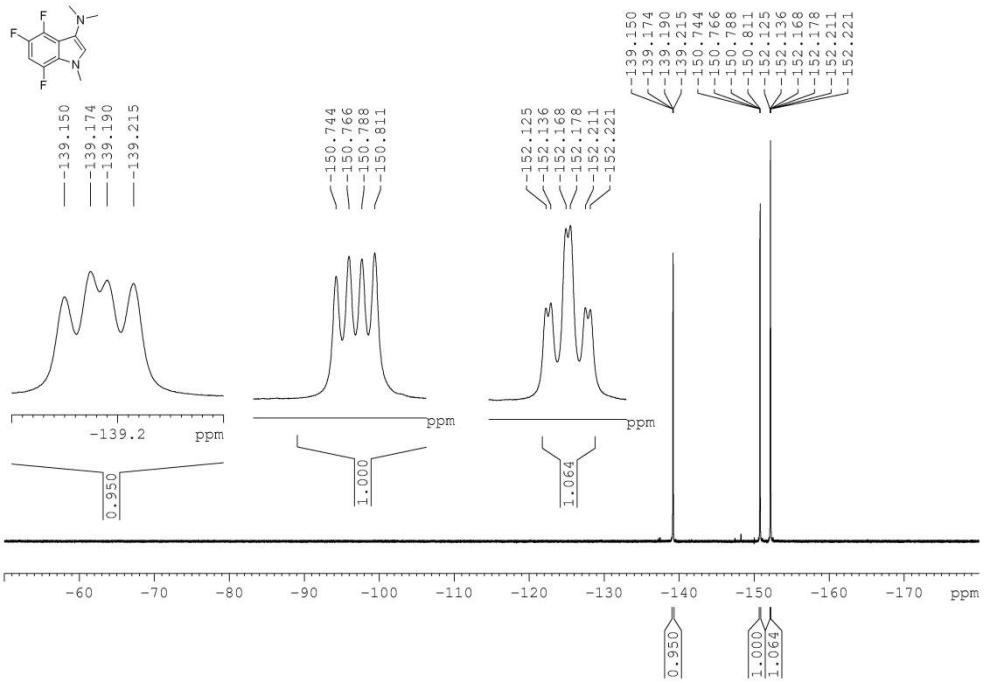
Compound 4-3c: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



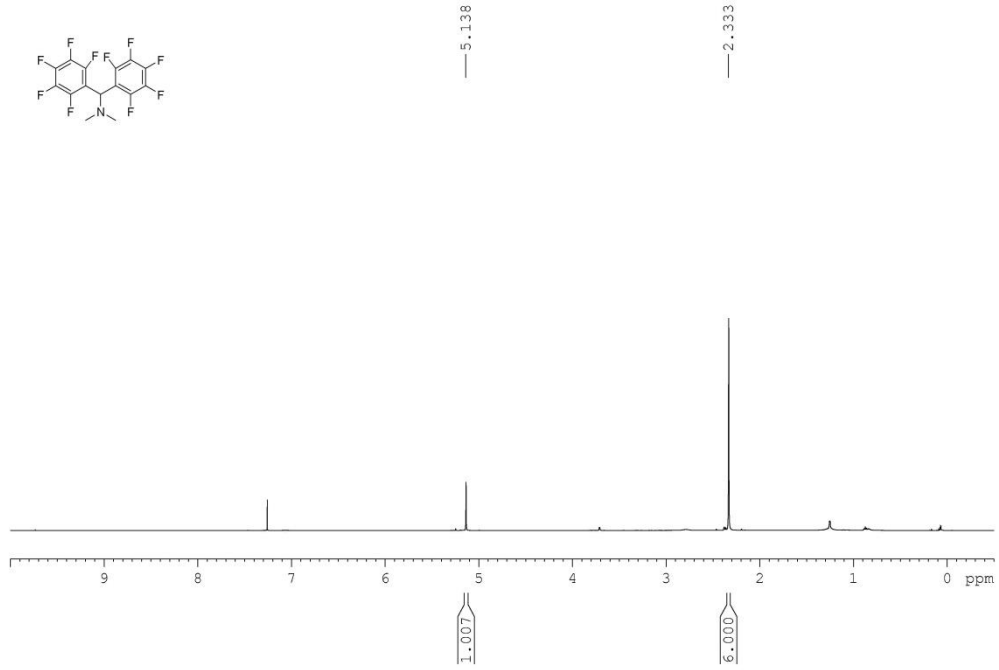
Compound 4-3c: $^{13}C\{^{19}F\}$ NMR spectrum (125 MHz, $CDCl_3$).



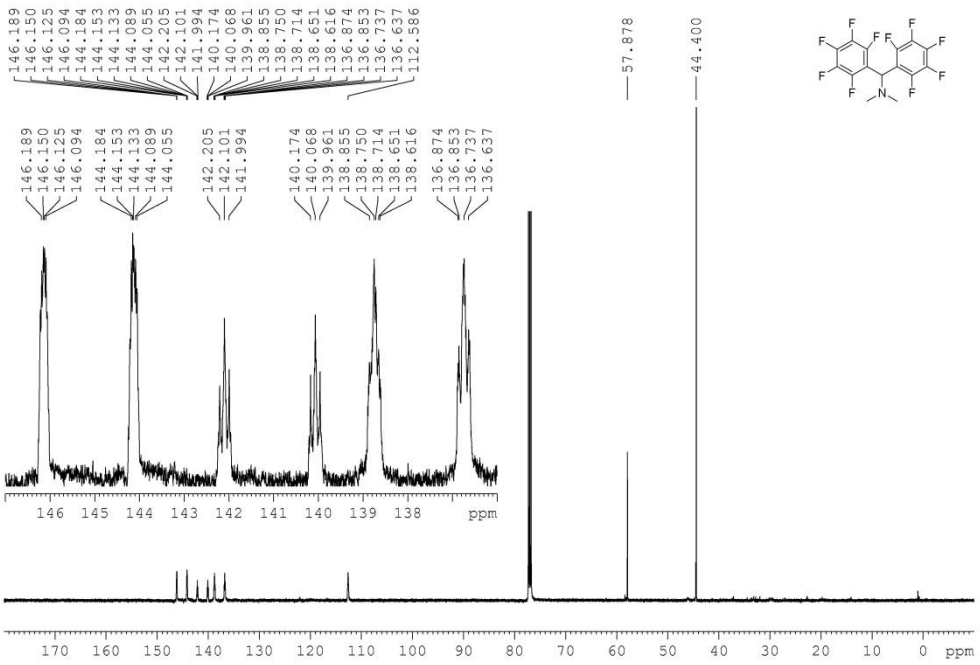
Compound 4-3c: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



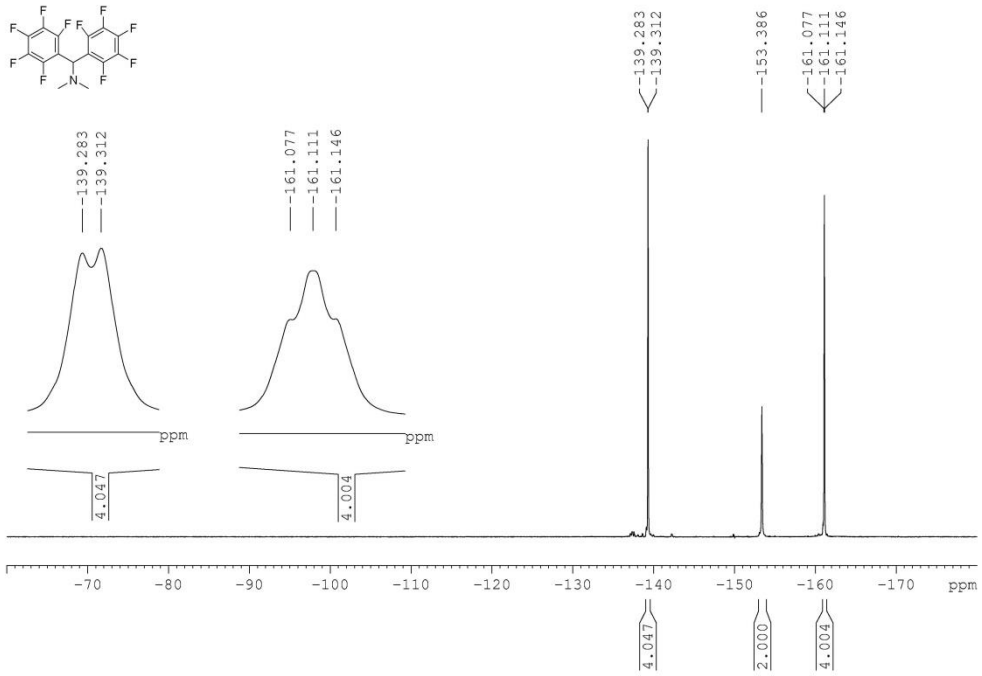
Compound 4-4a: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



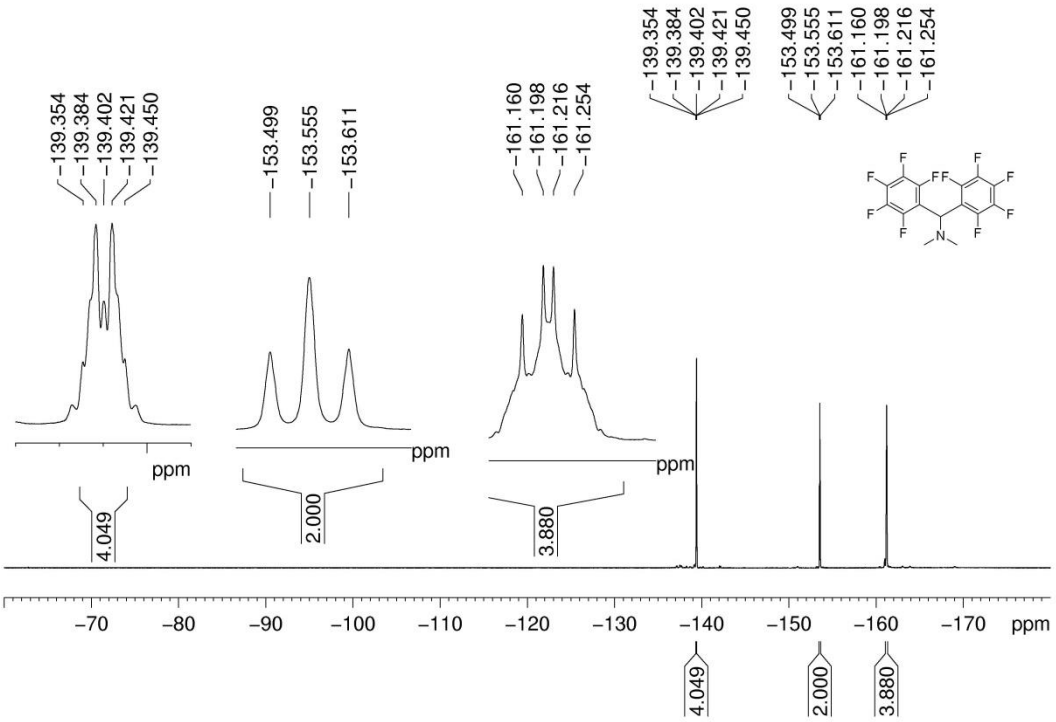
Compound 4-4a: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



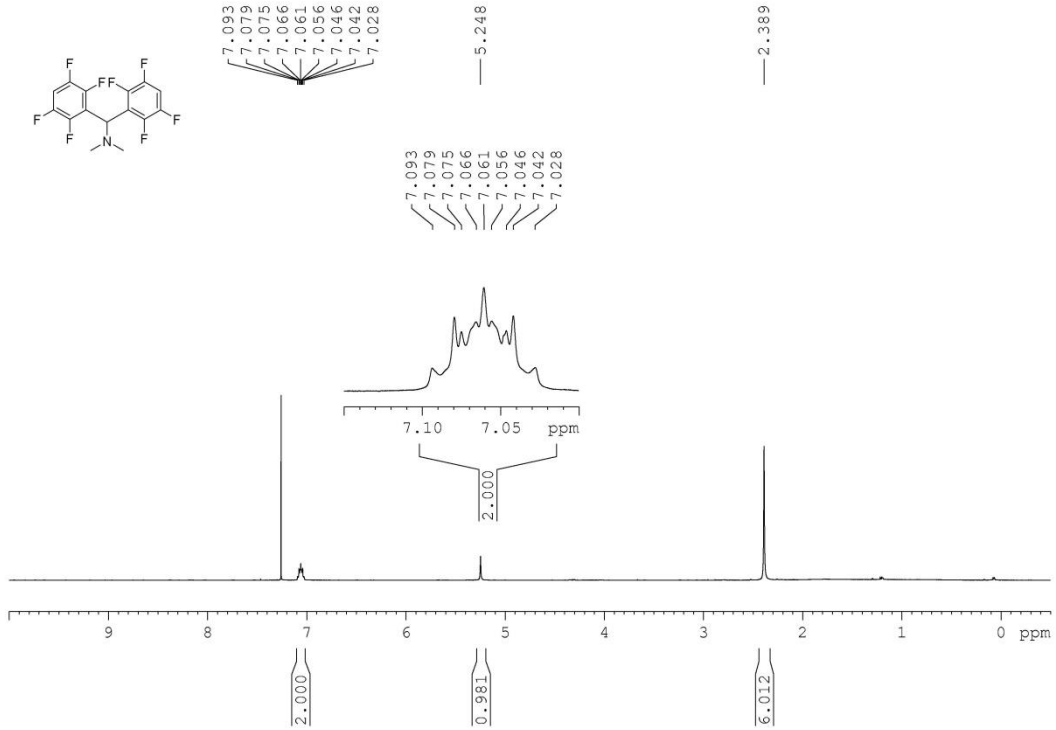
Compound 4-4a: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



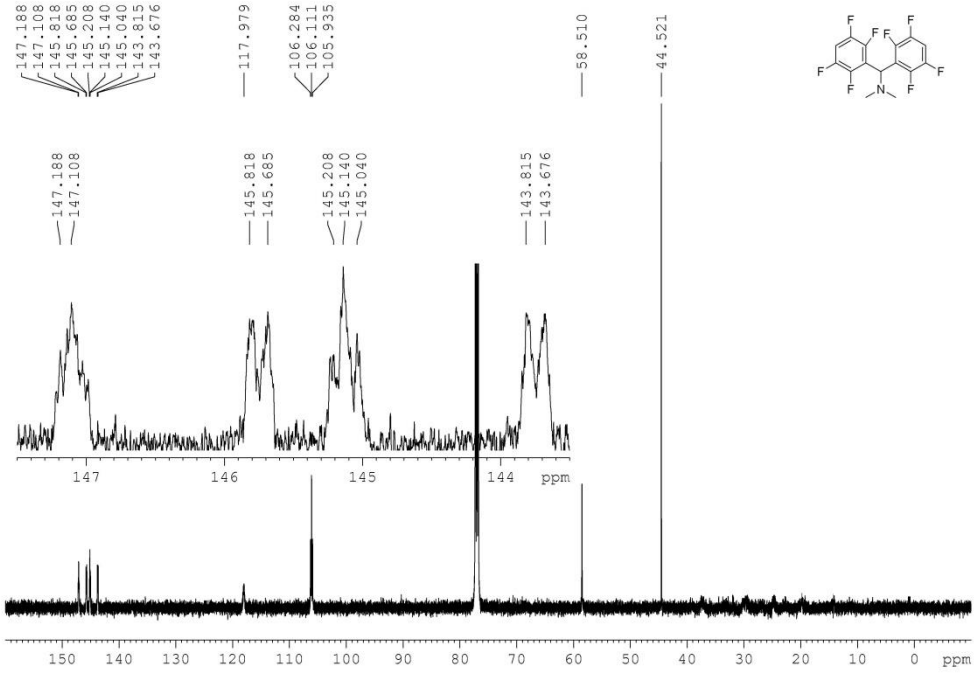
Compound 4-4a: $^{19}F\{^{1}H\}$ NMR spectrum (376 MHz, $CDCl_3$).



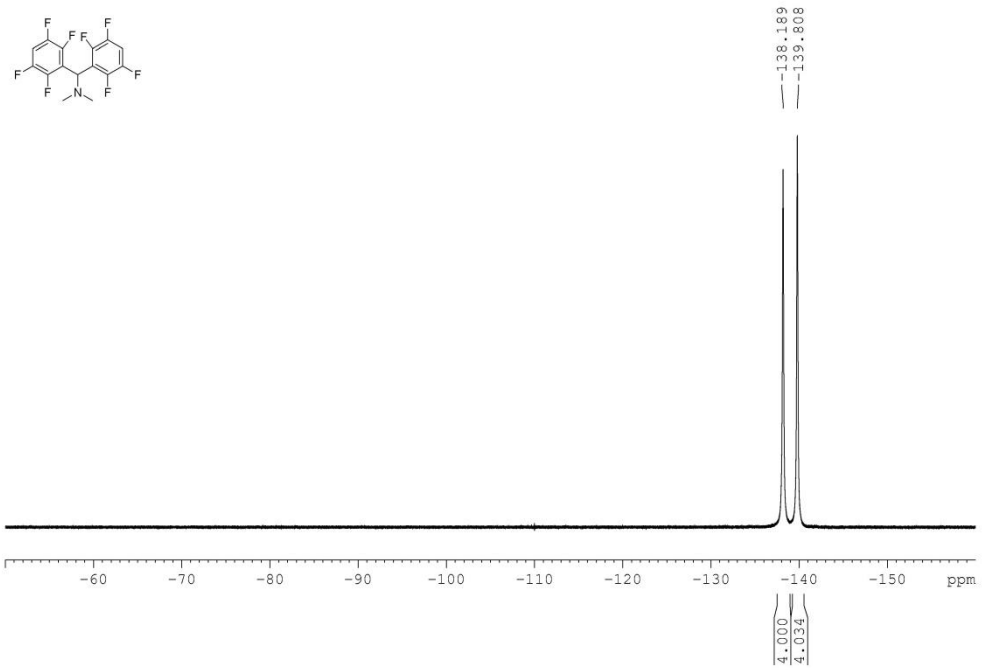
Compound 4-4b: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



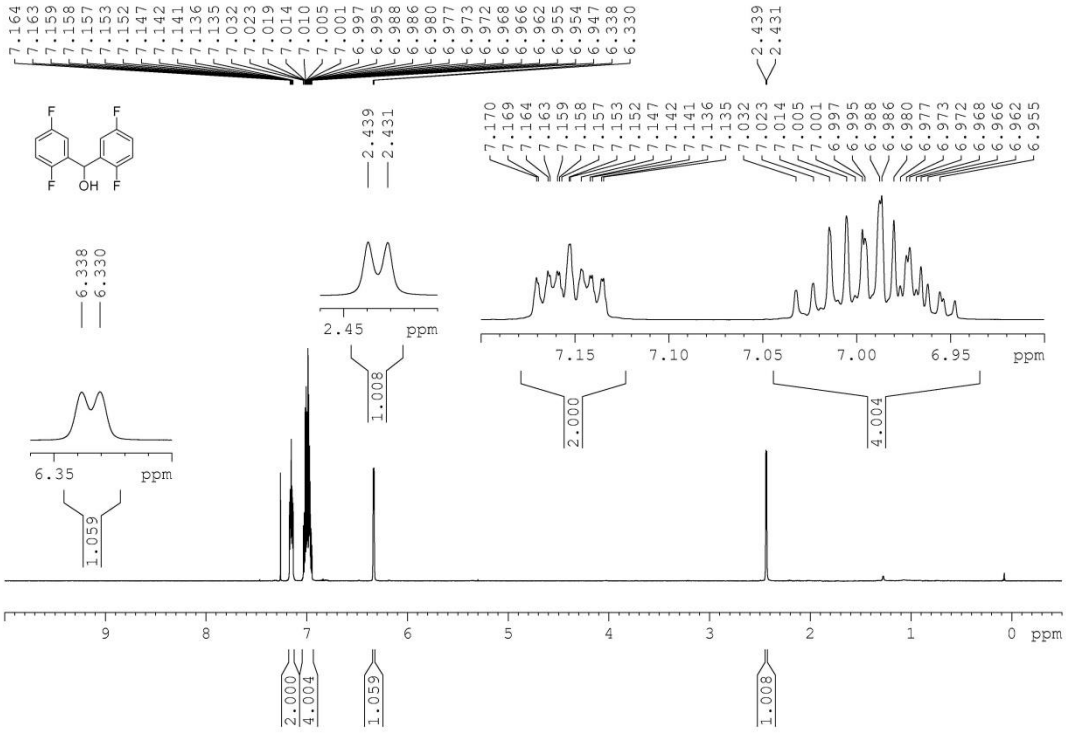
Compound 4-4b: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



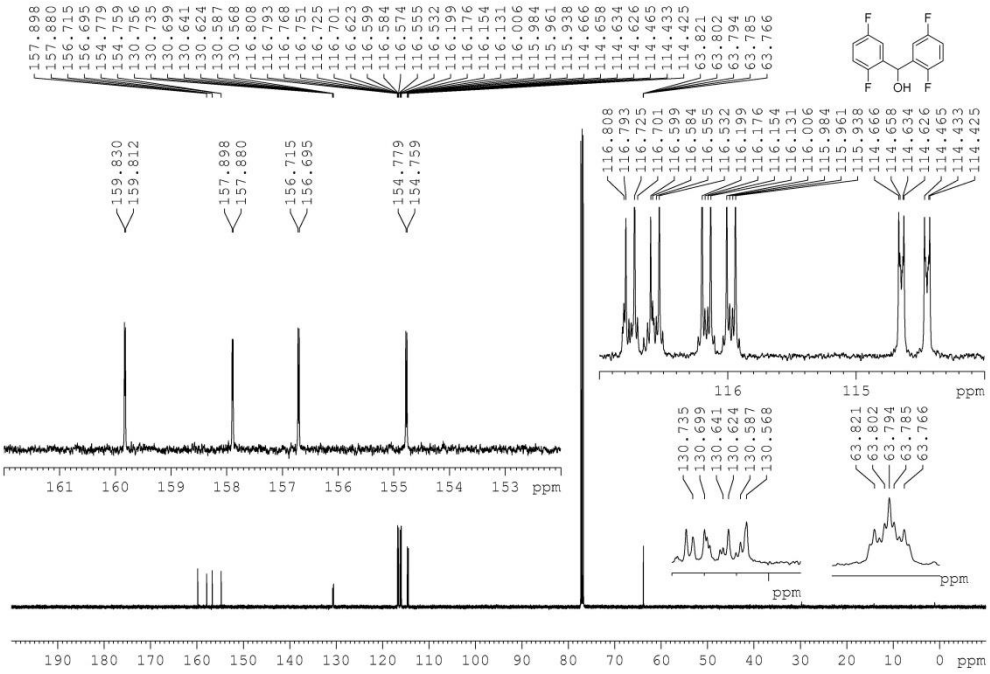
Compound 4-4b: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



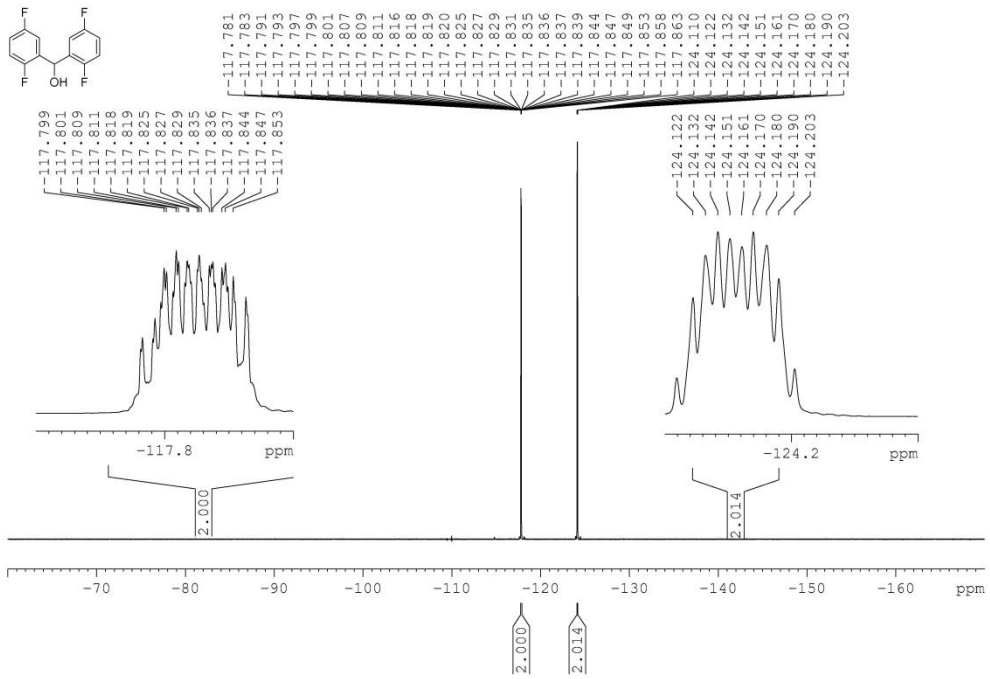
Compound 4-4c: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



Compound 4-4c: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



Compound 4-4c: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



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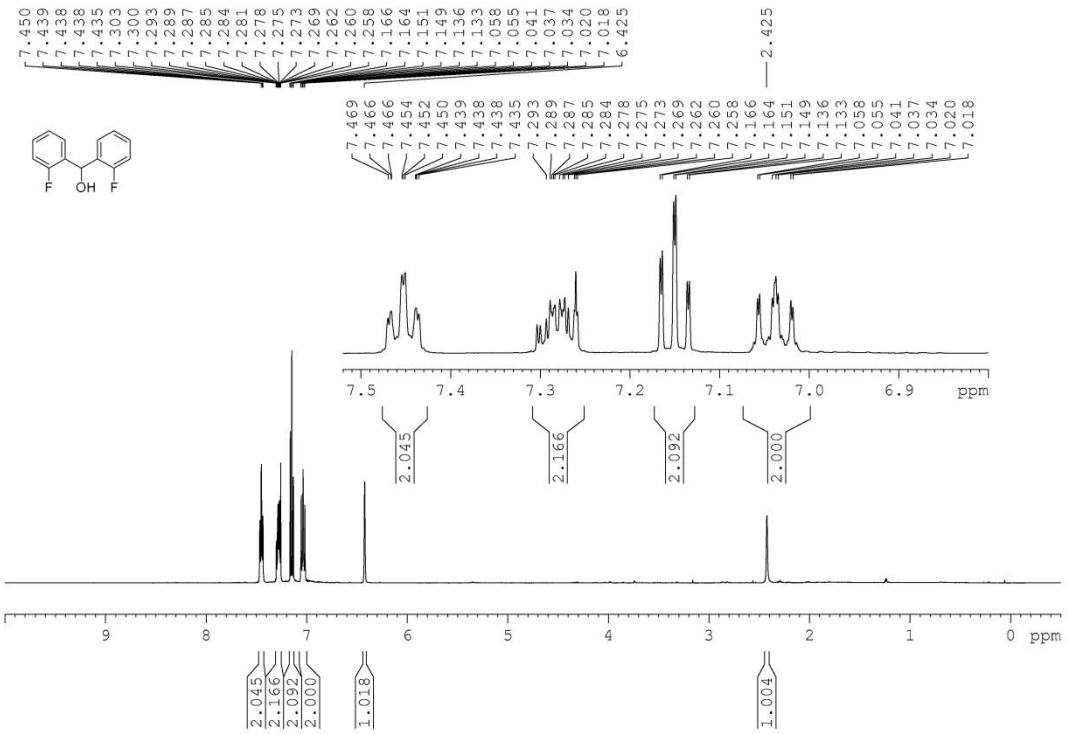
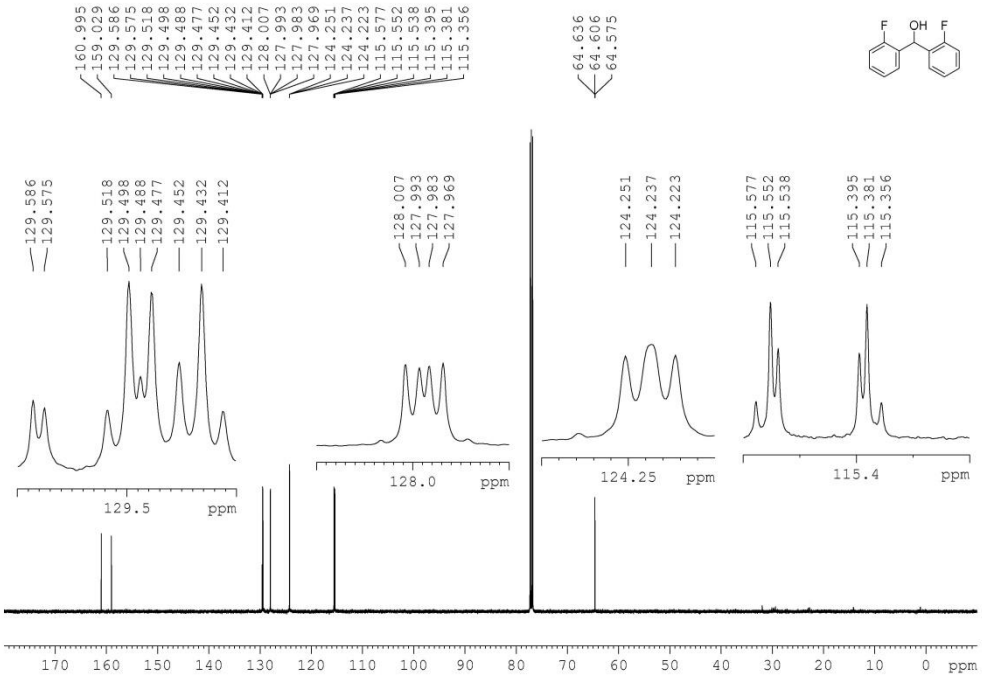
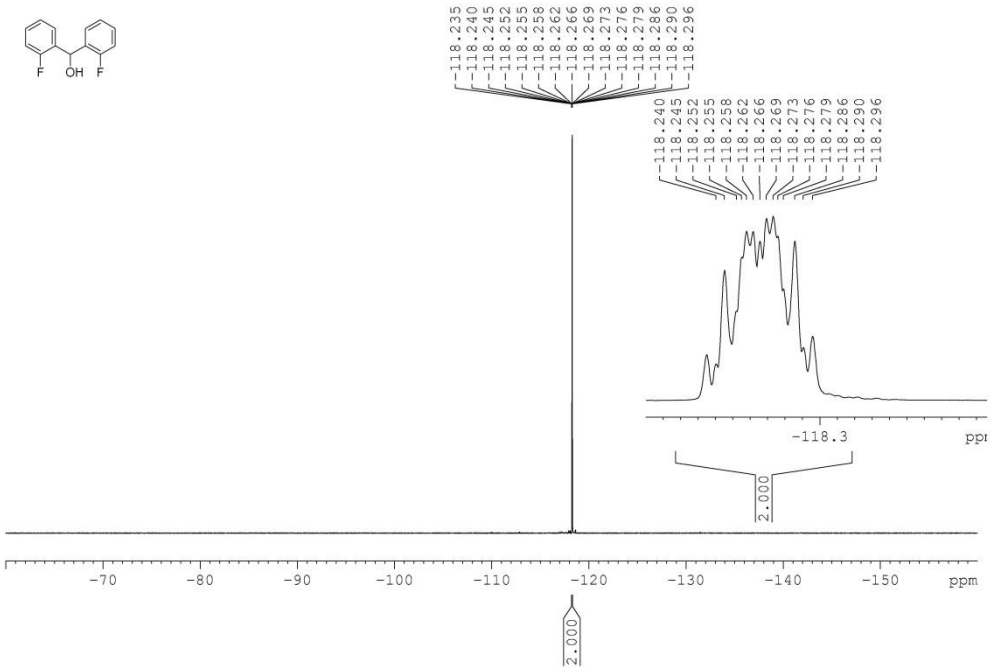


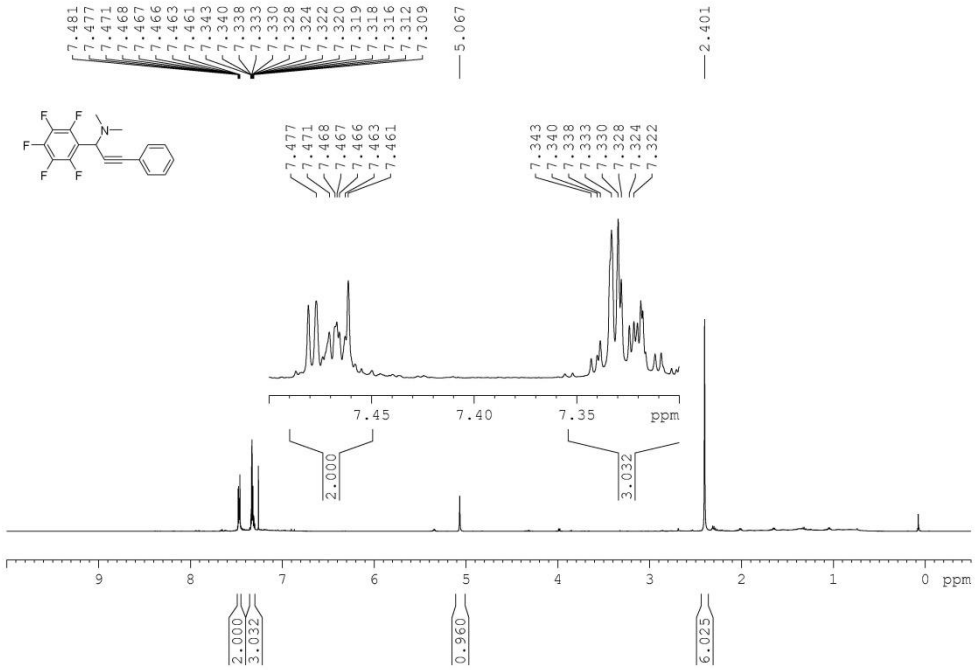
Compound 4-4d: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



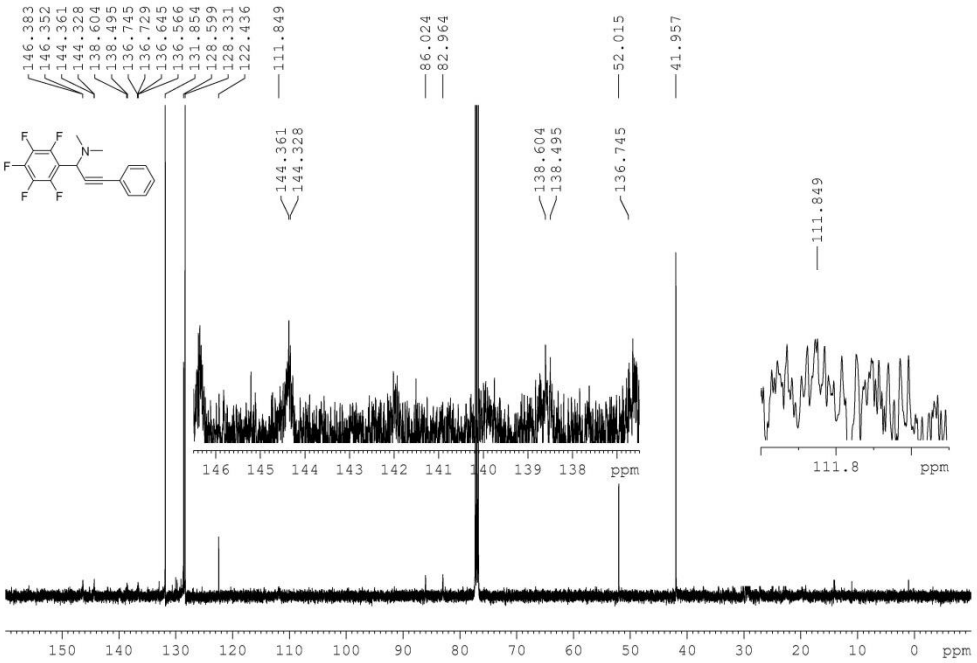
Compound 4-4d: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



Compound 4-6a: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



Compound 4-6a: ^{13}C{^{1}H} NMR spectrum (125 MHz, $CDCl_3$).



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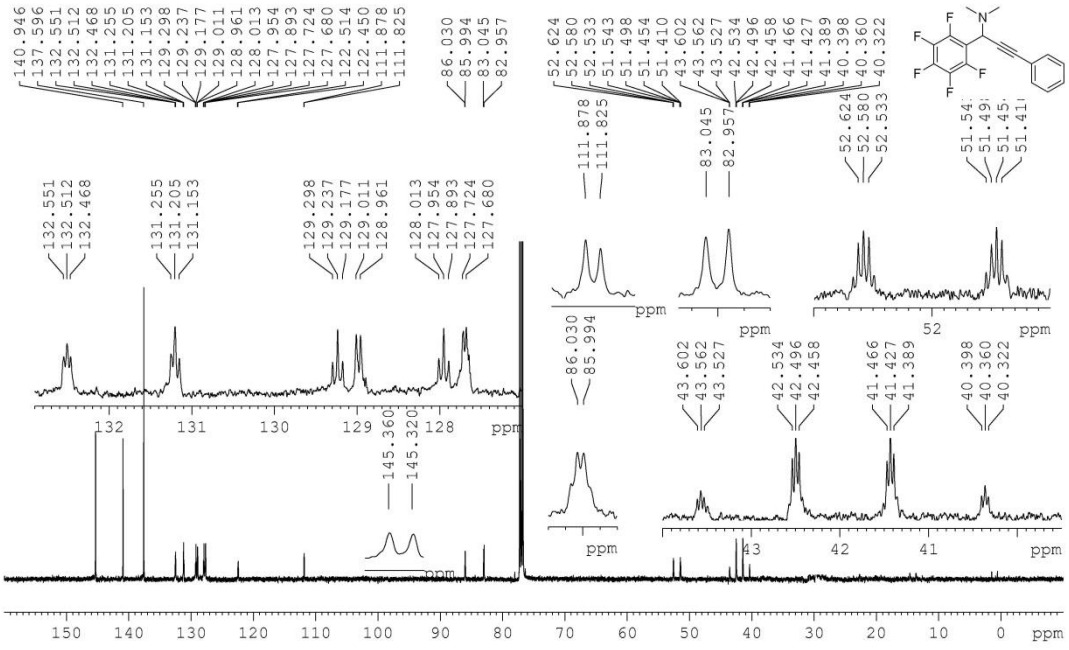
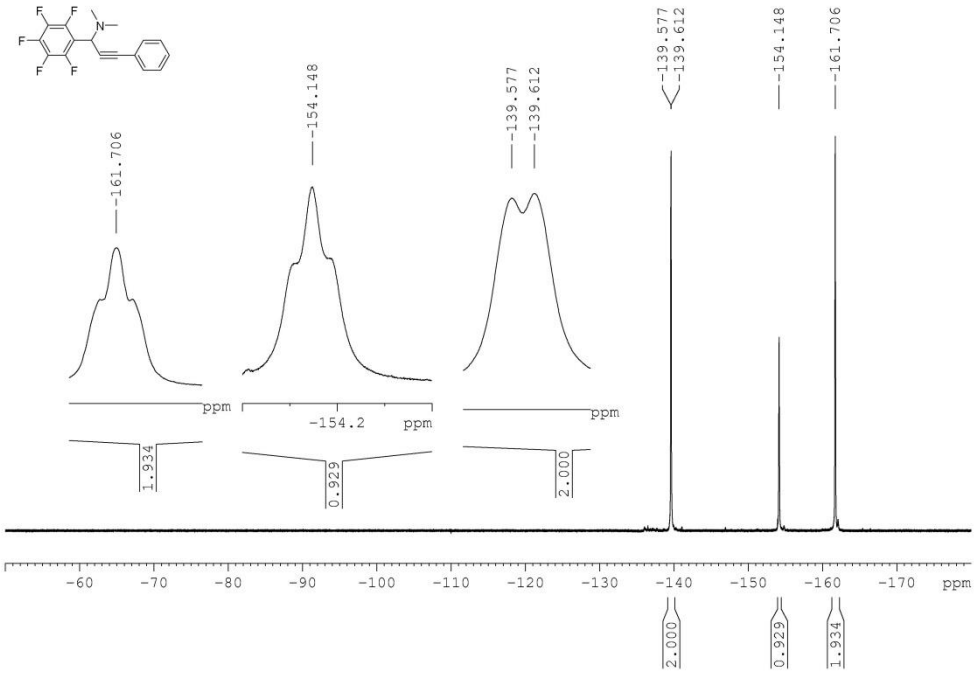
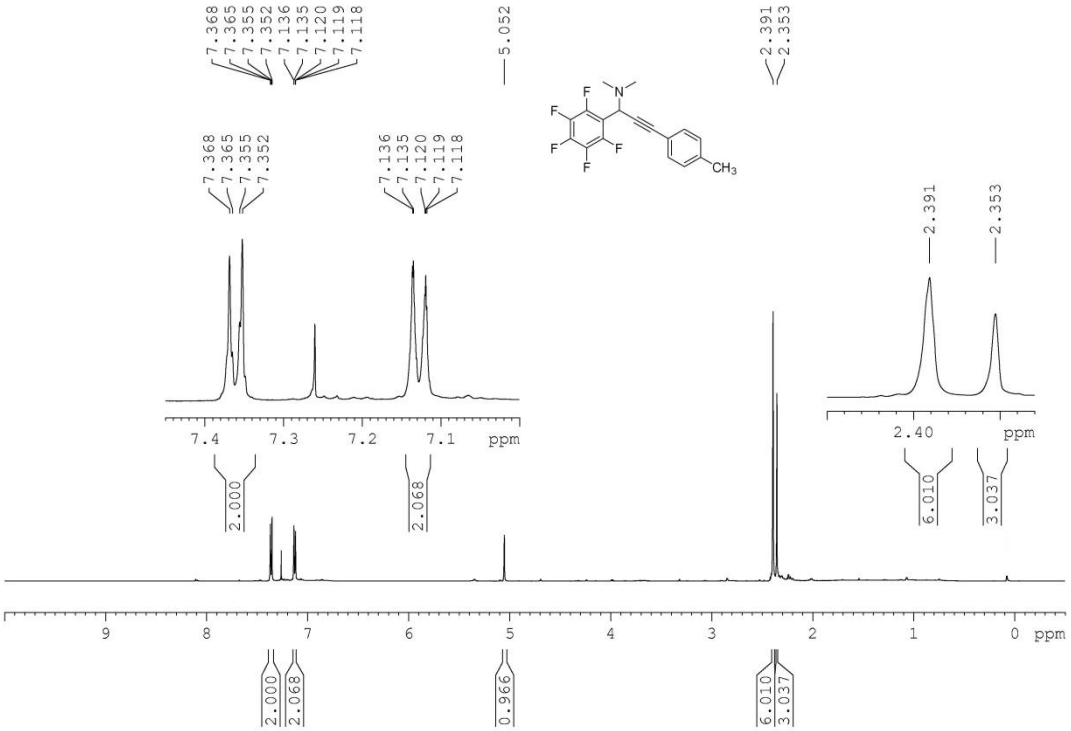


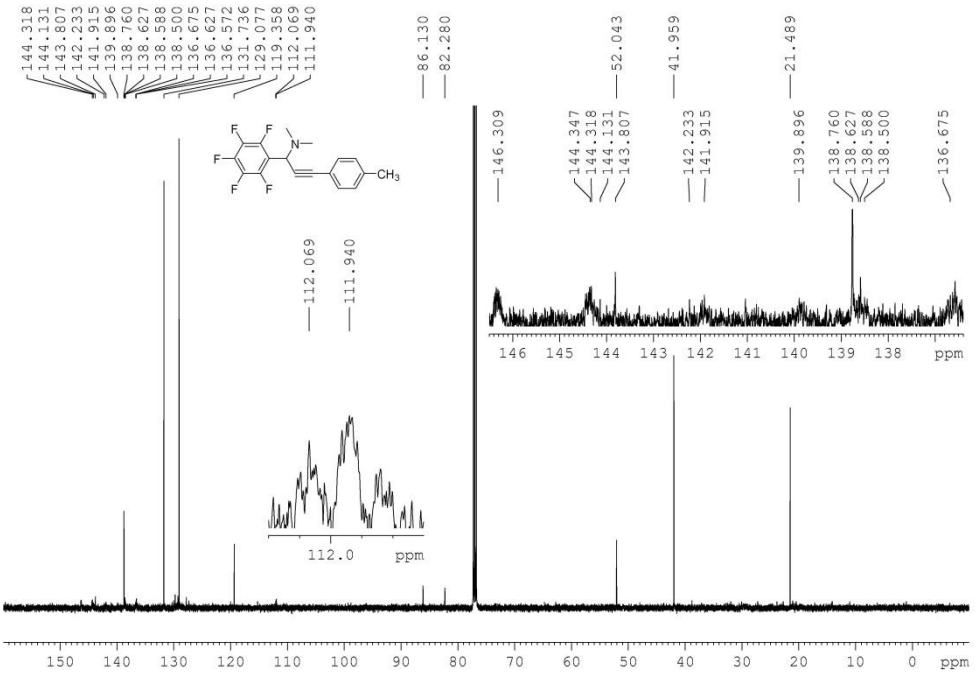
Compound 4-6a: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



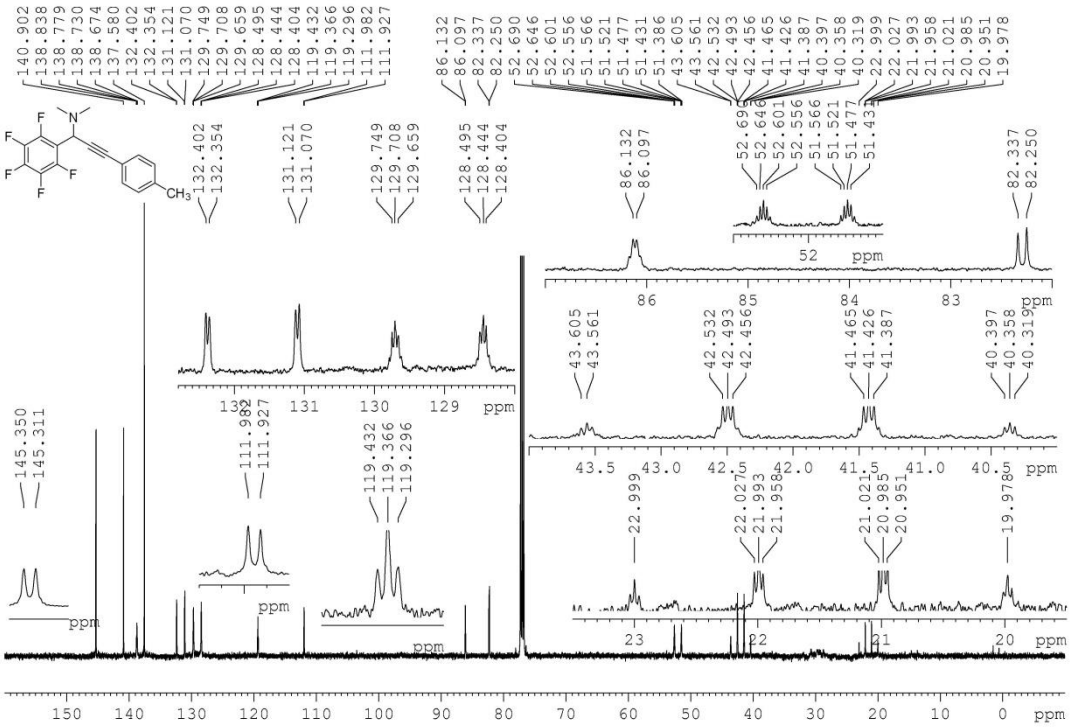
Compound 4-6b: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



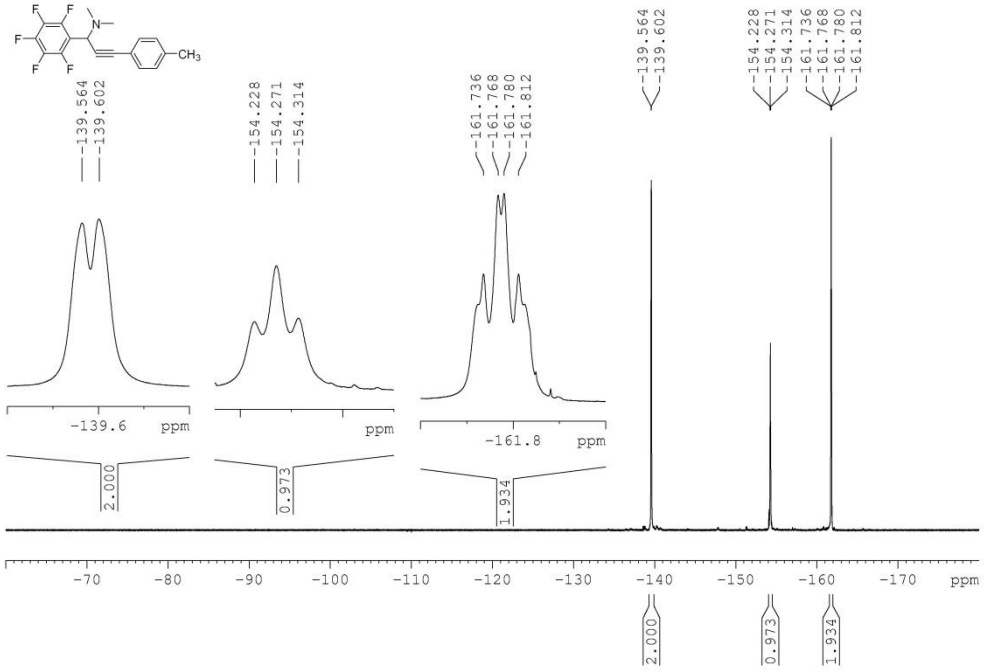
Compound 4-6b: ^{13}C{^{1}H} NMR spectrum (125 MHz, $CDCl_3$).



Compound 4-6b: $^{13}C\{^{19}F\}$ NMR spectrum (125 MHz, $CDCl_3$).



Compound 4-6b: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



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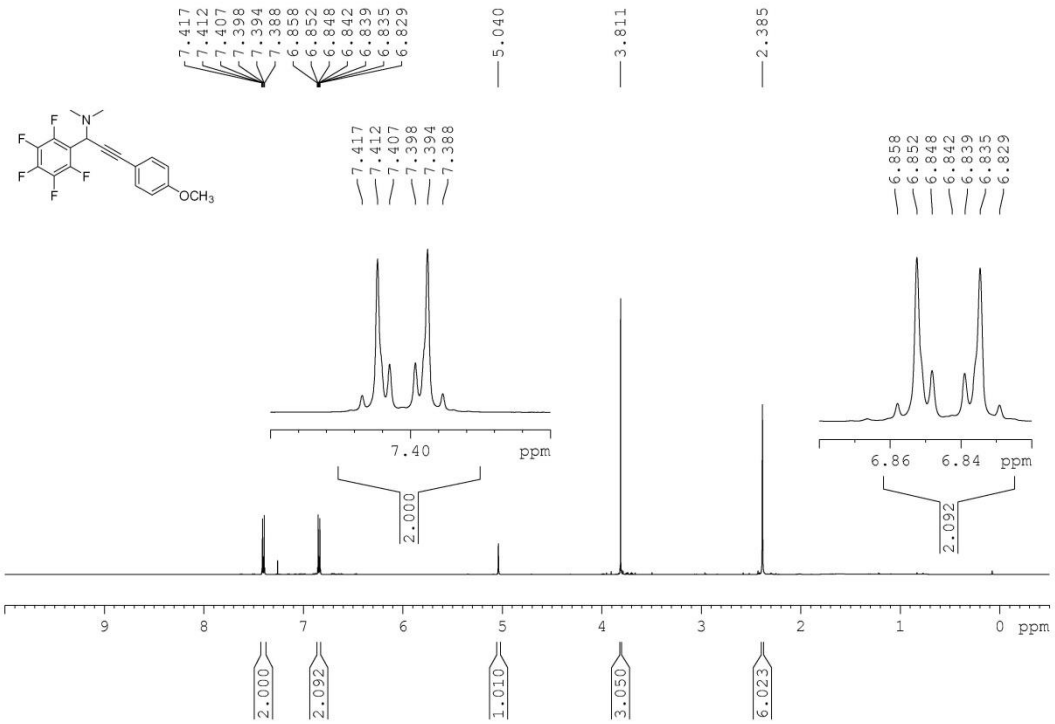
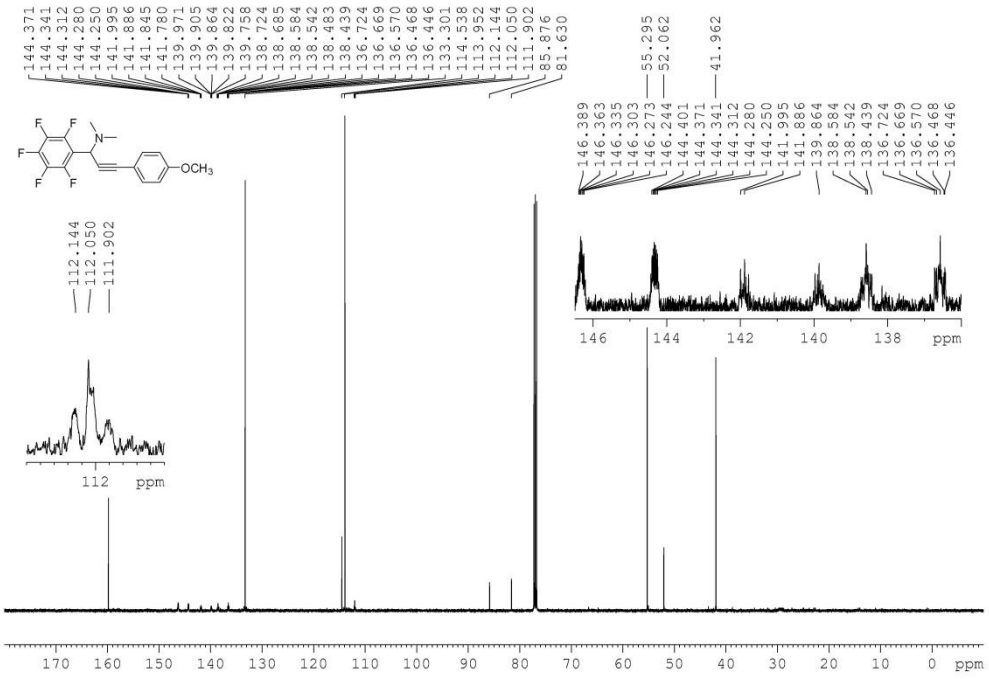
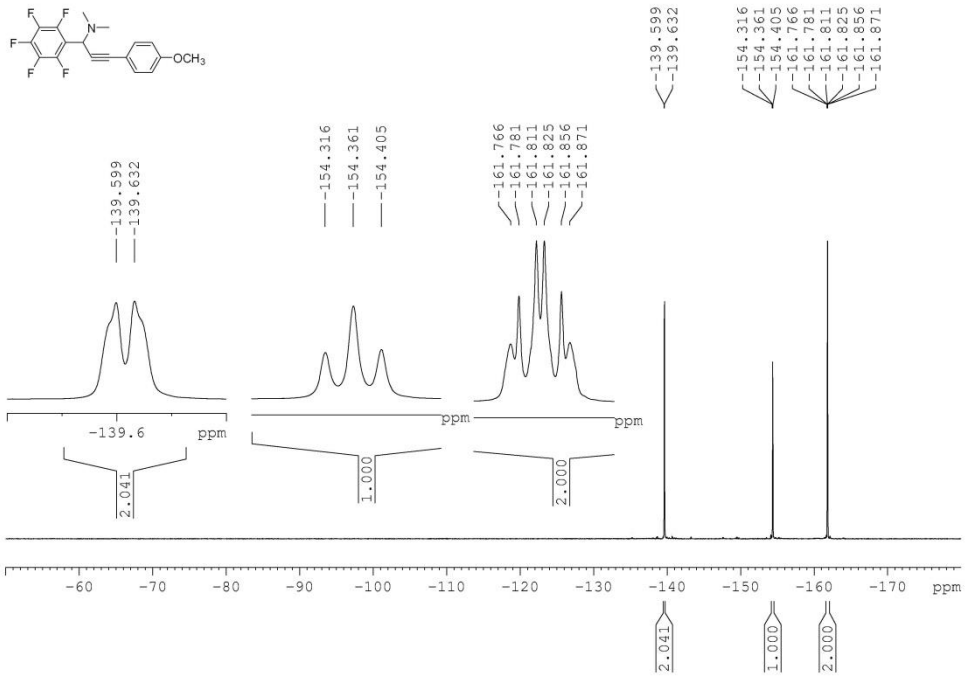


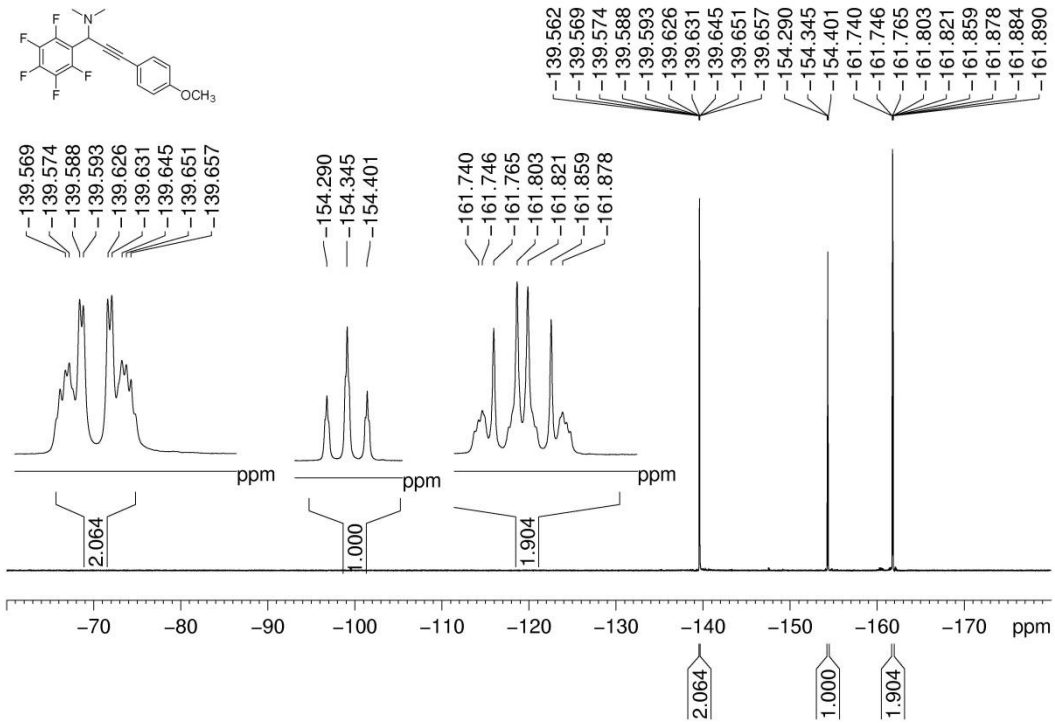
Compound 4-6c: ^{13}C{^{1}H} NMR spectrum (125 MHz, $CDCl_3$).



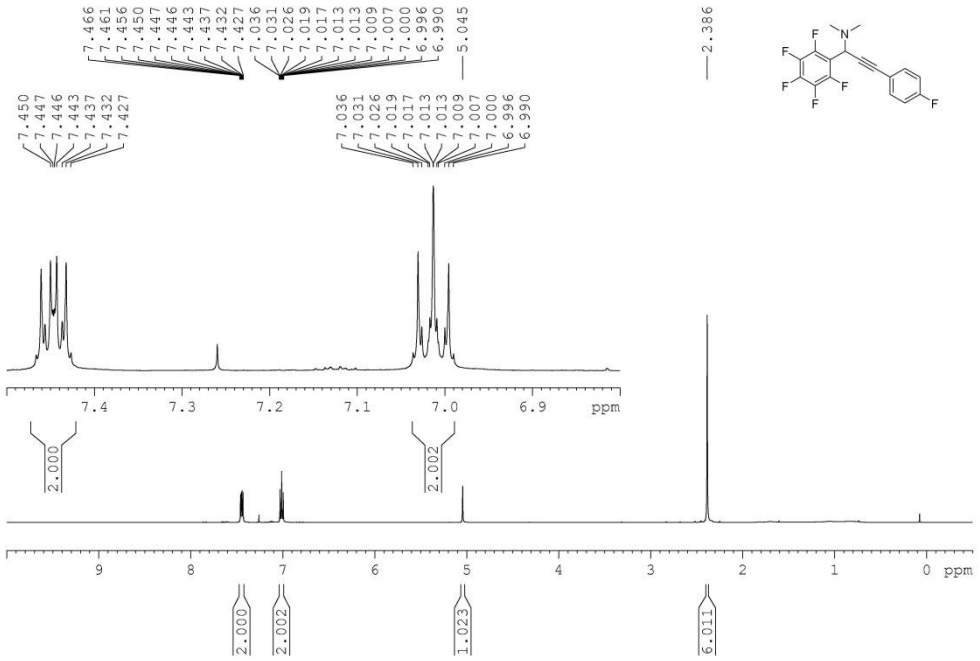
Compound 4-6c: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



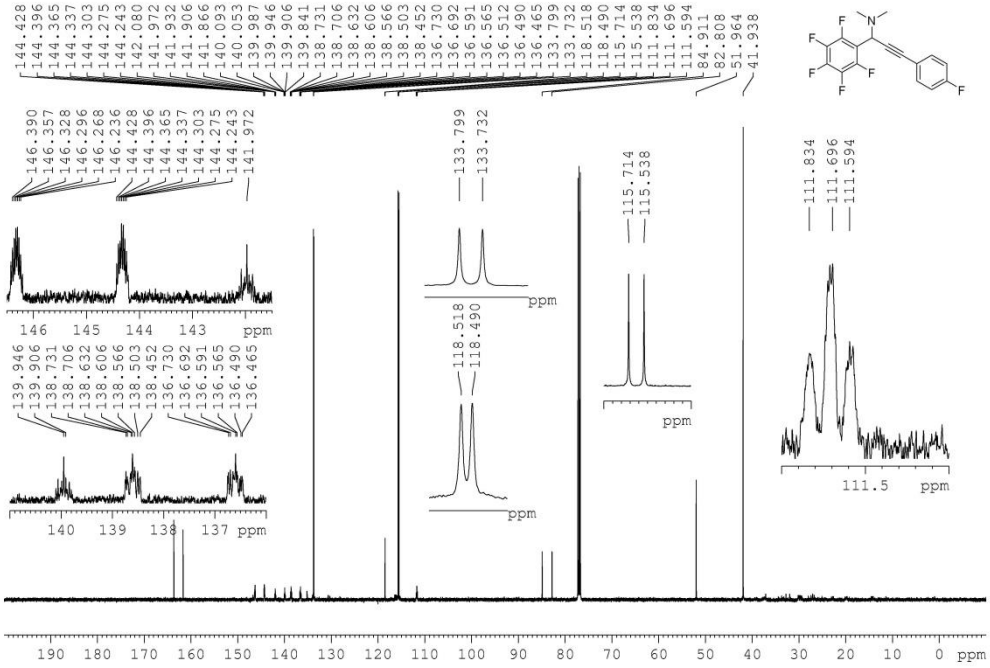
Compound 4-6c: $^{19}F\{^1H\}$ NMR spectrum (376 MHz, $CDCl_3$).



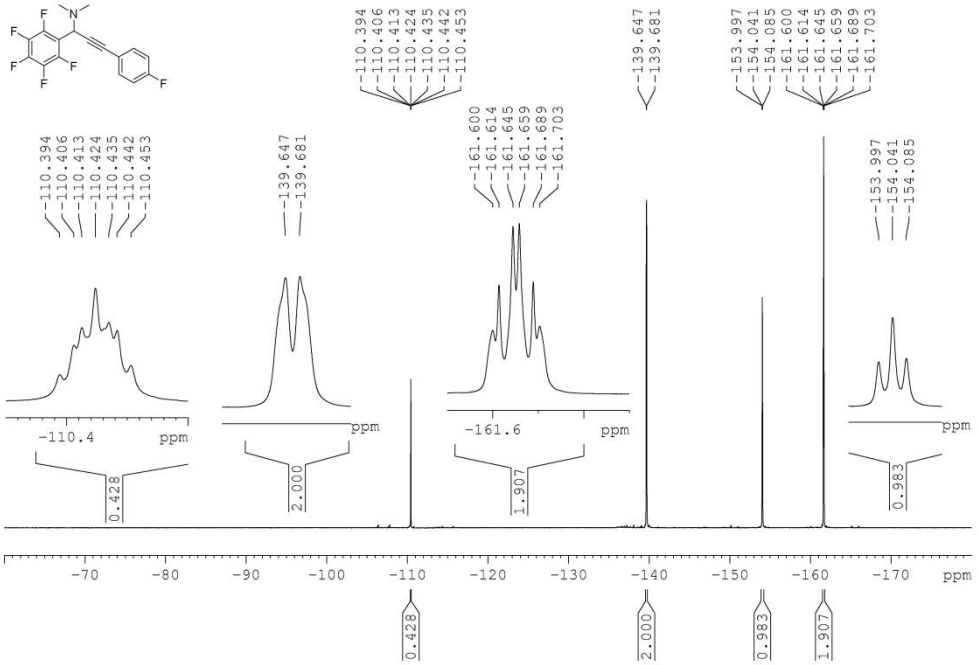
Compound 4-6d: ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



Compound 4-6d: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



Compound 4-6d: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



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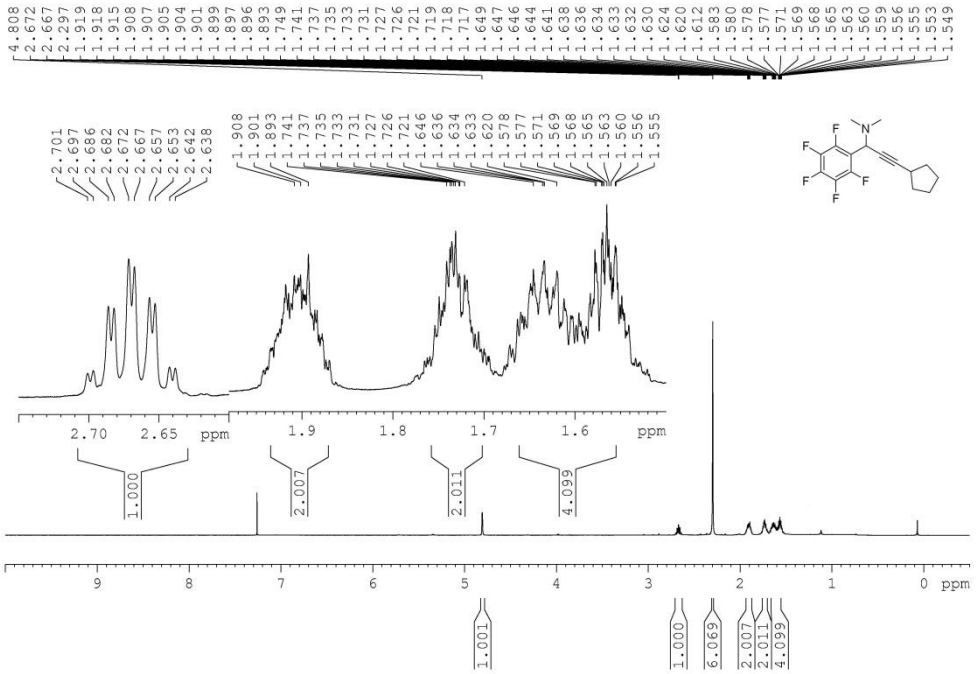
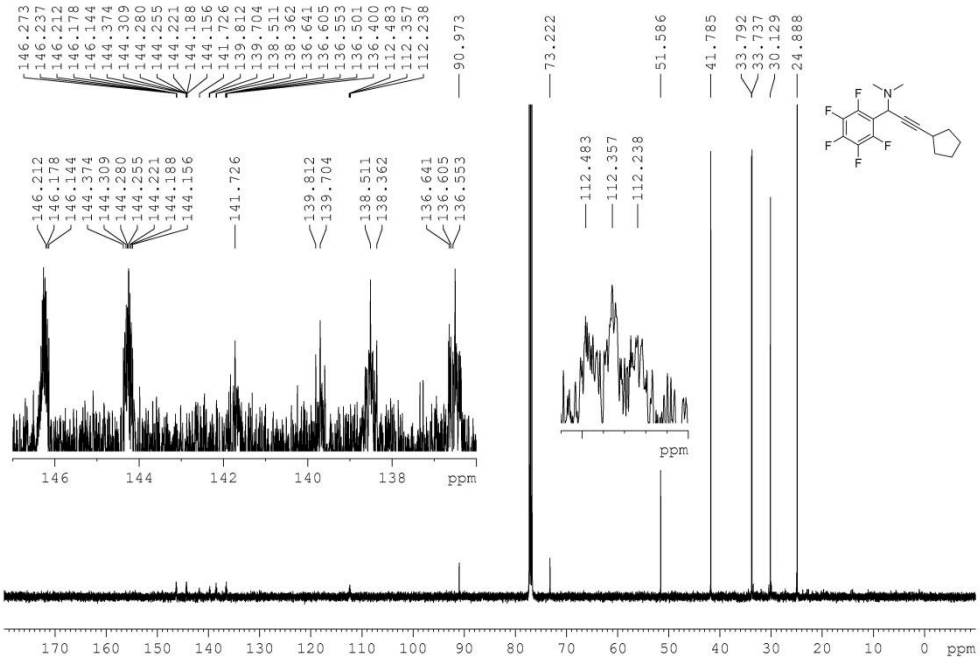
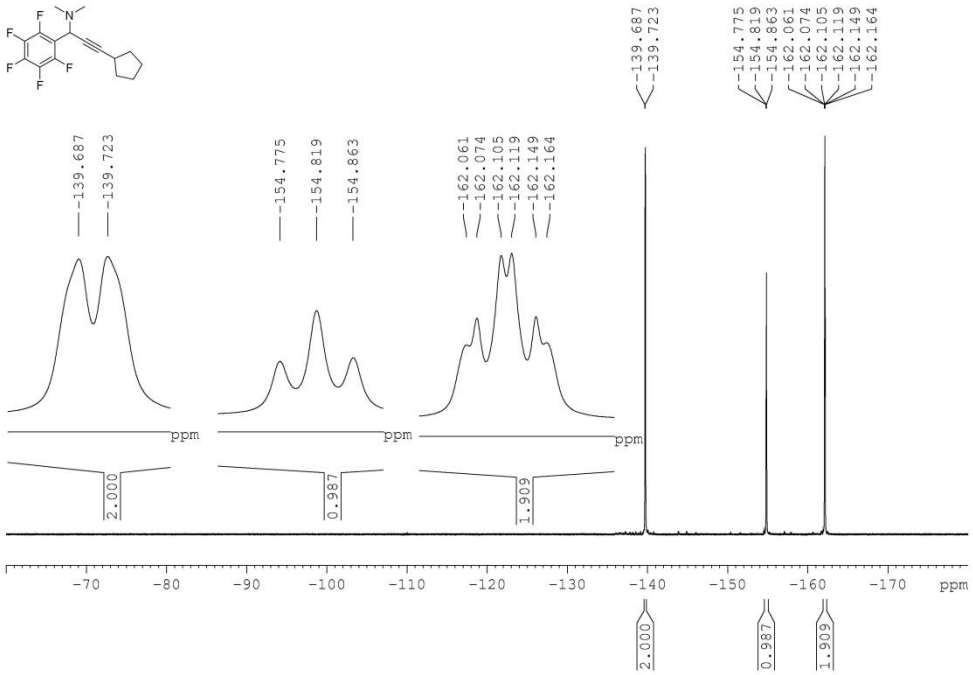


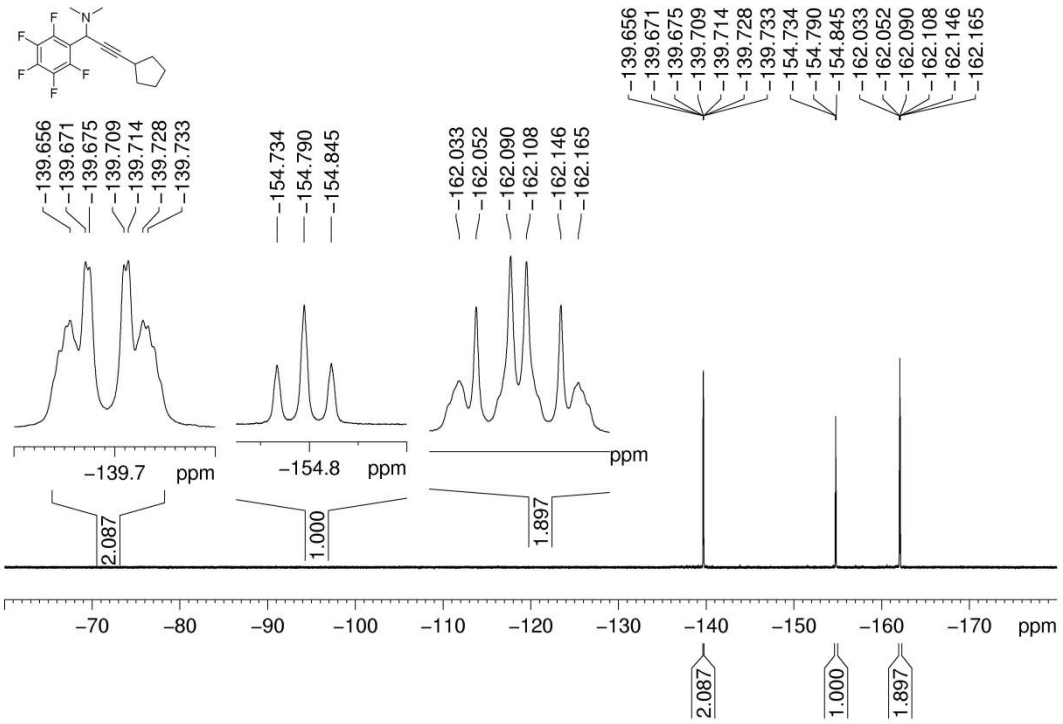
Compound 4-6e: $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, $CDCl_3$).



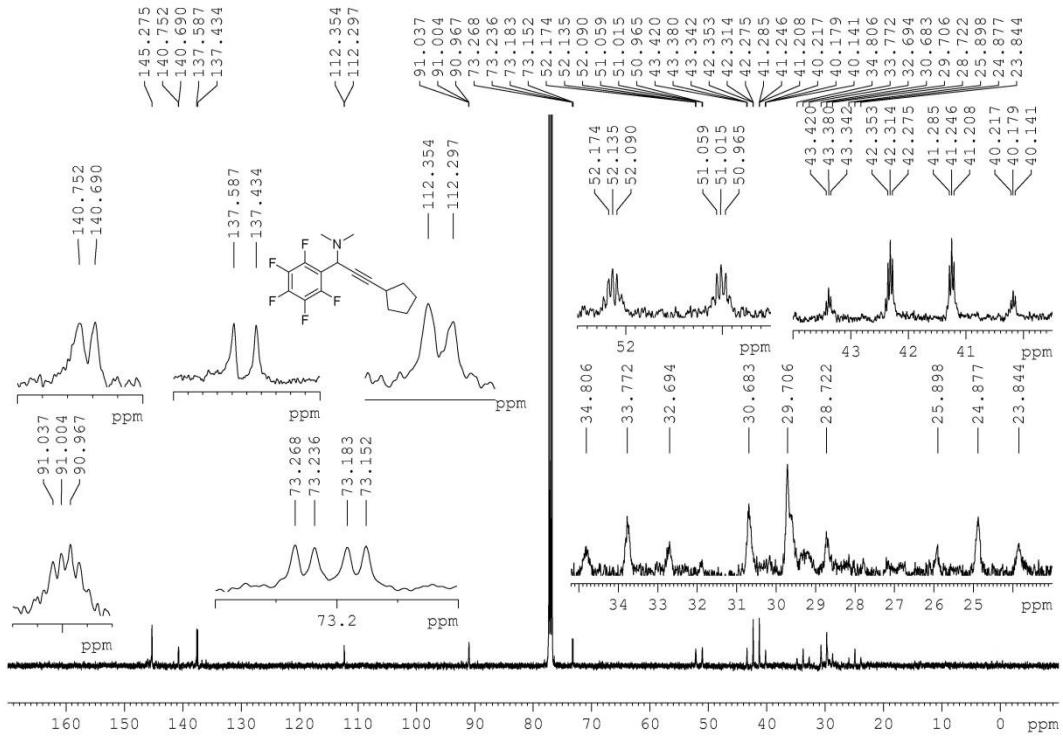
Compound 4-6e: ^{19}F NMR spectrum (470 MHz, $CDCl_3$).



Compound 4-6e: $^{19}F\{^{1}H\}$ NMR spectrum (376 MHz, $CDCl_3$).



Compound 4-6e: $^{13}C\{^{19}F\}$ NMR spectrum (125 MHz, $CDCl_3$).



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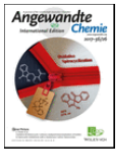
Copper-Catalyzed Oxidative Cross-Coupling of Electron-Deficient Polyfluorophenylboronate Esters with Terminal Alkynes

Author: Zhiqiang Liu, Yudha P. Budiman, Ya-Ming Tian, et al

Publication: Chemistry - A European Journal

Publisher: John Wiley and Sons

Date: Nov 9, 2020



Transition Metal Catalyst-Free, Base-Promoted 1,2-Additions of Polyfluorophenylboronates to Aldehydes and Ketones

Author: Zhiqiang Liu, Goutam Kumar Kole, Yudha P. Budiman, et al

Publication: Angewandte Chemie International Edition

Publisher: John Wiley and Sons

Date: Jun 17, 2021

Affidavit

Affidavit

I hereby confirm that my theses entitled "*Fluorinated Aryl Boronates as Units in Organic*" is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis. Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor similar form.

Würzburg, 30.07.2021

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Signature

Eidesstaatliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation "*Fluorinated Aryl Boronates as Units in Organic*" eigenständig, d.h. insbesondere selbstständig und ohne Hilfe eines kommerziellen Promotionsberaters angefertigt und keinen anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben. Ich erkläre außerdem, dass die Dissertation weder in gleicher noch ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, 30.07.2021

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Unterschrift