NANYANG TECHNOLOGICAL UNIVERSITY

NEW METHODS FOR THE SYNTHESIS OF ORGANOFLUORINE COMPOUNDS

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NEW METHODS FOR THE SYNTHESIS OF ORGANOFLUORINE COMPOUNDS

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
Ar	aryl
calcd	calculated
CH_2Cl_2	dichoromethane
$CDCl_3$	deuterated chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexyl
DCM	dichloromethane
d	doublet
dd	doublet of doublets
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereoselectivity
dt	doublet of triplets
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc or EA	ethyl acetate
FTIR	Fourier Transform Infrared Spectrometry
g	gram
h or hrs	hour(s)
HF	hydrogen fluoride
HRMS	high resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl

m	multiplet
L	ligand
LA	Lewis acid
m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	mass spectrometry
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NMP	1-Methyl-2-pyrrolidinone
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor

rt	room temperature
s	singlet
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
t	triplet
TBAF	tetrabutylammonium fluoride
^{t}Bu	tert-butyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
vol	Volume

SUMMARY

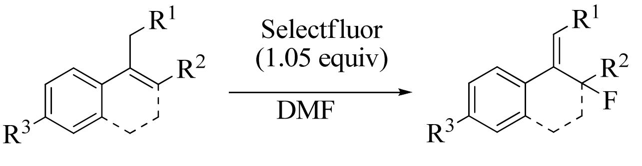
This thesis describes C–F bond formations and polyfluoroarenation reactions, including the direct electrophilic fluorination of olefins, the highly stereocontrolled synthesis of fluorinated 2,6-*trans* dihydropyrans *via* Prins cyclization, and the Pd-catalyzed coupling of polyfluoroarenes and polyfluorobenzoic acids with simple arenesas; providing an efficient entry to fluorobiphenyls.

Chapter 1.

A brief summary of fluorine chemistry and traditional C–F bond formation stragegies is given. Some recent examples of C–F bond formation by using F^+ (electrophilic reagents) and F^- (nucleophilic reagents) are highlighted in this chapter.

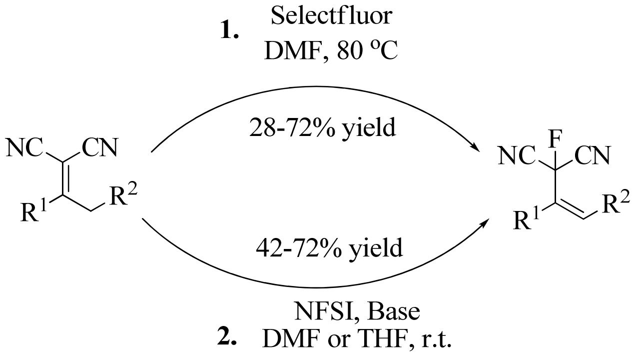
Chapter 2.

Part 1: Aryl allylic fluorides were synthesized in 47-83% yields by using Selectfluor as the electrophilic reagent in DMF. The outcome of this reaction may be rationalized by electronic effects while the reactivity was controlled by the stabilization effect of the aryl group on the benzylic cationic intermediates.



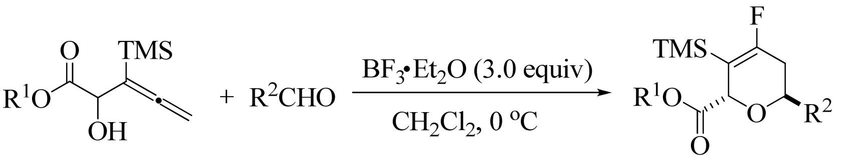
Part 2: Fluorinated dicyanoolefins were synthesized using Selectfluor as the electrophilic reagent in DMF. NFSI can also be used as the electrophilic reagent to afford the same fluorinated dicyanoolefins under basic conditions. These two

methods are complementary to one another.



Chapter 3.

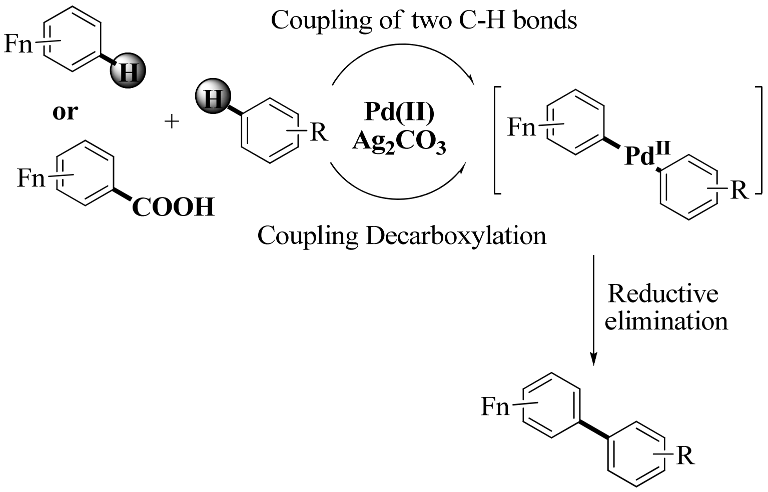
A highly efficient method for the synthesis of fluorinated 2,6-*trans* dihydropyrans *via* BF_3•Et_2O promoted Prins cyclization of allenic alcohols and aldehydes was developed. Various 2,6-*trans* fluorodihydropyrans were obtained in moderate to good yields with excellent diastereoselectivities.



2,6-*trans* dihydropyrans
up to 94:6 dr

Chapter 4.

Using a Pd/Ag bimetallic system, arylation of simple arenes with polyfluoroarenes or polyfluorobenzoic acids had been achieved by C–H/C–H bond functionalization and decarboxylative C–H bond functionalization, respectively. These two processes proceeded through the same intermediate, providing the desired coupling products in moderate to good yields. These two methods are complementary to one aother. These straightforward protocols provide novel and efficient methods for the synthesis of fluorobiphenyls under very mild reaction conditions.

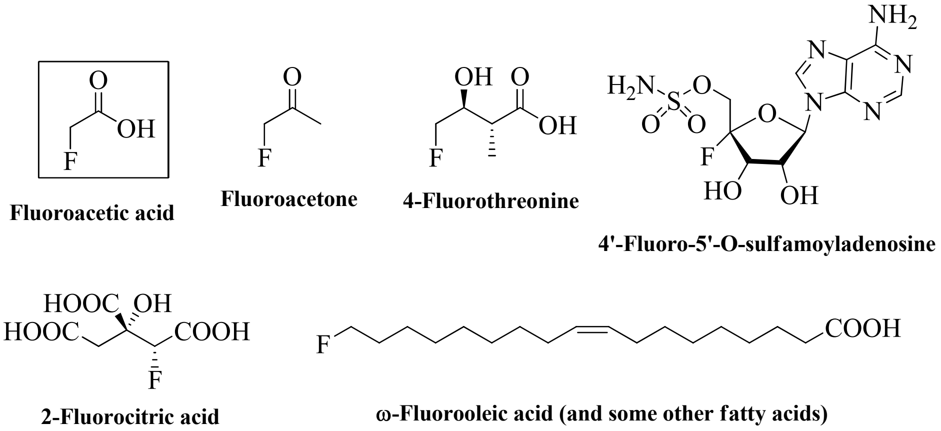

Coupling of two C-H bonds
Fn
H
or
Fn
COOH
+
H
R
Pd(II)
Ag_2CO_3
Fn
Pd^{II}
R
Coupling Decarboxylation
Reductive elimination
Fn
R

CHAPTER 1

Introduction: Fluorine Chemistry and C-F Bond Formation

1.1 Fluorine Chemistry

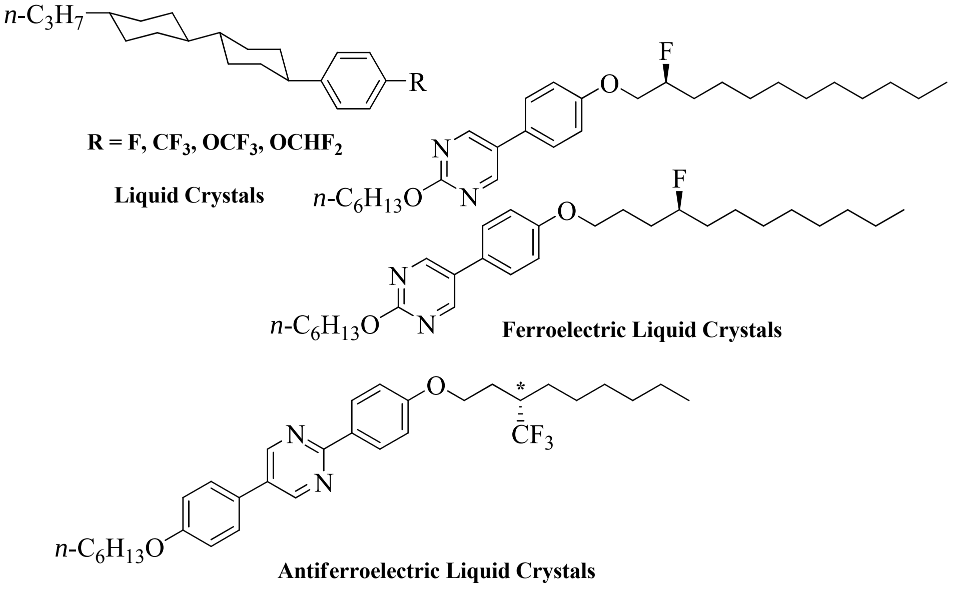
"Small atom with big ego" was the title of the ACS Symposium in San Francisco in 2000, where a number of pertinent scientific and industrial aspects of fluorine-related chemistry were discussed. Fluorine occupies a very special position in the periodic table. Fluorine atom has the highest electronegativity (EN) among all elements. Ionization potential (IP) of fluorin is the highest except for those of helium and neon. Therefore, electrons are drawn strongly toward the fluorine nucleus. For this reason, the electron dipole of fluorine atoms is small, and as a result, fluorine has a small intermolecular van der Waals (vdW) radius of 1.35Å, close to that of hydrogen (1.20Å), and thus mimics hydrogen at an enzyme receptor site with repect to steric requirement. Incorporation of fluorine into organic molecules perturbs the electron density of the compound over several sigma bonds. In contrast to other carbon–halogen bonds, the carbon–fluorine bond is extremely strong, and these have profound



Scheme 1.1 Selected Natural Organofluorine Compounds

effects on the biological activity, metabolism, solubility, hydrophobicity, and bulk properties of organofluorine substances, especially important for drug candidates.[1]

Fluorine mainly exists in nature as inorganic fluorides, such as fluorite (CaF_2), cryolite ($Na_3[AlF_6]$), and phosphorite($Ca_5[F, Cl][PO_4]_3$). There are only twelve known compounds from the resources of naturally occurring fluorinated organic compounds (Scheme 1.1).[2] Among these, fluoroacetic acid is a highly toxic compound. “Gifblaar” is one of the most poisonous plants known because it contains fluoroacetic acid. Biosynthesis of natural organofluorine compounds remains unknown until very recently, where a nucleophilic fluorination process is implicated.



Scheme 1.2 Selected Fluorine-containing Compounds in Material Science

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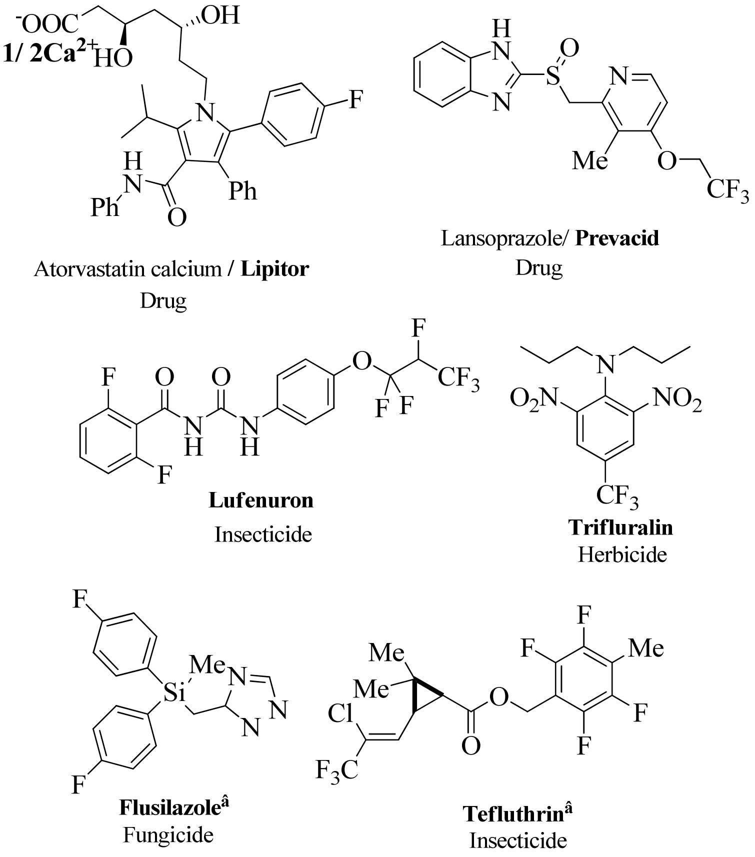
[1] (a) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214; and references therein; (b) For an important early review on the subject, see: Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; (c) Special Issue on “Fluorine in the Life Sciences”, *Chem-BioChem* **2004**, *5*, 557; (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; (e) Hiyama, T. *Organaofluorine Compounds: Chemistry and Applications.* Springer: Berlin, 2000; (f) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* 2004, *104*, 1.

[2] Harper, D.B.; O’Hagan, D. *Nat. Prod. Rep.* **1994**, 123.

Fluorinated organic compounds are widely applied in material science. A great impact on the chemical industry resulted from the discovery of poly(tetrafluoroethene) (PTFE), a highly heat- and chemical-resistant polymer given the tradename Teflon. Recently, many kinds of fluorine-containing organic semiconductors,[3] liquid crystals,[4] ferroelectric liquid crystals[5] and anti ferroelectric liquid crystals[6] were developed which benefited the area of material chemistry (Scheme 1.2).



Atorvastatin calcium / **Lipitor**
Drug

Lansoprazole/ **Prevacid**
Drug

Lufenuron
Insecticide

Trifluralin
Herbicide

Flusilazole$^{\hat{a}}$
Fungicide

Tefluthrin$^{\hat{a}}$
Insecticide

Scheme 1.3 Some Fluorides of Importance in Medicinal Chemistry

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[3] For selected recent reviews, see: (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (c) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066. (d) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003.

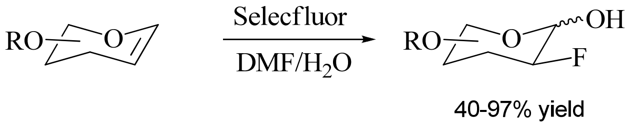
[4] (a) Goto, Y.; Ogawa, T.; Sawada, S, Sugimori, S. *Mol. Cryst. Liq. Cryst.* **1991**, *209*, 1; (b) Inukai, T.; Miyazawa, K. *Ekisho* **1997**, *1*, 9.

[5] (a) Nagashima, Y., Ichihashi, T., Noguchi, K., Iwamoto, M., Aoki, Y., Nohira, H. *Liq. Cryst.* **1997**, *23*, 537.

[6] Aoki, Y.; Nohira, H. *Liq. Cryst.* **1995**, *19*, 15; (b) Aoki, Y.; Nohira, H. *Ferroelectrics* **1996**, *178*, 213.

A very important application of fluorinated organic compounds is in medicinal chemistry. Recently, it has been demonstrated that the introduction of fluorine atom, trifluoromethyl, difluoromethyl, fluoromethyl, or fluorovinyl substituent is highly effective for the discovery of many biologically active compounds such as fluorinated amino acids,[7] anticancer agents,[8] fluorinated Vitamin D,[9] artificial blood substitutes,[10] insecticides,[11] herbicides,[12] fungicide[13] and proposed analogues (Scheme 1.3). Numerous fluorinated compounds with excellent biological activities are commercially available.

In addition, selectively fluorinated carbohydrates serve for modification of the glycoside activites and have many applications in biochemistry and medicinal chemistry. Typical fluorination methods are fluorinating dehydroxylation with diethylaminosulfur trifluoride (DAST). In 1997, Wong *et al.* developed a safe and efficient technique for synthesizing 2-deoxy-2-fluoro sugars and glycosides in one step with the use of Selectfluor (Scheme 1.4).[14]



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[7] (a) Kukhar, V. P.; Resnati, G.; Soloshonok, V. A. *Fluorine - Containing Amino Acids, Synthesis and Properties* John Wiley & Sons: Chichester, 1994; (b) Tolman, V. *Amino Acids* **1996**, *11*, 15.

[8] (a) Santi,. D. V.; Pogolotti, A. L.; Newman, E. M.; Wataya, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier Biomedicinal Press: New York: **1982**; p 123; (b) De Clercq E. *Clinical Microbiology Reviews* **1997**, *10*, 674.

[9] (a) Ohshima, E.; Sai, H.; Takatsuto, S.; Ikekawa, N.; Kobayashi, Y.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3525; (b) Posner, G. H.; Lee, J. K.; Wang, Q.; Peleg, S.; Burke, M.; Brem, H.; Dolan, P.; Kensler, T. W. *J. Med. Chem.* **1998**, *41*, 3008.

[10] (a) Yokoyama, K.; Suyama, T.; Naito, R. In: *Biomedical Aspects of. Fluorine Chemistry* Filler, R., Kobayashi, Y., Eds.; Elsevier: Amsterdam, **1982**; p 191; (b) Clark, L.C.; Gollan, F. *Science* **1966**, *152*, 1755.

[11] (a) Elliott, M.; Farnham, A.; Janes, N.; Needham, R.; Pulman, D.; Stevenson, J. *Nature*, **1973**, *246*, 169. (b) Elliott, M.; Farnham, A.; Janes, N.; Needham, R.; Pulman, D.; Stevenson, J. *Pestic. Sci.* **1975**, *6*, 537.

[12] (a) Fowler, J. S. In: *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications* Filler, R.; Kobayashi, Y.; Yagupolskii, L.M. Eds.; Elsevier: Amsterdam, 1993; p309.

[13] Ikura, K. *Development of New Agrochemicals* CMC: Tokyo, 1997.

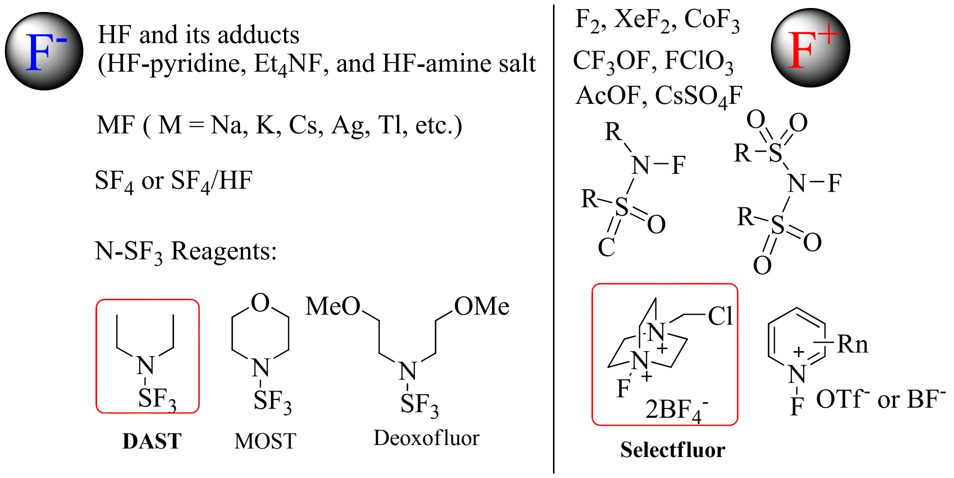
[14] Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743.

Scheme 1.4 Syntheses of Fluoro-Carbohydrates and Glycosides

Thus, development of efficient fluorination methodology is of current interest. Fluorine atom and the fluorine-containing compounds are of important effects on the properties, such as smallest vdV apart from H, largest electronegativity, very stable C-F bond, large lipophilicity, and hydrogen bonding *et al*, which led to remarkable progress in fluorinated materials and bioactive compounds that will play important roles in our daily life throughout the world.

1.2 C–F Bond Fomation

Since they are extremely rare compounds from natural sources, fluorinated compounds are mainly prepared by fluorination of organic compounds. The most basic fluorine sources are from fluorine gas (F_2) and hydrogen fluoride (HF). Starting from them or other sources of the fluoride ion, various kinds of electrophilic (F^+) and nucleophilic fluorinating (F^-) reagents have been synthesized (Seheme 1.5). It is worth to note that DAST and Selectfluor are by far the most commonly used reagents for nucleophilic fluorination and electrophilic fluorinations, respectively.



Scheme 1.5 Electrophilic (F^+) and Nucleophilic Fluorinating (F^-) Reagents

Using these F^+ or F^- reagents, many methods for C–F bond formations were developed, including additions to C=C bonds, C=O bonds, C=N bonds, and alkynes. Direct conversions of C–H, C–OH, C– Halogen, and C–M (M = B, Mg, etc.) bonds to C–F linkages were also reported. In order to enhance the reactivity and selectivity of fluorination, transition metal catalysts such as Pd, Au, and Ag, etc. were used in this field.

1.2.1 Nucleophilic Fluorination

Hydrogen fluoride (HF) is the basic nucleophilic fluorinating reagent. However, as HF is highly corrosive and toxic, special equipments are needed. In order to use HF conveniently, many easy to handle and less toxic HF-derived reagents such as HF/amine, and HF/pyridine have been invented. In addition, these reagents are more nucleophilic than HF.

HF and HF/amine reagents can easily undergo addition reaction to olefins,[15] selective fluorine subsitution reaction with organohalides,[16] secondary or tertiary alcohols,[17] and ring-opening reaction with oxiranes and aziridines.[18]

DAST is the most commonly used reagent for the dehydroxyfluorination of alcohols, difluorination of aldehydes, esters, ketones, epoxides, and sulfides etc. (Scheme 1.6).[19]

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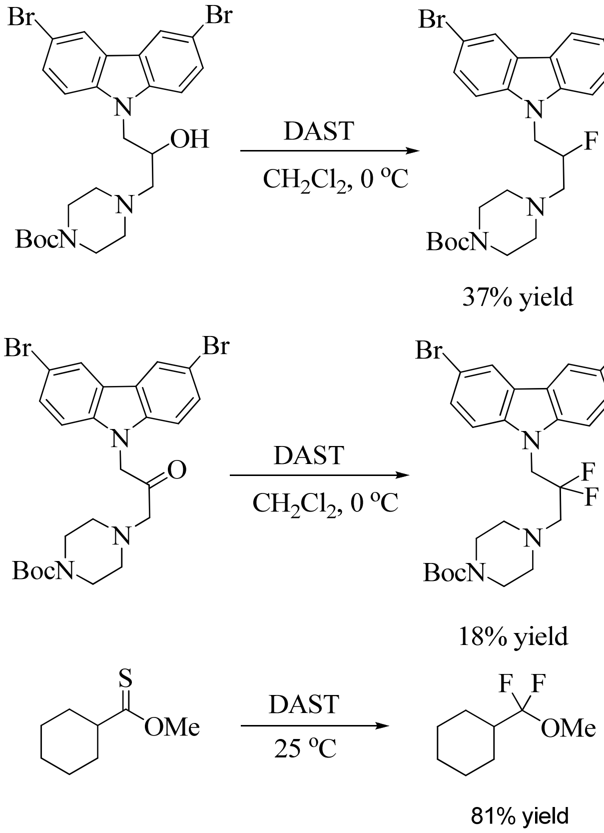
[15] (a) Yoneda, N.; Abe, T.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* **1983**, 1135; (b) Yoneda, N.; Nagata, S.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* **1984**, 1241.

[16] (a) Fukuhara, T.; Yoneda, N. *Chem. Lett.* **1993**, 509; (b) Tarrant, P.; Atlaway, J.; Lovelace, A. M. *J. Am. Chem. Soc.* **1954**, *76*, 2343.

[17] Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747.

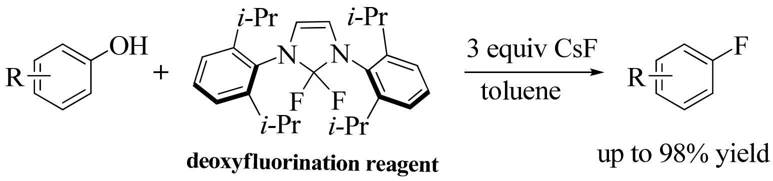
[18] (a) Muehlbacher, M.; and Poulter, C.D. *J. Org. Chem. 1988*, *53*, 1026; (b) Nohira, H.; Nakamura, S.; and Kamei, M. *Mol. Cryst. Liq. Cryst.* **1990**, *180B*, 379; (c) Wade, T. N.; Gaymard, F.; and Guedj, R. *Tetrahedron Lett.* **1979**, 2681.

[19] (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574; (b) Hudlicky, M. *Org. React.* **1988**, *35*, 513. (c) Bombrun, A. et al. *J. Med. Chem.* **2003**, *46*, 4365; (d) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063; (e) Bunnelle, W. H.; McKinnis B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768.



Scheme 1.6 Nucleophilic Fluorination by DAST

For low yields of the dehydroxyfluorination of phenols using DAST, Ritter and co-workers developed a practical dehydroxyfluorination of phenols that can be used conveniently from milligram to multigram scale using a new deoxyfluorination reagent (Scheme 1.7).[20]



Scheme 1.7 Nucleophilic Dehydroxyfluorination of Phenols

Recently, some methods were developed to perform fluorinations using fluoride reagents such as CsF, AgF, BF_3-Et_2O, and $Bu_4N^+F^-$(TBAF). Compared with the fluorinating reagents mentioned above, these fluoride reagents are much less expensive, less toxic, stable, and easy to handle.

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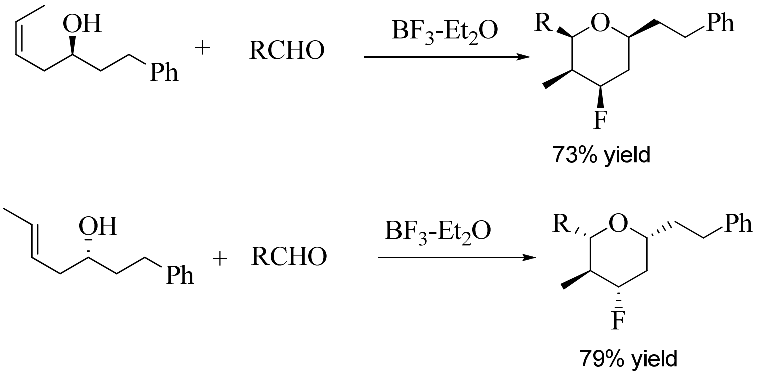
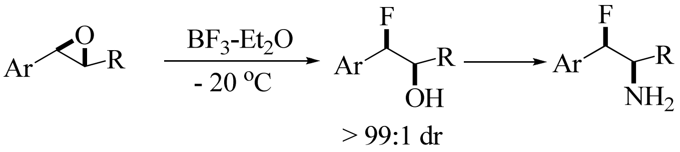
[20] Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

In 2006, using BF_3-Et_2O both as Lewis acid and fluoride source, Nokami *et al.* reported the synthesis of 2,6-*cis* fluorinated THP derivatives *via* Prins cyclization reaction (Scheme 1.8),[21] which are very useful intermediates in the further synthesis of fluorine containing bioactive compounds.



Scheme 1.8 Synthesis of 2,6-*cis* Fluorinated THP Derivatives *via* Prins Cyclization Reaction

In 2010, Davies group also used BF_3-Et_2O as Lewis acid and fluoride source for the stereoselective S_N1-type epoxide ring-opening hydrofluorination of a range of substituted aryl epoxides.[22] The *syn*- fluorohydrin products of these reactions are useful for the preparation of a range of β-fluoroamphetamines (Scheme 1.9).



Scheme 1.9 Fluoroamphetamines *via* the Stereoselective Synthesis of Benzylic Fluorides

Anhydrous tetrabutylammonium fluoride ($TBAF_{anh}$) is a soluble, highly nucleophilic fluoride-ion source.[23] In 2006, DiMagno et al. reported the room-

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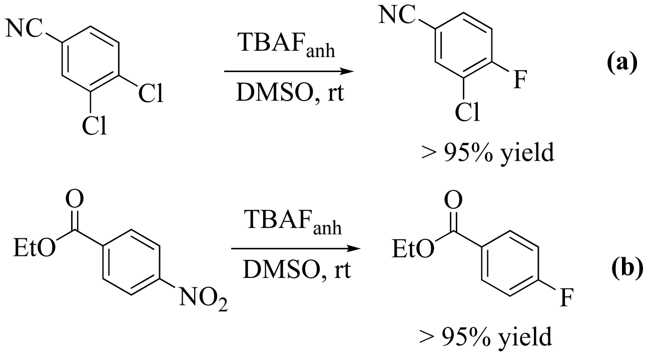
[21] (a) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471.

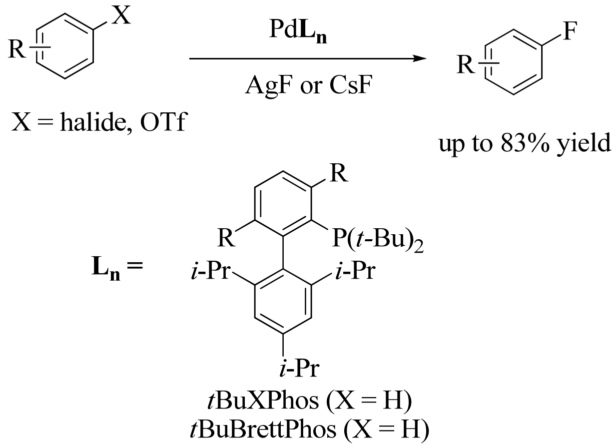
[22] Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte M. J. *Org. Lett.* **2010**, *12*, 2936.

[23] Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

temperature nucleophilic aromatic Halex and fluorodenitration reactions using $TBAF_{anh}$ (Scheme 1.10a).[24] In addition, tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride, TBAF(*t*BuOH)$_4$ is also a good nucleophilic reagent for the facile fluorination of mesylate, which was reported (Scheme 1.10b).[25]



Scheme 1.10 Nucleophilic Aromatic Halex and Fluorodenitration Reactions Using $TBAF_{anh}$



Scheme 1.11 Pd-catalyzed Conversion of Aryl triflates and Aryl Halides to Aryl Fluorides

Besides these simple fluorinating reagents, transition metal catalysts were also used to develop nucleophilic fluorinations. In 2009, Buchwald and

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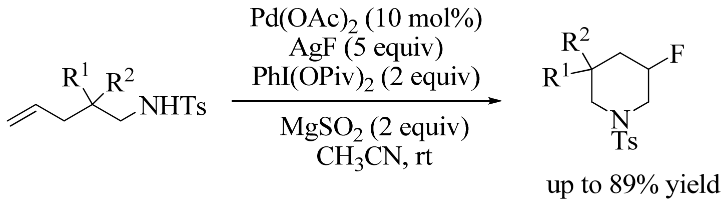
[24] Sun, H.; DiMagno, S. G. *Angew. Chem. Int. Ed.* **2006**, *47*, 2720.
[25] Kim, D. W.; Jeong, H. -J.; Lim, S. T.; Sohn, M.- H. *Angew. Chem. Int. Ed.* **2008**, *47*, 8404.

co-workers reported the Pd-catalyzed conversion of aryl triflates and aryl halides to aryl fluorides using AgF or CsF as the fluorine sources (Scheme 1.11).[26]

Also using Pd as catalyst and AgF as the fluorine source, Liu *et al.* reported a highly regioselective catalytic intramolecular oxidative aminofluorination of unactivated alkenes in 2009 (Scheme 1.12).[27]



Scheme 1.12 Pd-Catalyzed Intramolecular Aminofluorination of Unactivated Alkenes

1.2.2 Electrophilic Fluorination

Fluorine gas is the basic electrophilic fluorinating reagent, so it was used for the selective fluorination at the tertiary carbon, synthesis of α-fluoro carbonyl compounds, and addition to alkenes.

Although fluorine gas is very reactive, it is a very dangerous reagent because it is extremely toxic and corrosive and reacts explosively with organic compounds. So a variety of N-F electrophilic fluorinating reagents were invented and some are even commercially available.

Organometallics were also used to perform fluorination for the synthesis of aryl fluorides. The electrophilic fluorination of aryl lithium or aryl Grignard reagents can afford aryl fluorides.[28] Very recently, Knochel[29] and Beller[30] both developed a general and convenient protocol for the electrophilic fluorination of

---

[26] Watson, D. A. ; Su, M. ; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

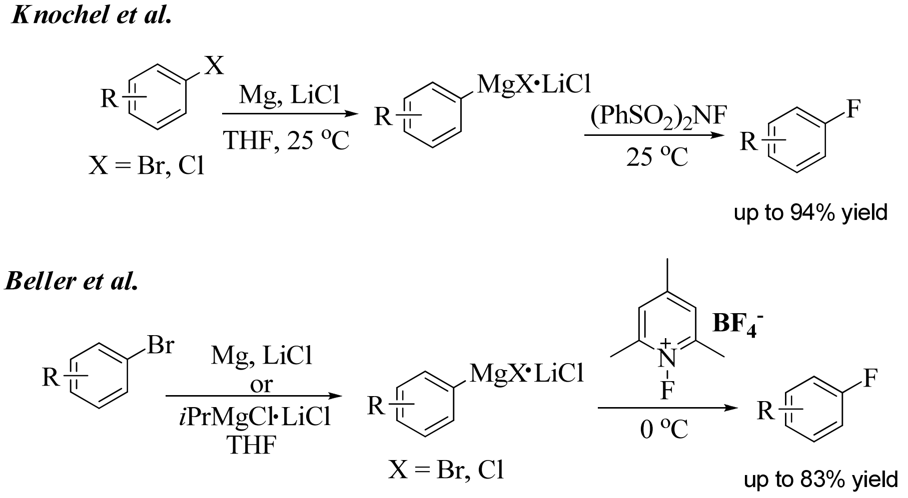
[27] Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.

[28] (a) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730; A review: (b) Baudoux, X; Cahard, *Org. React.* **2007**, *69*, 347.

[29] Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 2215.

[30] Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2219.

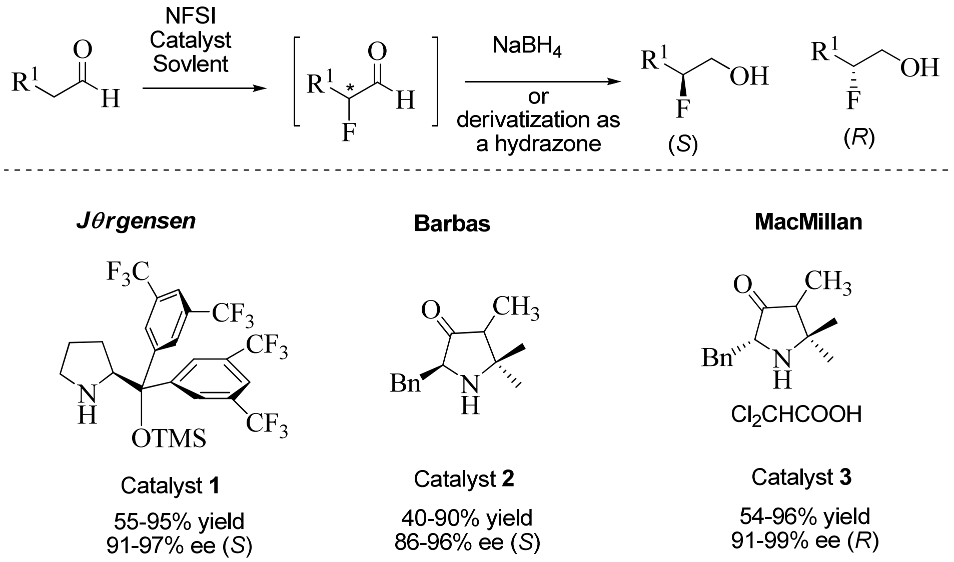
aryl and heteroaryl Grignard reagents (Scheme 1.13).


Knochel et al.

Beller et al.

Scheme 1.13 Convenient Electrophilic Fluorination of Functionalized Aryl and Heteroaryl Magnesium Reagents

In 2008, Ritter's group developed several electrophilic fluorination methods such as palladium-mediated fluorination of arylboronic acids,[31] silver (I) Triflate mediated fluorination of boronic acids,[32] and functionalized aryl stannanes.[33]



Catalyst **1**
55-95% yield
91-97% ee (*S*)

Catalyst **2**
40-90% yield
86-96% ee (*S*)

Catalyst **3**
54-96% yield
91-99% ee (*R*)

Scheme 1.14 Enantioselective Fluorination of Aldehydes

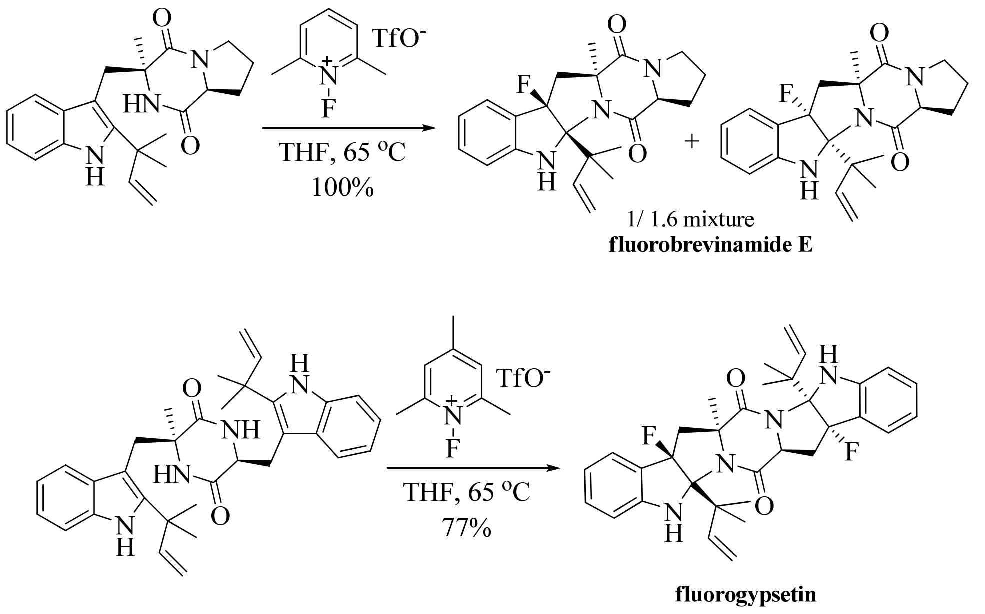
---

[31] (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060; (b) Furuya, T.; Martin, K.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

[32] Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *130*, 2860.

[33] Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *130*, 1662.

Since carbonyl compounds are readily enolized, electrophilic fluorination has proven to be an effective method for the synthesis of α-fluoro carbonyl compounds, especially for enantioselective fluorination (Scheme 1.14).[34] In 2005, Jøgensen, Barbas, and MacMillan groups each described independently highly enantioselective variants of organocatalytic α-fluorinations of aldehydes by using a variety of secondary amines or amine salts as catalysts.[35] The latest example was reported by MacMillan and co-workers in this year, where using primary amine as catalyst and NFSI as electrophilic fluorine reagent, they accomplished a highly enantioselective α-fluorination of ketone.[36]



fluorobrevinamide E

fluorogypsetin

Scheme 1.15 Novel Electrophilic Fluorination-Cyclization

In 2001, Shibata and co-workers reported an elegant route for the synthesis of fluorobrevinamide E and fluorogypsetin by a novel tandem electrophilic fluorination-cyclization, though the diastereoselectivity was poor

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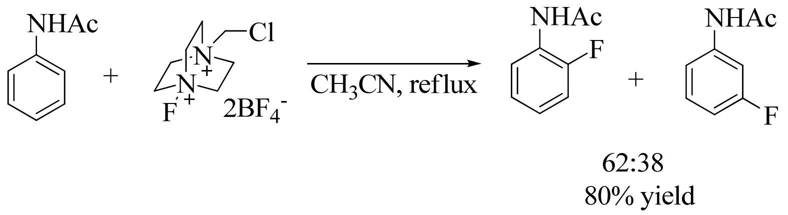
[34] Ma, J. A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1-PR43.

[35] (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703; (b) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706; (c) Beeson, T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

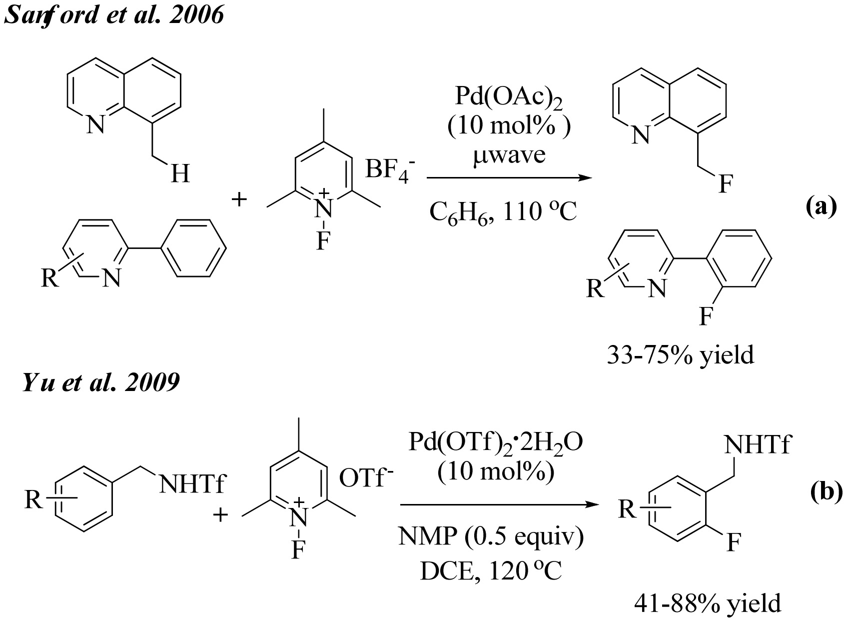
[36] Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *127*, 1738.

(Scheme 1.15).[37]



Scheme 1.16 Direct Fluorination of Acetanilide

Carbon-hydrogen bond can also be directly fluorinated to generate C–F bond. In 1992, using Selecfluor as the electrophilic reagent, Banks and co-workers reported the direct fluorination of electron-rich substrates such as acetanilides under mild conditions (Scheme 1.16).[38]



Scheme 1.17 Pd-Catalyzed C–F bond Construction *via* C–H Activation

Transition metal catalyzed methods for C–F bond construction *via* C–H activation is of current interest. In 2006, Sanford and co-workers described the first example of a Pd(OAc)$_2$-catalyzed electrophilic fluorination for the

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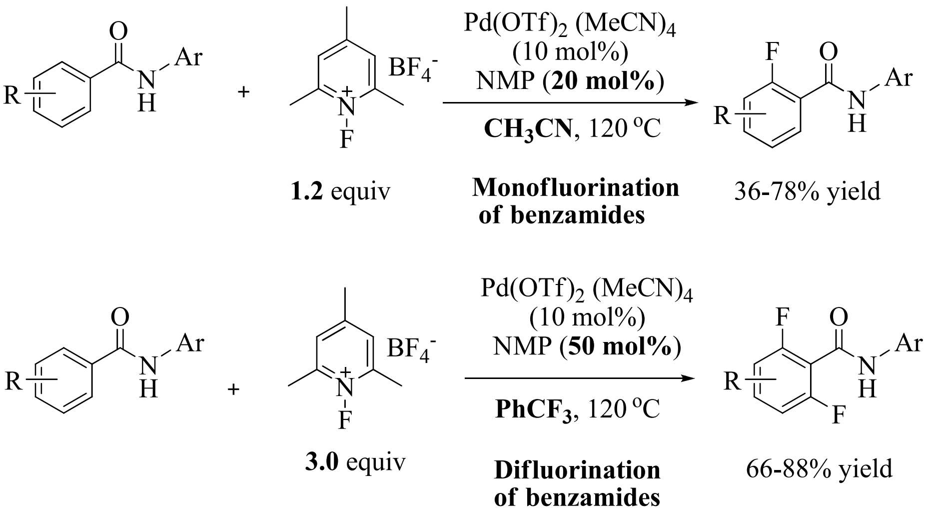
[37] Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 4461.

[38] Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.;Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.

formation of aromatic and benzylic C–F bonds (Scheme 17a).[39] Subsequently, Yu's group reported the development of an efficient orthofluorination using $Pd(OTf)_2 \cdot 2H_2O$ as the catalyst, and NMP as the crucial promoter (Scheme 17b).[40] *N*-fluoro-2,4,6-trimethylpyridinium salts as the electrophilic fluorinating source was applied in both cased.

Very recently, Yu's group also have developed a highly selective Pd-catalyzed ortho- monofluorination and difluorination protocols for benzoic acids using a practical N-arylamide auxiliary (Scheme 18).[41] They found that the use of MeCN as the solvent was essential for obtaining high monoselectivity. They also observed that fluorination in $PhCF_3$ with 3.0 equivalents of electrophilic fluorinating reagent afforded the desired difluorinated products in good yield.

Yu et al. 2011



Scheme 1.18 Pd-Catalyzed Selective Mono- or Difluorination of Benzamides

From this chapter, we have reviewed the importance of the properties of the fluorine atom and its effects on the orgnofluorine compouds. Applications

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[39] Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

[40] Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

[41] Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081.

of these kinds of organofluorine compounds are widely used in medicinal chemistry and material chemistry. Different methods including nucleophilic fluorination and electrophilic fluorination have been reviewed.

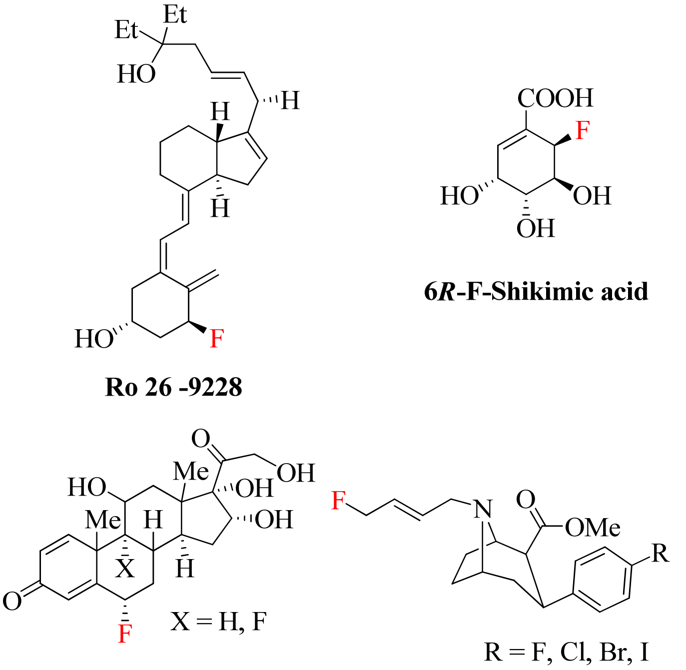
In addition, it is worth mentioning that electrochemical fluorination is also one of the most important and reliable methods for C–F bonds formation. In thesis, this method will not be discussed.

CHAPTER 2

Synthesis of Allylic Fluorides by Direct Electrophilic Fluorination of Alkenes

2.1 Introduction

Allylic fluorides are key components found in important life science chemicals such as bioactive pharmaceuticals and imaging agents,[42, 43] rendering their efficient synthesis of great interest (Scheme 2.2.1). A number of methods including both nucleophilic fluorination and electrophilic fluorination have been reported to prepare allylic fluorides in recent years.



Ro 26 -9228

6*R*-F-Shikimic acid

X = H: **flurandrenolone;**
X = F: **flucinolone**

Imaging fluoride agents

Scheme 2.1.1 Selected Allylic Fluorides of Importance in Life Science

2.1.1 Nucleophilic Fluorination (F^-)

DAST is the most widely used reagent for the dehydroxyfluorination of allylic alcohols.[44] The first example of such dehydroxyfluorination was

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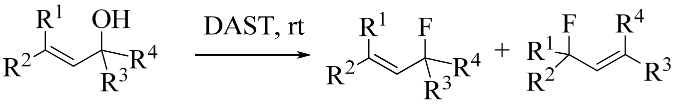
[42] For a review, see: Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943.

[43] For examples of allylic fluoride motifs in pharmaceutical or imaging agents, see: (a) Khan, M. O. F.; Lee, H. J. *Chem. Rev.* **2008**, *108*, 5131. (b) Stehouwer, J. S.; Daniel, L. M.; Chen, P.; Voll, R. J.; Williams, L.; Plott, S. J.; Votaw, J. R.; Owens, M. J.; Howell, L.; Goodman, M. M. *J. Med. Chem.* **2010**, *53*, 5549.

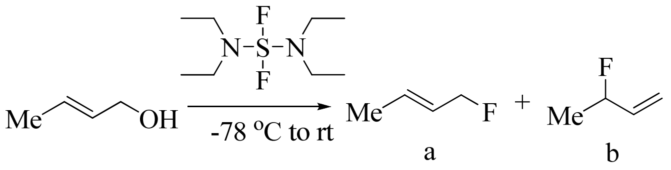
[44] (a) Boukerb, A.; Grée, D.; Laabassi, M.; Grée, R. *J. Fluorine Chem.***1998**, *88*, 23. (b) Grée, D.; Vallerie, L.; Grée, R.; Toupet, L.; Washington, I.; Pelicier, J.-P.; Villacampa, M.; Pérez, J. M.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 2374. (c) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511. (d) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913. (e) Hammond, G. B.; deMendonca, D. J. *J. Fluorine Chem.* **2000**, *102*, 189.

conducted by Middleton in 1975 for allylic alcohols (Scheme 2.1.2).[45] The product outcome was a mixture of two allylic fluorides. Control of regio- and stereoselectivity is not always favorable, the reason being that the fluorination step can proceed through either a S_N2, S_N2' , S_N1' or S_N1 mechanism, despending on the structure of the substrate.[46]



Scheme 2.1.2 DAST-Mediated Dehydroxyfluorination of Allylic Alcohols

In strive to impove the regioselectivity of the fluorination of allylic achohols, a more selective reagent, bis(dialkyamino)sulfur difluorides, was reported by Middleton and Mann (Scheme 2.2.3).[47]



Solvnet	Yield, %	a:b
diethylene glycol dimethyl ether	72	79:21
Isooctane	65	87:13

Scheme 2.1.3 Dehydroxyfluorination of Allylic Alcohols Using Bis(dialkyamino)-sulfur Difluorides Reported by Middleton and Mann

Allylic halides, activated allylic alcohols, and allylic sulfides are the most common substrates for synthesis of allylic fluorides. In such kind of fluorination, nucleophilic reagents such as tetraalkylammonium and inorganic fluorides are used as the source of fluorine.

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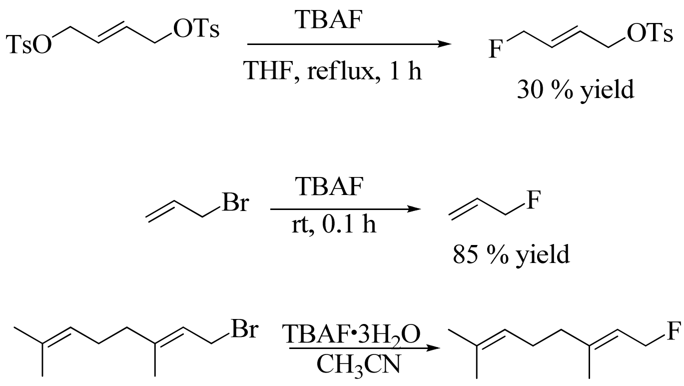
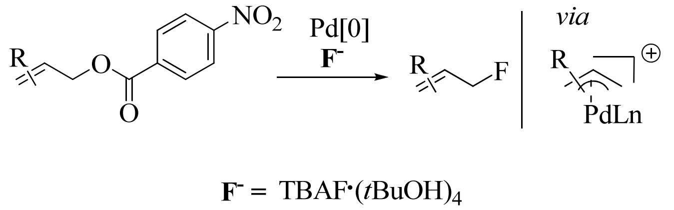
[45] Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
[46] Roig, R.; Percy, J. M. *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, New York, 2006; p319.
[47] Mann, J.; Smith, G. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2884.



Scheme 2.1.4 Fluorination of Allylic Bromides

Allylic tosylates and allylic bromides are converted to allyl fluoride using anhydrous TBAF.[48, 49] TBAF·3H_2O is also a good fluorine source for the synthesis of geranyl fluoride (Scheme 2.2.4).[50]



Scheme 2.1.5 Pd-Catalyzed Allylic Fluorination Reported by Gouverneur

Very recently, Gouverneur's group reported a Pd(0)-catalyzed method for synthesis of allylic fluorides from allylic *p*-nitrobenzoate at room temperature (Scheme 2.1.5).[51] In this work, they selected tetra-*n*-butylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride [TBAF·(*t*BuOH)$_4$] as the fluorine source; a reagent that possesses low hygroscopicity and is reported to display good nucleophilicity and low basicity.[52]

---

[48] Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.

[49] (a) Guijarro, D.; Yus, M. *J. Organomet. Chem.* 2001, 624, 53. (b) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1998**, *63*, 9587.

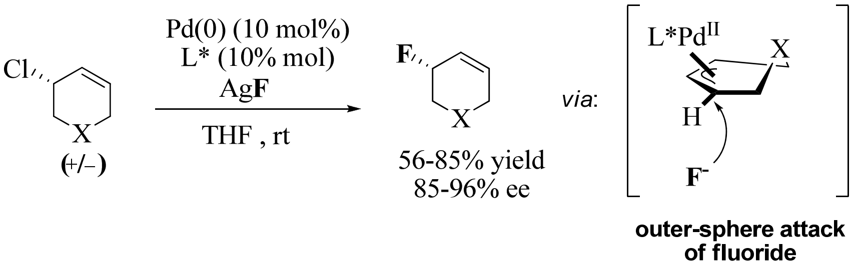
[50] (a) Guijarro, D.; Yus, M. *J. Organomet. Chem.* 2001, 624, 53. (b) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1998**, *63*, 9587.

[51] (a) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 2613.

[52] (a) Kim, D. W.; Jeong, H.-J.; Lim, S. T.; Sohn, M.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 8404–8406. (b) Kim, D.W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16394.

The use of inorganic fluorides as source of fluorine is also widely studied widely. Due to the low solubility and poor nucleophilicity of inorganic fluorides, high temperatures and long reaction time are required. Various additives and catalysts have been used to improve the reactivity.

Primary allylic fluoride is obtained almost exclusively when KF is used as the fluoride source.[53] Ichihara *et al.* further investigated the scope and limitations of PbF_2 as a fluorinating reagent.[54] Subsequently, AgF,[55] CsF[56] and Olah's reagent[57] were developed as the fluorine sources for allylic substitutions.



Scheme 2.1.6 Pd-Catalyzed Asymmetric Synthesis of Allylic Fluorination Reported by Doyle

Conceptually based on Trost's allylic ester deracemization,[58] recently, Katcher and Doyle have developed a methodology for the enantioseclective synthesis of of allylic fluorides by Pd(0)-catalyzed C–F bond formation using AgF as the fluorine sourceoccurs by an S_N2-type (outer-sphere attack) of fluoride attack of fluoride on a Pd(II)-allyl intermediate is presented (Scheme 2.1.6).[59]

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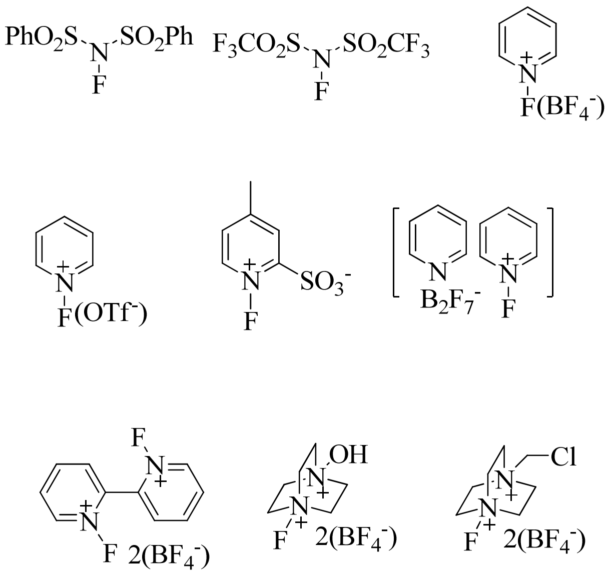
[53] Ichihara, J.; Matsuo, T.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* **1986**, 793.
[54] Ichihara, J.; Takai, Y.; Hanafusa, T.; Tomioka, K. *J. Fluorine Chem.* **1995**, *71*, 131.
[55] (a) Bannai, K.; Toru, T.; Ojba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Hazato, A.; Kurozumi, S. *Tetrahedron* **1986**, *42*, 6735. (b) Sugiura, S.; Toru, T.; Tanaka, T.; Okamura, N.; Hazato, A.; Bannai, K.; Manabe, K.; Kurozumi, S. *Chem. Pharm. Bull.* **1984**, **32**, 1248.
[56] Ichikawa, J.; Sugimoto, K.-I.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1987**, 1985.
[57] (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, 44, 3872.(b) Mann, J.; Pietrzak, B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2681.
[58] Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320.
[59] Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.

2.1.1 Electrophilic Fluorination (F^+)

A variety of electrophilic fluorinating reagents (O-F, N-F, XeF_2, F_2/N_2) have been used as electrophilic sources of fluorine. Among all these reagents, N-F reagents are the safer sources of fluorine (Scheme 2.1.7), which do not require any sepecialized equipment and are easy to handle, air-stable solids.[60]



Scheme 2.1.7 Some Selected Useful N–F Reagents

By addition of base, allylic fluorides are obtained *via* fluorination of less activated olefins using more reactive N-F reagents (Scheme 2.1.8 a).[61] Addition of a catalytic amount of Ytterbium triflate led the conversion of alkenes to allylic fluorides (Scheme 2.1.8 b).[62]

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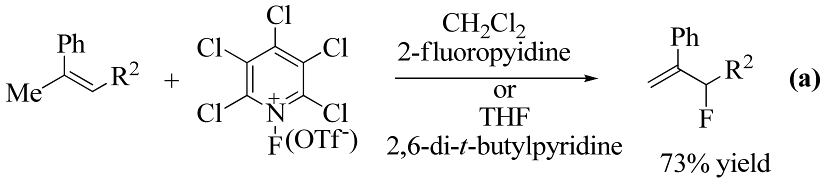
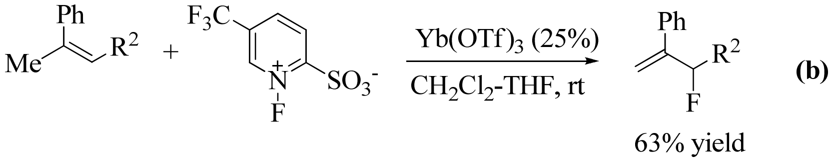
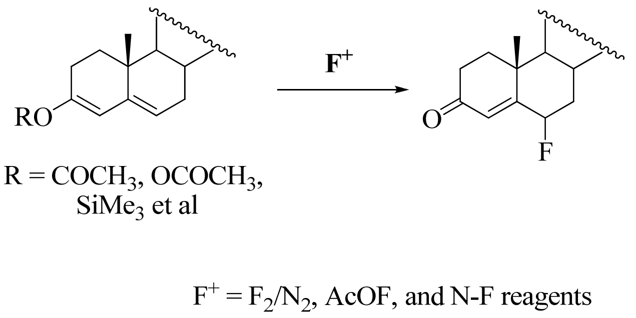
[60] (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737; (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.
[61] Herz, J. E.; Vazquez, E.; Cruz, S.; Zietz, E. *J. Fluorine Chem.* **1976**, *8*, 209.
[62] Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2002**, *43*, 2403.





Scheme 2.1.8 Base Mediated or Yb Catalyzed Electrophilic Fluorination of Alkenes

Electrophilic fluorination has been used extensively for the preparation of 6-fluorosteroids from conjugated enol ethers, [63] acetates, [64] and silylated acetal (Scheme 2.1.9). [65]



Scheme 2.1.9 Synthesis of Fluorinated steroids by Electrophilic Fluorination

Gouverneur and co-workers developed the electrophilic fluorodesilylation reaction for the synthesis of allylic fluorides (Scheme 2.1.10).[66] The diastereoselectivity and mechanism of the fluorodesilylation were also studied in details. [67]

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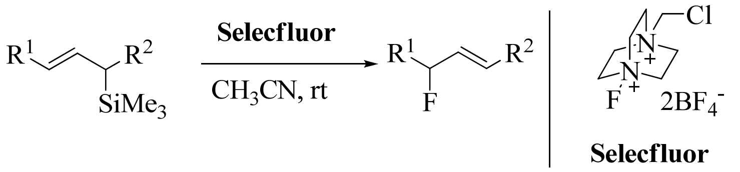
[63] (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563. (b) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1999**, *40*, 2673.

[64] (a) Magerlein, B. J.; Pike, J. E.; Jackson, R. W.; Vanderberg, G. E.; Kagan, F. *J. Org. Chem.* **1964**, *29*, 2982. (b)Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.

[65] Purrington, S. T.; Woodard, D. L.; Cale, N. C. *J. Fluorine Chem.* **1990**, *48*, 345.

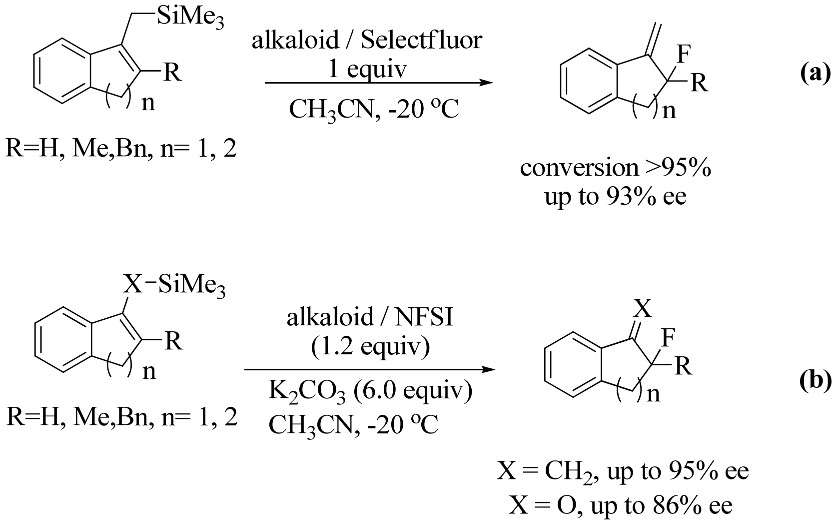
[66] Thibaudeaur, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891; (c) Teare, H.; Robins, E. G.; Ǎrstad, E.; Luthra S. K.; Gouverneur, V. *Chem. Commun.* **2007**, 2330.

[67] Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26. (b) Lam, Y.-h.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5106.



Scheme 2.1.10 Electrophilic Fluorodesilylation for the Synthesis of Allylic Fluorides

Subsequently, Gouverneur's group developed an enantioselective electrophilic fluorodesilylation using Selectfluor-Cinchona alkaloid.[68] In 2008, Shibata and co-workers made contribution to the enantioselective electrophilic fluorodesilylation using NFSI-Cinchona alkaloid (Scheme 2.1.11 b).[69]



Scheme 2.1.11 Enantioselective Electrophilic Fluorodesilylation using N-F reagents-Cinchona alkaloid Reported by Gouverneur and Shibata

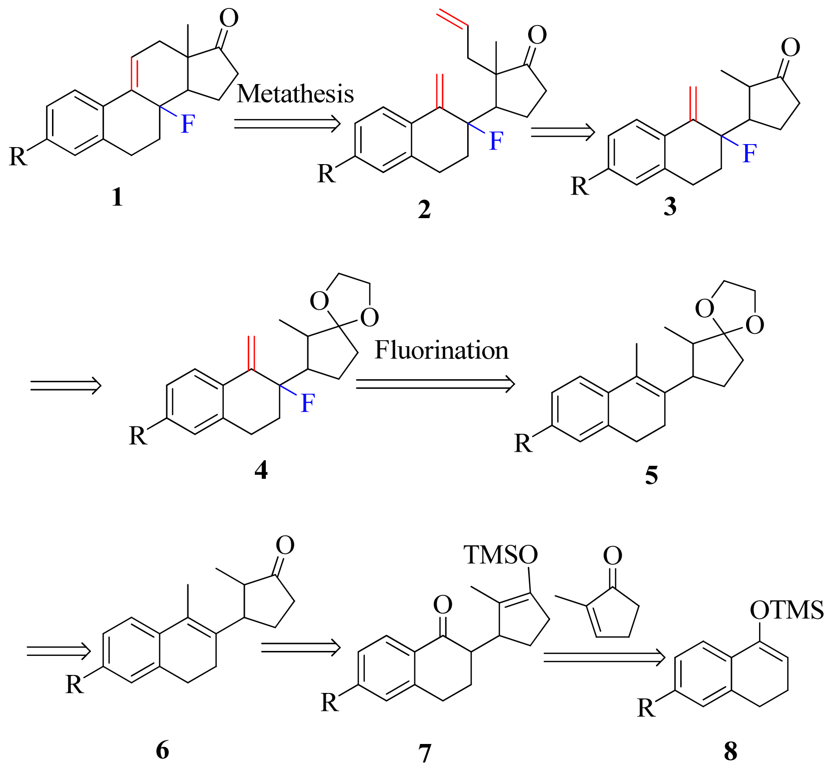
---

[68] Greedy, B.; Paris, J. M.; Vidal, T.; and Gouverneur, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3291.

[69] Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *42*,4157.

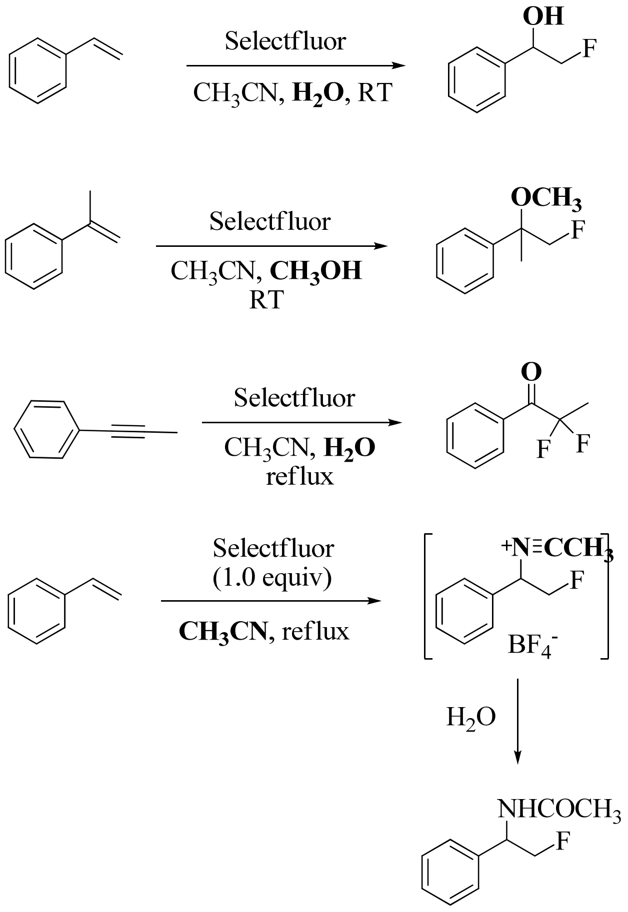
2.2 Synthesis of Aryl Allylic Fluorides by Direct Electrophilic Fluorination of Alkenes

In connection with our interest in the synthesis of fluorinated steroids (**1**, Scheme 2.2.1), we were interested in developing a method to obtain aryl allylic fluoride **4**. There are reported methods for the synthesis of aryl allylic fluorides. The nucleophilic displacement of allylic alcohols with reagents such as DAST has been widely used to produce allylic fluorides, but this transformation suffers from problems of low stereo-and regioselectivity as a result of allylic transposition.[46] Recently, the electrophilicfluorodesilylation to synthesize the allylic fluroride by Gouvereur group with good yield was obtained, but it is difficult to prepare the allyltrimethylsilanes substrates.[66-69] Previously activated alkenes and alkynes have been shown to react with the electrophilic fluorinating reagents (Scheme 2.2.2).



Scheme 2.2.1 Designed Route to Synthesize Fluorinated Steroids

In these reactions, it is worth to noting that solvent systems were selected to participate as the nucleophiles to capture the fluoracarbocationic intermediates.[70] In our synthesis, we required a more direct entry to aryl allylic fluorides using alkenes as starting materials.



Scheme 2.2.2 Some Examples of the Electrophilic Flurorination of Activated Alkenes and Alkynes with Selectfluor

2.2.1 Results and Discussion

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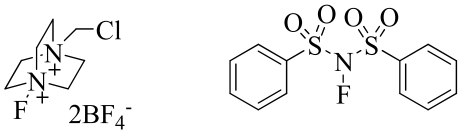
[70] (a) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791; (b) Stavber, S.; Sotler, T.; Zupan, M. *Tetrahedron Lett.* **1994**, *35*, 1105; (c) Zhou, C.; Li, J.; Fu, C.; Ma, S. *Org. Lett.* **2008**, *10*, 581; (d) Zupan, M.; Iskra, J.; Stavber, S. *J. Org. Chem.* **1995**, *60*, 259; (e) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, l; (f) Stavber, S.; Pecan, T. S.; Papez, M.; Zupan, M. *J. Chem. Commun.* **1996**, 2247.

Our initial studies focused on screening fluorine sources such as Selectfluor[71] (**S₁**, Scheme 2.2.3) and *N*-fluorobenzenesulfonimide (NFSI)[72] (**S₂**, Scheme 2.2.3) for the conversion of **9a** into **10a**. As shown in Table 2.1, no reaction was observed when NFSI was used as the fluorine source, which can be explained the weaker fluorinating ability of NFSI. However, the reaction proceeded smoothly to afford the desired product **10a** when Selectfluor was used as the fluorine source (entries 8, 9 and 11). The best conditions involved reaction in *N*,*N*-dimethylformamide (DMF) for 4 h at 75 °C (entry 11). In this reaction, dry DMF was required, as the yield of the product decreased substantially in the presence of water, with formation of a byproduct, produced by capture of a fluorocarbocationic intermediate by water.

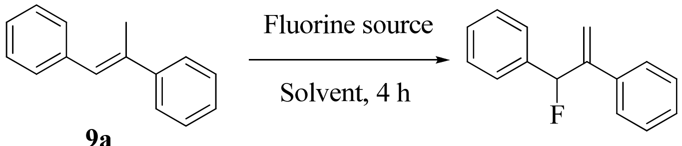


S₁: Selectfluor

S₂: *N*-fluorobenzene-sulfonimide (NFSi)

Scheme 2.2.3 Sources of Eelectrophilic N-F Reagents

Table 2.1
Reaction of α-methylstilbene (9a) with Fluorine Sources[a]



9a

10a

Entry	Solvent	Fluorine source	Reaction Temperature (°C)	Conversion	Yield (%)[b]

---

[71] (a) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *Chem. Commun.* **1968**, 804; (b) Schack, C. J.; Christe, K. O. *Inorg. Chem.* **1979**, *18*, 2619; (c) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605; (d) Schmutzler, R. *Angew. Chem. Int. Ed.* **1968**, *7*, 440; (e) Rozen, S. *Chem. Rev.***1996**, *96*, 1717; (f) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.

[72] (a) Differding, E., Ofner, H. *Synlett* **1991**, 187; (b) For an investigation of the reactivity of NFSI, see: Antelo, J. M.; Crugeiras, J.; Leis, J. R.; Ríos, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2071.

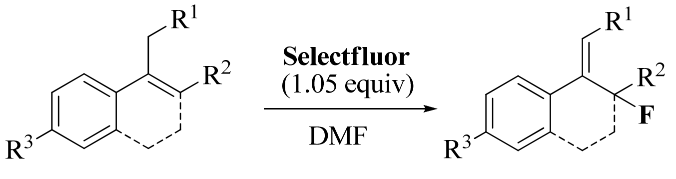
1	CH_2Cl_2	NFSI	r. t.	No reaction	-
2	THF	NFSI	r. t.	No reaction	-
3	CH_3CN	NFSI	75	No reaction	-
4	DMSO	NFSI	75	No reaction	-
5	DMF	NFSI	75	No reaction	-
6[c]	DMF	NFSI	75	No reaction	-
7	CH_3CN/H_2O =10:1	NFSI	75	No reaction	-
8	CH_3CN/H_2O =10:1	Selectfluor	r. t.	>98%	8
9	CH_3CN	Selectfluor	r. t.	>98%	12
10	DMSO	Selectfluor	75	No reaction	-
11	**DMF**	**Selectfluor**	**75**	**>95%**	**83**

[a] Conditions: a-Methylstilbene (0.50 mmol), fluorine source (0.525 mmol), reaction time 4 h. [b] Isolated yield. [c] 2.0 equiv K_3PO_4 was added.

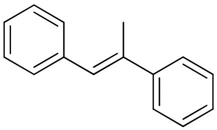
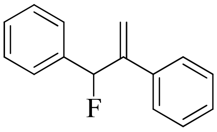
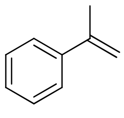
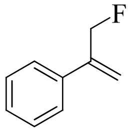
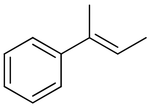
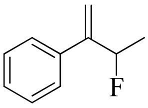
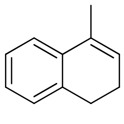
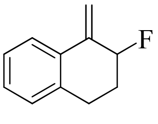
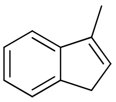
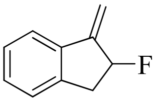
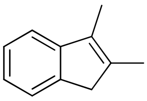
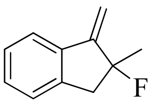
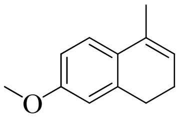
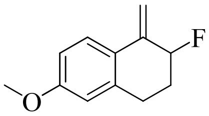
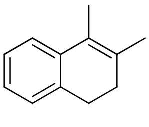
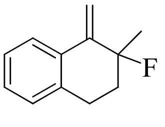
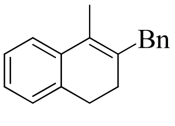
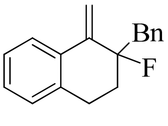
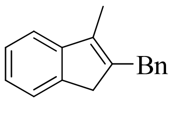
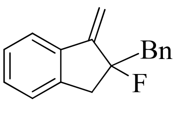
Using the optimized conditions, we explored the scope of this reaction with various aryl alkenes. The results are summarized in Table 2. In all cases, the desired aryl allylic fluorides were obtained in moderate to good yields (entries 1-11, Table 2.2). Interestingly, a substrate **9k** without a 1-methyl group also gave the desired product **10k** in 47% yield at lower temperature. The tetra-substituted aryl alkenes (entries 6 and 8, Table 2.2) reacted at a lower temperature to afford aryl allylic fluorides as the main products. Carbocation stabilization of the phenyl group is essential for clean reactions. No reaction was detected with allylic alkene **9m**.

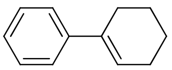
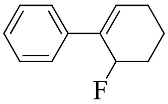
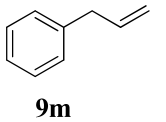
Table 2.2

Fluorination of Various Aryl Alkenes with Selectfluor in DMF [a]



9a-m **10a-m**

Entry	Aryl alkene	Reaction Time (h)	Reaction Temperature (^{o}C)	Main Product	Yield (%)[b]
1	 **9a**	4	75	 **10a**	83%
2	 **9b**	4	75	 **10b**	65%[c]
3	 **9c**	4	75	 **10c**	67%[c]
4	 **9d**	4	75	 **10d**	82%
5	 **9e**	4	75	 **10e**	80%
6	 **9f**	6	45	 **10f**	59%
7	 **9g**	4	75	 **10g**	81%
8	 **9h**	6	45	 **10h**	68%
9	 **9i**	5	70	 **10i**	78%
10	 **9j**	5	70	 **10j**	71%

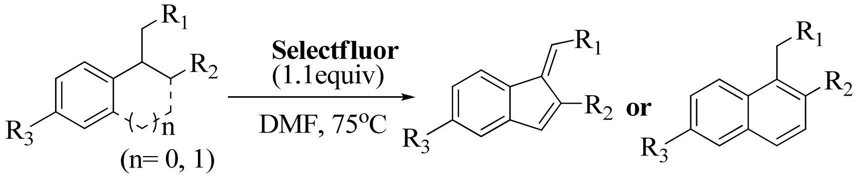
11	 **9k**	6	40	 **10k**	47%[c]
12	 **9m**	4	75	No reaction	-

[a] All reactions were performed in DMF protected with N_2. [b] Isolated yield. [c] Isolated yield. [c] The isolated yield is low , because it is easily volatile or decommposible.

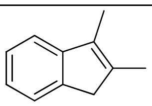
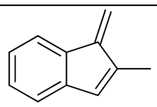
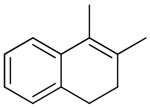
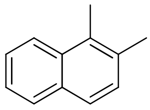
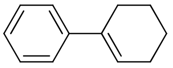
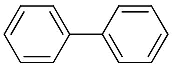
Especially, as seen in Table 2.3, the tetrasubstituted of the aryl alkenes (beraing a 2-methyl substituent) readily led to diene as product at higher temperature easily (**9f'**). In particular, six-membered substrates gave the correponding naphthalene derivatives as product (**9h'**, **9m'**), In addition, the substrate **9k** without the 1-methyl substituent afforded biphenyl as product at higher temperature (**9k'**). We suspected that the reason outcome is due to the ease of elimination in this kind of aryl allylic fluorides.

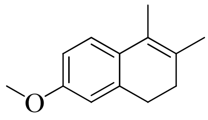
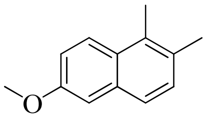
Table 2.3

Elimination of Allylic Fluorides Mediated by Selectfluor [a]



9 **10'**

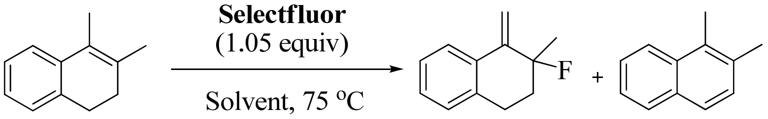
Entry	Aryl alkene	Reaction Time (h)	Conversion	Main Product	Yield (%)[b]
1	 **9f**	8	>90%	 **10f'**	58[c]
2	 **9h**	10	>95%	 **10h'**	76
3[d]	 **9k**	16	>95%	 **10k'**	63

4	 **9n**	10	>95%	 **10n'**	77

[a] All reactions were performed in DMF protected with N_2. [b] Isolated yield. [c] Isolated yield. [c] The isolated yield is low , because it is easily volatile or decommposible. [d] 2.0 equiv selecfluor was used in this reacion.

In order to confirm the existence of this elimination process, we decided to vary the reaction time in attempt to study the formation of the products. As seen in Table 2.4, with short reaction time, starting material (**9h**) and the two products (**10h**, **10h'**) were present. With longer reaction time, the amount of starting material (**9h**) and fluorinated product (**10h**) decreased with an increase of the elimination product (**10h'**). After 6 hours, there was little amount of (**10h**) and starting material remained, with the main product being the elimination product (74% yield). From this table, we ascertained that such type of aryl allylic (bearing 2-methyl substituent) fluoride can undergo elimination as proposed in Scheme 2.2.4.

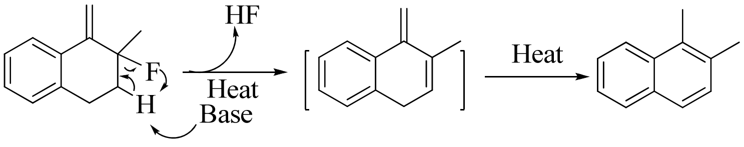
Table 2.4
Elimination of Allylic Fluorides With Vary Reaction Time[a]



9h **10h** **10h'**

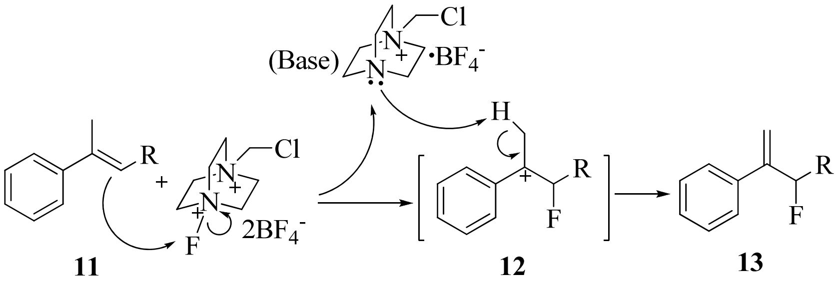
Entry	Time (h)	Yield (**10h**)[b]	Yield (**10h'**)[b]	Recovery (**9h**)[b]
1	0.5	18 %	11 %	53 %
2	1	31%	20%	30 %
3	2	29 %	34 %	16 %
4	6	3 %	74 %	2 %

[a] All reactions were performed in DMF protected with N_2. [b] Isolated yield.



Scheme 2.2.4 Proposed Elimination of Process Allylic Fluorides

The following mechanism is also proposed to account for the observed fluorinated products. The fluorocarbocationic intermediate **12** (Scheme 2.2.5) was generated upon electrophilic addition of Selectfluor to the alkene **11**, which underwent loss of a proton to produce the aryl allylic fluoride **13**.



Scheme 2.2.5 Proposed Fluorination Mechanism

2.2.2 Conclusion

Here we described a direct reaction of carbon–fluorine bond formation reaction by using selectfluor as the fluorine source in DMF, which provided an efficient and simple way for the synthesis of aryl allylic fluorides. In addition, a reaction mechanism was proposed. This reaction may be useful in organic synthesis of fluorinated compounds. The application of this reaction to the synthesis of other fluorinated compounds is in progress.

2.2.3 Experimental Supporting Information

2.2.3.1 General Methods

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred *via* syringe and were introduced into the reaction vessels though a rubber septum.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness).Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy wereperformed on a Bruker Advance 300, 400 and 500 NMR spectrometers. Chemical shifts ^{1}H NMR spectra are reported as in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-*d* (*J* = 7.264, singlet).

Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); dddd (doublet of doublets of doublets of doublets); dt (doublet of triplets); m (multiplets) and etc. The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (13C NMR) are reported as d in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-*d* (*J* = 77.03, triplet).

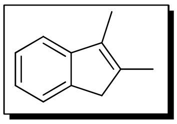
Low resolution mass spectrum analysis was performed on Finnigan polaris Q, GCMS XP mass spectrometer (Thermo Electron Corporation). High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer(Thermo Electron Corporation).

2.2.3.2 General Procedure for Preparation of Some Aryl Alkenes.

Some aryl alkenes were prepared according to the literature procedures. [73, 74]

To a solution of aryl ketone (12 mmol) in THF was added to LDA (12 mmol) at -78 °C and stirred for 1h. The mixture was allowed to warm to room temperature before Iodomethane (18 mmol) was added and stirred for 2h. After completion of the reaction, the reaction was quenched with NH_4Cl saturated solution and extracted with EA (25 ml × 3). The organic layers were combined and washed with brine twice. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography packed with silica gel to afford the pure 2-methyl substituted aryl ketone. To the solution of 2-methyl substituted aryl ketone (6 mmol) in diethyl ether was added methyl Grignard reagent (9 mmol) dropwise at 0 °C and the mixture was stirred for 6 h in room temperature. After completion, the reaction was cooled to 0 °C and treated by 2 M HCl (5 ml). The mixture was stirred for overnight. The mixture was extracted with diethyl ether (10 ml × 3). The organic layers were combined and washed with brine twice. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography packed with silica gel to afford the desired product.

2,3-dimethyl-1*H*-indene (9f) [73]



Purified by column chromatography over silica gel (Hexane, $R_f = 0.45$) to give the product as a colourless oil (Overall Yield: 43%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, 1H, *J* = 7.29 Hz), 7.19-7.28 (m, 2H),

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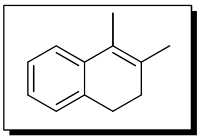
[73] Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3293.
[74] Banks, H.; Ziffer, H. *J. Org.Chem.* **1982**, *47*, 3743.

7.08-7.13 (m, 1H), 3.25 (s, 2 H), 2.06 (s, 3 H), 2.02 (d, 3H, *J* = 0.96 Hz) ppm;

MS (EI$^+$, m/z) 144.11 ([M]$^+$, 61.4%), 129.12 (100%);

HRMS (EI$^+$) $C_{11}H_{12}$ Exact Mass Calcd 144.0934, Found 144.0936.

3,4-dimethyl-1,2-dihydronaphthalene (9h) [73]



Purified by column chromatography over silica gel (Hexane, R_f = 0.47) to give the product as colourless oil (Overall Yield: 58%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.09-7.23 (m, 4H), 2.74 (t, 2H, *J* = 7.62 Hz), 2.23 (t, 2H, *J* = 8.19), 2.04 (d, 3H, *J* = 0.87), 1.93 (t, 3H, *J* = 0.72) ppm;

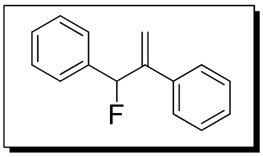
^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.2, 20.4, 28.5, 30.6, 122.4, 125.0, 125.5, 126.3, 127.0, 132.3, 135.4, 137.2 ppm;

IR (KBr) (Solution film in CHCl$_3$) ν_{max} (cm^{-1}) 3063.0, 3016.7, 2955.0, 2922.2, 1641.4, 1487.1, 1450.5, 1037.7, 758.0.

2.2.3.3 General Procedure for Preparation of Aryl Allylic Fluorides.

A solution of aryl alkenes (0.34 mmol) in dry DMF (2 mL) was treated with Selectfluor (128 mg, 0.36 mmol, dried in oven at 125 °C for 3 h) and the reaction mixture stirred at 75 °C. The reaction was monitored by TLC until completion. After approximately 4 h the reaction was complete. The reaction mixture was poured into a separating funnel containing saturated aqueous sodium hydrogen carbonate (10 mL). The product was extracted into Et_2O (4×10 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filter and evaporated in vacuo to afford the crude fluorides, which were purified by preparative TLC to afford the desired product.

(1-fluoroprop-2-ene-1,2-diyl)dibenzene (10a)



Purified by preparative TLC (Hexane, $R_f = 0.42$) to give the product as a pale yellow oil (Yield: 83%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.25-7.40 (m, 10H), 6.33 (d, 1H, *J* = 46.8 Hz), 5.48-5.62 (dd, 2H, *J* = 39.0, 2.1 Hz) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ = 94.3 (d, CH, *J* = 174.8 Hz), 115.6 (d, CH$_2$, *J* = 9.9 Hz), 126.9 (CH), 127.0 (CH), 127.9 (d, CH, *J* = 10.6 Hz), 128.3 (CH), 128.5 (CH), 128.6 (d, CH, *J* = 2.4 Hz), 137.9 (d, *J* = 15.0 Hz), 138.1 (d, *J* = 3.2 Hz), 146.6 (d, *J* = 19.2 Hz) ppm;

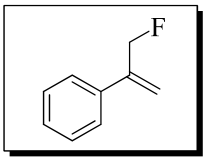
^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -167.11 (s) ppm;

MS (EI$^+$, m/z): 212.08 ([M]$^+$,42.1%), 192.14 (70.2%);

IR (KBr): (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3084.2, 3061.0, 2924.1, 2850.8, 1494.8, 1444.7, 1217.1,1004.9, 916.2;

HRMS (EI$^+$): $C_{15}H_{13}F_1$ Exact Mass Calcd 212.0996, Found 212.0993.

(3-fluoroprop-1-en-2-yl) benzene (10b)



Purified by preparative TLC (Hexane, $R_f = 0.32$) to give the product as a colourless oil (Yield: 65%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.30-7.48 (m, 5H), 5.62 (s, 1H), 5.43-5.44

(dd, 1H, J = 4.12, 0.87 Hz), 5.33 (d, 1H, J = 4.12 Hz), 5.17 (d, 1H, J = 0.87 Hz) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ = 84.4 (d, CH$_2$ J = 168.1 Hz), 115.3 (d, CH$_2$, J = 10.6 Hz), 125.9 (CH), 128.2 (CH), 128.6 (CH), 137.3, 143.0 (d, J = 14.6 Hz) ppm;

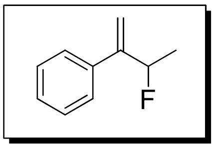
^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -212.75 (s) ppm;

MS (EI$^+$, m/z): 136.07 ([M]$^+$,100%);

IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3086.1, 3059.1, 2927.9, 1635.6, 1496.8, 1022.3, 908.5;

HRMS (EI$^+$): $C_9H_9F_1$ Exact Mass Calcd 136.0683, Found 136.0684.

(3-fluorobut-1-en-2-yl)benzene (10c)



Purified by preparative TLC (Hexane, R$_f$ = 0.31) to give the product as a colourless oil (Yield: 67%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.30-7.48 (m, 5H), 5.41-5.64 (q, 1H, J = 6.36 Hz), 5.38-5.41 (dd, 2H, $J_{H\text{-}H}$ = 6.93, 1.2 Hz), 1.41-1.51 (dd, 3H, $J_{H\text{-}H}$ = 6.36 Hz, $J_{F\text{-}H}$ = 37.1 Hz) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.7(d, CH$_3$, J = 24.2 Hz), 90.6 (d, CH, J = 169.0 Hz), 113.6(d, CH$_2$, J = 10.4 Hz), 126.9 (CH), 127.9 (CH), 128.4 (CH), 138.6(d, J = 3.0 Hz), 148.7(d, J = 16.3 Hz) ppm;

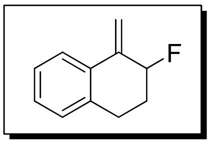
^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -170.17 (s) ppm;

MS (EI$^+$, m/z): 150.07 ([M]$^+$, 70.2%), 151.09 (8.1%);

IR (KBr) (Solution film in CHCl$_3$) ν$_{max}$ (cm^{-1}): 3084, 2986, 2932, 163.6, 1495, 1445, 1375, 1128, 910;

HRMS (EI$^+$): $C_{10}H_{11}F_1$ Exact Mass Calcd 150.0839, found 150.0839.

2-fluoro-1-methylene-1, 2, 3, 4-tetrahydronaphthalene (10d)



Purified by preparative TLC (Hexane), R$_f$ = 0.33) to give the product as a colourless oil (Yield: 82%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.64-7.67 (m, 1H), 7.13-7.23 (m, 3H), 5.74 (s, 1H), 5.37 (d, 1H, *J* = 3.1 Hz), 5.31 (dm, 1H, *J* = 50.7 Hz), δ = 3.04-3.14 (m, 1H), δ = 2.81-2.91 (m, 1H), δ = 2.01-2.32 (m, 2H) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ = 25.6 (d, CH$_2$, *J* = 8.02 Hz), δ = 29.3 (d, CH$_2$, *J* = 20.9 Hz), 91.2 (d, CH, *J* = 171.4 Hz), 111.4 (d, CH$_2$, *J* = 10.8 Hz), 124.7 (CH), 126.4 (CH), 128.2 (CH), 128.8 (CH), 132.1 (d, *J* = 2.1 Hz), 135.7, 141.5 (d, 15.3 Hz) ppm;

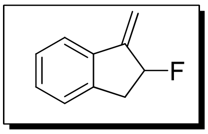
^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -175.25 (s) ppm;

MS (EI$^+$,m/z): 162.07 ([M]$^+$, 98%);

IR (KBr) (Solution film in CHCl$_3$): ν$_{max}$ (cm^{-1}) 3069, 2949, 1636, 1487, 1429, 1034, 924, 775;

HRMS (EI$^+$): $C_{11}H_{11}F_1$ Exact Mass Calcd 162.0839, Found 162.0837.

2-fluoro-1-methylene-2, 3-dihydro-1*H*-indene (10e)



Purified by preparative TLC (Hexane, R_f = 0.26) to give the product as a colourless oil (Yield: 80%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51-7.54 (m, 1H), 7.24-7.28 (m, 3H), 5.55-5.79 (m, 2H), 5.49-5.51(dd, 2H, *J* = 5.43, 1.11 Hz), 3.08-3.41 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.1 (d, CH_2, *J* = 22.7 Hz), 94.1 (d, CH, *J* = 176.5 Hz), 109.5 (d, CH_2, *J* = 7.88 Hz), 121.1 (CH), 125.4 (CH), 127.2 (CH), 129.3 (CH), 138.1 (d, *J* = 2.25 Hz), 142.0, 148.4 (d, *J* = 13.6 Hz) ppm;

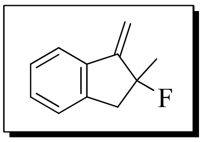
^{19}F NMR (282.4 MHz, $CDCl_3$): δ = -167.23(s) ppm;

MS (EI^+, m/z): 148.08 ($[M]^+$,100%);

IR (KBr) (Solution film in $CHCl_3$): ν_{max} (cm^{-1}) 3075, 2959, 1649, 1464, 1017, 899, 779;

HRMS (EI^+): $C_{10}H_9F_1$ Exact Mass Calcd 148.0683, Found 148.0678.

2-fluoro-2-methyl-1-methylene-2, 3-dihydro-1*H*-indene (10f)



Purified by preparative TLC (Hexane, R_f = 0.23) to give the product as a colourless oil (Yield: 59%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49-7.52 (m, 1H), 7.24-7.26 (m, 3H), 5.68 (d, 1H, *J* = 4.62 Hz), 5.40 (d, 1H, *J* = 4.50 Hz), 3.07-3.43 (m, 2H), 1.67 (d, 3H, 20.9 Hz) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (d, CH_3, J = 29.7 Hz), 44.7 (d, CH_2, J = 25.0 Hz), 100.2 (d, CH_2, 175.5 Hz), 106.2 (d, CH, J = 6.0 Hz), 121.2 (CH), 125.3 (CH), 127.2 (CH), 129.3 (CH), 138.4 (d, J = 2.63 Hz), 141.0 (d, J = 2.25 Hz), 151.9 (d, J = 17.1 Hz) ppm;

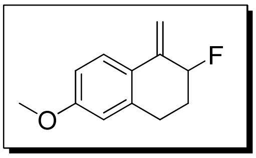
^{19}F NMR (282.4 MHz, $CDCl_3$): δ = -130.45 (s) ppm;

MS (EI$^+$, m/z): 162.08 ($[M]^+$, 98%), 147.10 (100%);

IR (KBr) (Solution film in $CHCl_3$): ν_{max} (cm^{-1}) 3024, 2924, 1647, 1473, 1375, 1290, 1074, 807, 777;

HRMS (EI$^+$): $C_{11}H_{11}F_1$ Exact Mass Calcd 162.0839, Found 162.0842.

2-fluoro-6-methoxy-1-methylene-1, 2, 3, 4-tetrahydronaphthalene (10g)



Purified by preparative TLC (Hexane/EA (10/1), R_f = 0.38) to give the product as a colourless oil (Yield: 81%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, 1H, J = 8.7 Hz), 6.78 (dd, 1H, J_1 = 8.7, 2.5 Hz), 6.65 (d, 1H, J = 2.2 Hz), 5.60 (s, 1H), 5.36 (dd, 0.5H, J = 6.8, 2.4 Hz), 5.26 (d, 1H, J = 3.4 Hz), 5.18 (dd, 0.5H, J = 6.9, 2.4 Hz), 3.81 (s, 1H), 2.76-3.12 (m, 2H), 1.98-2.32 (m, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8 (d, CH_2, J = 7.8 Hz), δ = 29.3 (d, CH_2, J = 21.2 Hz), δ = 55.3 (s, CH_3), 90.4 (d, CH, J = 171.2 Hz), 109.4 (d, CH_2, J=10.9 Hz), 112.8 (CH), 113.2 (CH), 125.0 (d, J = 2.18 Hz), 126.1 (CH), 137.2, 141.0 (d, 15.2 Hz), 159.5 (s) ppm;

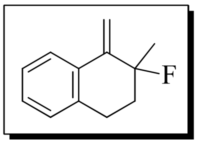
^{19}F NMR (282.4 MHz, $CDCl_3$): δ= -175.04 (s) ppm;

MS (EI$^+$, m/z) 191.14 (100%), 192.17 ($[M]^+$, 10.8%);

IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 2999, 2943, 2937, 1607, 1497, 1321.2, 1271, 1234, 1032, 895;

HRMS (EI$^+$): $C_{12}H_{13}O_1F_1$ Exact Mass Calcd 192.0945, Found 192.0945.

2-fluoro-2-methyl-1-methylene-1, 2, 3, 4-tetrahydronaphthalene (10h)



Purified by preparative TLC (Hexane, R_f = 0.27) to give the product as a colourless oil (Yield: 68%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.12-7.63 (m, 4H), 5.61 (d, 1H, J = 1.86 Hz), 5.45 (s, 1H), 2.0-2.23 (m, 2H), 2.82-3.09 (m, 2H), 1.56 (d, 3H, J = 21.7 Hz) ppm;

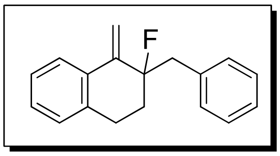
^{13}C NMR (75 MHz, CDCl$_3$): δ = 25.1 (d, CH$_3$, J = 26.5 Hz), δ = 27.1(d, CH$_2$, J = 9.83 Hz), δ = 35.2 (d, CH$_2$, J = 22.1 Hz), δ = 94.2 (d, J = 173.2 Hz), 107.6 (d, CH$_2$, J = 11.0 Hz), 125.0 (CH), 126.4 (CH), 127.9 (CH), 128.7 (CH), 133.3 (d, J = 3.38 Hz)，135.0, 146.4 (d, 17.6 Hz) ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -139.22 (s); MS (EI$^+$,m/z) 176.09 ([M]$^+$,58.8%);

IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3068, 2926, 1634,1485, 1433.1, 921;

HRMS (EI$^+$): $C_{12}H_{13}F_1$ Exact Mass Calcd 176.0996, Found 176.0994.

2-benzyl-2-fluoro-1-methylene-1, 2, 3, 4-tetrahydronaphthalene (10i)



Purified by preparative TLC (Hexane/EA (10/1), $R_f = 0.45$) to give the product as colourless oil (Yield: 78%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.58-7.61 (m, 1H), 7.13-7.30 (m, 8H), 5.56 (d, 1H, *J* = 3.3 Hz), 5.26 (s, 1H), 2.87-3.15 (m, 4H), 1.98-2.14 (m, 2H) ppm;

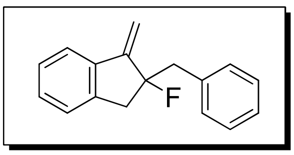
^{13}C NMR (75 MHz, CDCl$_3$): δ = 27.1 (d, *J* = 11.0 Hz), 32.3 (d, *J* = 21.8 Hz), 43.1 (d, *J* = 24.2 Hz), 95.8 (d, *J* = 183.7 Hz), 108.6 (d, *J* = 12.0 Hz), 125.1 (d, *J* = 2.1 Hz), 126.6, 126.6, 128.0, 128.1, 130.6, 133.6 (d, *J* = 3.82 Hz), 134.7, 135.9, 145.8 (d, *J* = 17.2 Hz) ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -146.10 (s); MS (EI$^+$,m/z) 252.10 ([M]$^+$, 26.4%);

IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3061, 3026, 2030, 1738, 1601, 1492.9, 1452, 1371, 1242, 1045, 909;

HRMS (EI$^+$): $C_{18}H_{17}F_1$ Exact Mass Calcd 252.1309, Found 252.1315.

2-benzyl-2-fluoro-1-methylene-2, 3-dihydro-1*H*-indene (10j)



Purified by preparative TLC (Hexane/EA (10/1), $R_f = 0.41$) to give the product as a pale yellow solid (Yield: 78%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.48-7.51 (m, 1H), 7.16-7.30 (m, 8H), 5.71 (d, 1H, *J* = 4.32 Hz), 5.28 (d, 1H, *J* = 4.02 Hz), 2.88-3.37 (m, 4H) ppm;

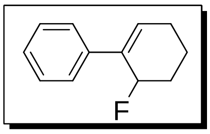
^{13}C NMR (75 MHz, CDCl$_3$): δ = 41.9 (d, *J* = 24.3 Hz), δ = 44.3 (d, *J* = 27.0 Hz), δ = 101.8 (d, *J* = 183.8 Hz), 107.1 (d, *J* = 5.7 Hz), 121.1, 125.2 (d, *J* = 1.73 Hz), 126.8, 127.2, 128.1, 129.3, 130.6 (d, *J* = 1.43 Hz), 136.0, 138.3(d, *J* = 2.85 Hz), 140.9 (d, *J* = 3.45 Hz), 151.1 (d, *J* = 17.7 Hz) ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -137.91 (s); MS (EI$^+$,m/z) 238.10 ([M]$^+$, 100%);

IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3064, 3029, 2018, 1648, 1463, 899;

HRMS (EI$^+$): $C_{17}H_{15}F_1$ Exact Mass Calcd 238.1158, Found 238.1169.

(6-fluorocyclohex-1-enyl)benzene (10k)



Purified by preparative TLC (Hexane, R_f = 0.31) to give the product as a colourless oil (Yield: 47%);

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.47 (d, 1H, *J* = 8.04 Hz)， 7.23-7.37 (m, 4H), 6.36-6.40 (m, 1H), 5.31-5.49 (m, 1H), 2.13-2.41 (m, 3H), 1.68-1.88 (m, 3H);

^{13}C NMR (75 MHz, CDCl$_3$): δ = 16.8 (CH$_2$), δ = 25.9 (d, CH$_2$, *J* = 3.24 Hz), 29.5 (d, CH$_2$, *J* = 21.6 Hz), 86.3 (d, CH, *J* = 164.4 Hz), 125.6 (CH), 127.1 (CH), 128.4 (CH), 131.8 (d, CH, *J* = 8.18Hz), 135.1(d, *J* = 12.2 Hz), 139.9 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): δ = -163.72 (s) ppm;

MS (EI$^+$,m/z):176.07 ([M]$^+$, 100%), 156.10 (90.4%);

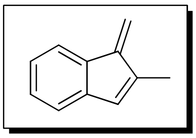
IR (KBr) (Solution film in CHCl$_3$): ν_{max} (cm^{-1}) 3017, 2934, 1715, 1599, 1445, 1215, 756;

HRMS (EI$^+$): $C_{12}H_{13}F_1$ Exact Mass Calcd 176.0996, Found 176.1001.

2.2.3.4 General Procedure for Elimination of Allylic Fluorides Mediated by Selectfluor

A solution of aryl alkenes (0.30 mmol) in dry DMF (2 mL) was treated with Selectfluor (117 mg, 0.33 mmol, dried in oven at 125 °C for 3 h) and the reaction mixture stirred at 75 °C. The reaction was monitored by TLC until completion. After the reaction was complete, the mixture was poured into a separating funnel containing saturated aqueous sodium hydrogen carbonate (10 mL). The product was extracted into Et_2O (4×10 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filter and evaporated in vacuo to afford the crude fluorides, which were purified by preparative TLC to afford the desired product.

2-methyl-1-methylene-1*H*-indene[75]



Purified by preparative TLC (Hexane, $R_f = 0.41$) to give the product as a yellow solid (Yield: 58%);

^{1}H NMR: δ (400 MHz, $CDCl_3$): 7.51 (d, *J* = 7.30 Hz, 1H), 7.08-7.23 (m, 3H), 6.56 (s, 1H), 6.01 (s, 1H), 5.69 (s, 1H), 2.15 (s, 3H) ppm;

^{13}C NMR (75 MHz): 149.4, 135.3, 134.1, 132.6, 128.2, 127.8, 126.3, 125.2, 121.4, 115.1, 21.9 ppm;

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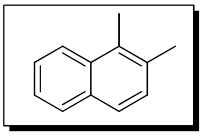
[75] Satoshi, K.; Satoru, N.; Ikuko, T.; Hideki, K.; Hiroshi, M.; Teiji, C. *J. Mol. Catal. A: Chem.* **2006**, *255*, 117.

1,2-dimethylnaphthalene[76]

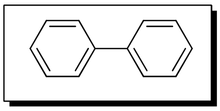


Purified by preparative TLC (Hexane, $R_f = 0.43$) to give the product as a white solid (Yield: 76%);

^{1}H NMR: δ (300 MHz, CDCl$_3$): 7.78 (d, *J* = 8.01 Hz, 1H), 7.61 (d, *J* = 8.31 Hz, 1H), 7.49 (d, *J* = 8.05 Hz, 1H), 7.32 (t, *J* = 8.28 Hz, 1H), 7.24 (t, *J* = 8.04 Hz, 1H), 7.13 (d, *J* = 8.34 Hz, 1H), 2.60 (s, 3H), 2.49 (s, 3H) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): 133.2, 132.9, 132.3, 131.2, 129.1, 128.5, 125.8, 125.7, 124.5, 123.8, 20.8, 14.6 ppm;

Biphenyl[77]

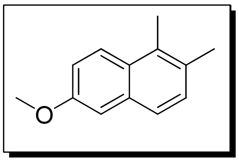


Purified by preparative TLC (Hexane, $R_f = 0.46$) to give the product as a white solid (Yield: 63%);

^{1}H NMR: δ (400 MHz, CDCl$_3$): 7.59 (d, *J* = 8.34 Hz, 4H), 7.44 (t, *J* = 8.01 Hz, 4H), 7.39 (t, J = 7.62 Hz, 2H) ppm;

^{13}C NMR (100 MHz, CDCl$_3$): 141.2, 129.9, 128.7, 127.2 ppm.

6-methoxy-1,2-dimethylnaphthalene[78]



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[76] Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Tetrahedron* **2009**, *65*, 1859.

[77] Shi, S.; Zhang, Y. *J. Org. Chem.* **2007**, *72*, 5927.

[78] Rosowsky, A.; Chen, K. K. N.; Papathanasopoulos, N.; Modest, E. J. *J. Heterocycl. Chem.* 2009, 9, 263.

Purified by preparative TLC (hexane/ Ethyl Acetate = 10:1, $R_f = 0.33$) to give the product as a white solid (Yield: 76%);

^{1}H NMR: δ (300 MHz, $CDCl_3$): 7.93 (d, *J* = 8.34 Hz, 1H), 7.51 (d, *J* = 8.34 Hz, 1H), 7.25 (d, *J* = 8.31 Hz, 1H), 7.14 (d, *J* = 8.76 Hz, 1H), 7.10 (s, 1H), 3.91 (s, 1H), 2.56 (s, 1H), 2.45 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): 156.6, 133.4, 132.2, 130.9, 129.6, 128.3, 125.4, 124.6, 118.2, 106.4, 55.3, 20.5, 14.6 ppm.

2.3 Synthesis of Fluorinated Dicyanoolefins by Electrophilic Fluorination

Dicyanoolefins represent one class of important compounds with extensive biological activities and utility in organic synthesis. It has been reported that α,α-dicyanoolefins can selectively behave as acceptors or vinylogous donors in asymmetric Michael reactions under easily controlled conditions.[79] Recently, our group made some contributions in this field (Scheme 2.3.1). In 2006, our group developed the enantioselective direct vinylogous Michael addition reaction of vinylmalononitriles to α, β-unsaturated aldehydes in aqueous medium using dialkyl-(*S*)-prolinols as the catalysts.[80] Almost at the same time, an organocatalytic enantioselective direct vinylogous Michael addition of dicyanoolefins to maleimide has been developed; the products could be

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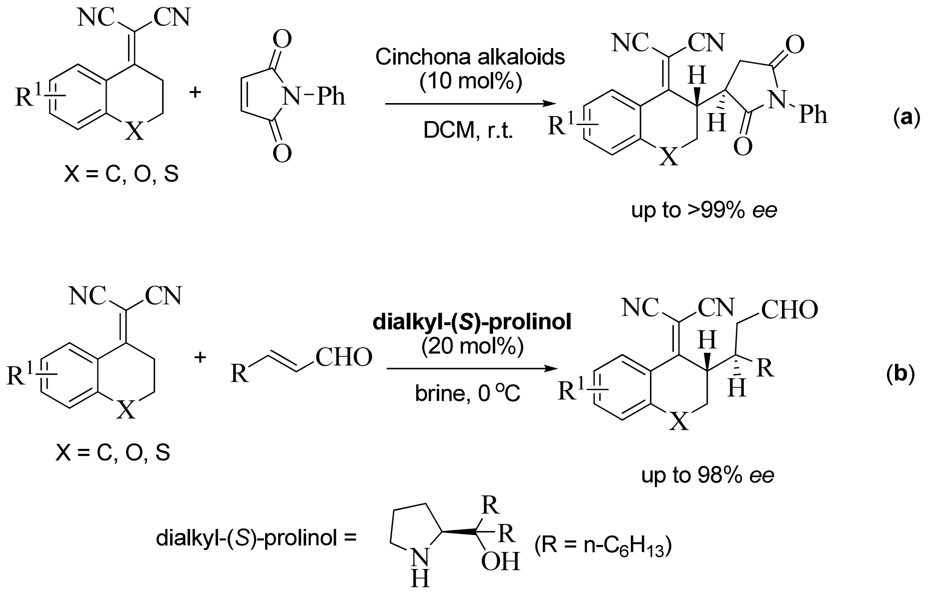
[79] Xie, J. W.; Yue, L.; Xue, D.; Ma, X. L.; Chen, Y. C.; Wu, Y.; Zhu, J.; Deng, J. G. *Chem. Commun.* **2006**, 1563. (b) Xue, D.; Chen, Y. C.; Cui, X.; Wang, Q. W.; Zhu, J.; Deng, J. G.; J. *Org. Chem.* **2005**, *70*, 3584. (c) Xue, D.; Chen, Y. C.; Cun, L. F.; Wang, Q. W. Zhu, J.; Deng, J. G. *Org. Lett.* **2005**, *7*, 5293. (d) Xie, J. W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y. C.; Wu, Y.; Zhu, J.; Deng, J. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389.

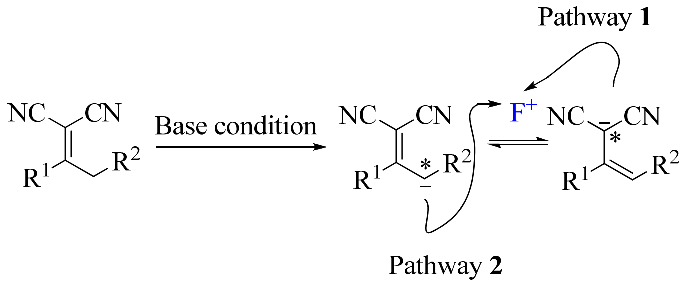
[80] Lu, J.; Liu, F.; Loh, T-P. *Adv. Synth. Catal.* **2008**, *350*, 1781.

obtained in good yields and high enantioselectivities.[81] In this method, cinchona alkaloids were used as the efficient catalysts.



Scheme 2.3.1 Enantioselective Michael Addition of Dicyanoolefins Reported by our group

Furthermore, nitrile groups are versatile building blocks which can be to manipulated the corresponding amides, aldehydes, ketones, primary amines, and heterocycles.[82]



Scheme 2.3.2 Proposed Two Fluorination Pathways of Dicyanoolefins

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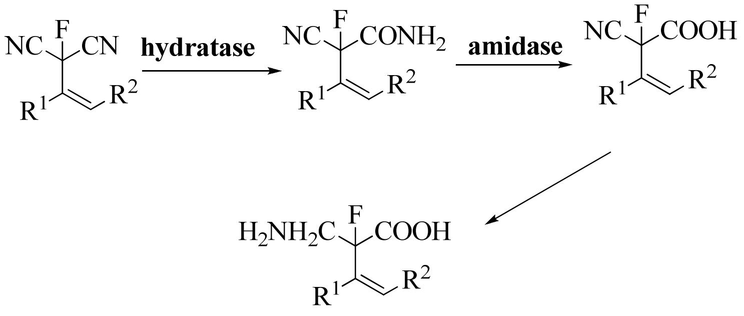
[81] Lu, J.; Zhou, W-J.; Liu, F.; Loh, T-P. *Adv. Synth. Catal.* **2008**, *350*, 1796.

[82] (a) Bendale, P. M.; Khadilkar, B. M. *Synth. Commun.* **2000**, *30*, 1713. (b) Pascal, C.; Dubois, J.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Tetrahedron* **1998**, *54*, 14737. (c) Prashad, M.; Seth, M.; Bhaduri, A. P. *J. Indian Chem. Soc.* **1980**, *57*, 1115. (d) Convery, M. A.; Davis, A. P.; Dunne, C. J.; MacKinnon, *J. W. Tetrahedron Lett.* **1995**, *36*, 4279.

Driven by our interest in the development of direct electrophilic fluorination,[83] we extended our research work to apply this method for the synthesis of fluorinated dicyanoolefins by electrophilic fluorination.

Under basic conditions, deprotonation of dicyanoolefin occurs generating two possible electrophilic fluorination pathways (Scheme 2.3.2). In light of our work on the direct electrophilic fluorination of aryl alkenes, pathway **1** of fluorination is more reasonable, which gives an α-fluorinated dicyanolefin. These kinds of compounds are potential useful precursors for the synthesis of fluorinated β-amino acids and useful fluorinated bioactive molecules such as α-fluoro-α-phenylacetic acid (CFPA) by the hydrolysis of the nitrile group (Scheme 2.3.3).[84]



Fluorinated β-amino acid

Scheme 2.3.3 Potential Applications of Fluorinated Dicyanoolefins

2.3.1 Results and Discussion

In our initial exploration, we tested the conditions for the synthesis of aryl allylic fluorides by direct electrophilic fluorination of alkenes. The reaction proceeded smoothly to afford the desired product **15a** when Selectfluor was used as the fluorine source, with the best conditions involving reaction in *N*,*N*-

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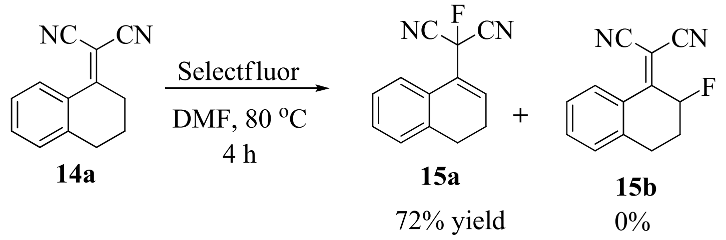
[83] Luo, H-Q.; Loh, T-P. *Tetrahedron Lett.* **2009**, *50*, 1554.
[84] Yokyama, M.; Kashiwagi, M.; Iwasaki, M.; Fuhshuku, K.; Ohta, H.; Sugai, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2817.

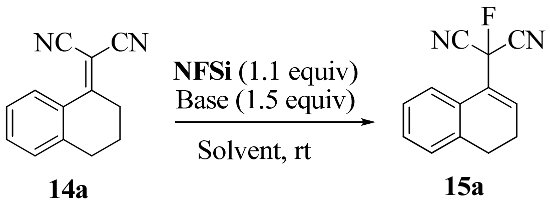
dimethylformamide (DMF) for 4 h at 80 °C (Scheme 2.3.4). It is worth to mention that the alternative regioismer **15b** was not detected under this condition. When the reaction was carried out for 12 h at room temperature, the product **15a** was obtained only in 24% yield. In this reaction, dry DMF was required, as yield of the product decreased substantially in the presence of water, with formation of a byproduct, arising from capture of the fluorocarbocationic intermediate by water.



Scheme 2.3.4 Electrophilic Fluorination of Vinylmalononitrile with Selectfluor

N-fluorobenzenesulfonimide (NFSI) was also used as the fluorine source to synthesize the fluorinated dicyanoolefins. Without the additive, no desired product was obtained. Since under basic conditions, dicyanoolefin occur as a result of deprotonation. So bases were added to promote the reaction. To our delight, the fluorinated dicyanoolefin **15a** could be obtained in the present of base at room temperature (entries 5-8, Table 2.3.1). Various bases and solvent were examined, and it was found that K_3PO_4 and DMF proved to be the best base and solvent in terms of reaction efficiency (entries 7, Table 2.3.1).

Table 2.3.1
Electrophilic Fluorination of vinylmalononitrile (**14a**) with NFSI [a]



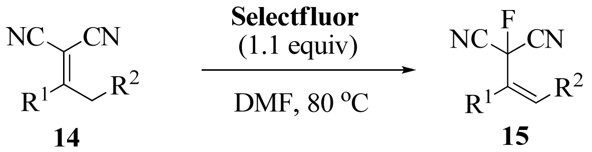
entry	Solvent	Base	Yield (%)[b]

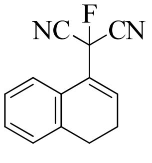
1	THF	-	0
2	CH_3CN		0
3	DMF	-	0
4[c]	DMF	-	0
5	DMF	Na_2CO_3	65
6	DMF	K_2CO_3	57
7	**DMF**	**K_3PO_4**	**70**
8	**THF**	**K_3PO_4**	**68**

[a] Conditions: vinylmalononitrile **14a** (0.30 mmol), NFSI (0.33 mmol) and base (0.45 mmol), reaction time 4 h. [b] Isolated yield. [c] The reaction was run at 80 °C.

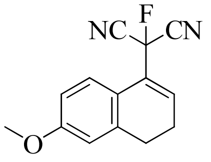
Table 2.3.2

Electrophilic Fluorination with Various Dicyanoolefins using Selectfluor[a]

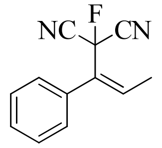




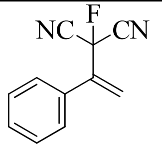
4 h
15a
72% yield



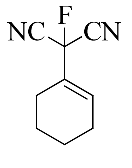
4 h
15b
28% yield



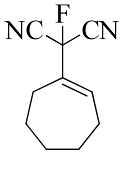
4 h
15c
60% yield
(E/Z = 5/ 1)



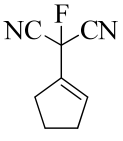
4 h
15d
0% yield



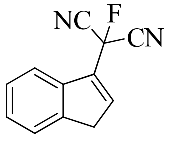
8 h
15e
65% yield



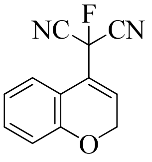
8 h
15f
60% yield



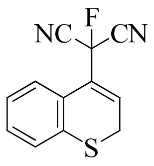
8 h
15g
53% yield



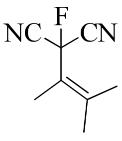
4 h
15h
0% yield



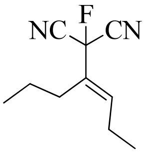
5 h
15i
60% yield



4 h
15j
0% yield



8 h
15k
0% yield

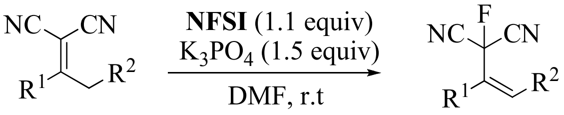


8 h
15l
43% yield
(E/Z = 5.3/ 1)

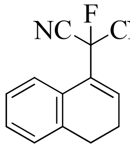
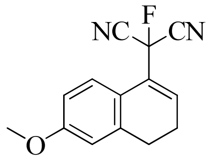
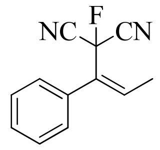
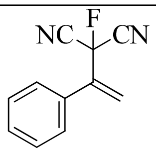
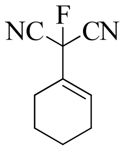
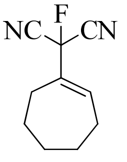
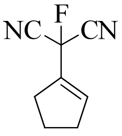
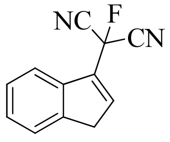
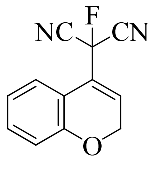
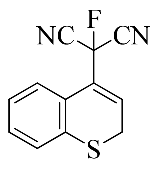
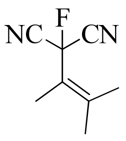
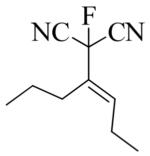
[a] Conditions: Dicyanoolefins (0.30 mmol), Selectfluor (0.33 mmol), all reactions were performed in DMF protected with N_2. [b] Isolated yield.

Encouraged by the above results, we explored the scope of the electrophilic fluorination with various dicyanoolefins using Selectfluor and NFSI/Base systems. The results are summarized in Table 2.3.2 and Table 2.3.3.

Table 2.3.3
Electrophilic Fluorination with Various Dicyanoolefins using NFSI/Base System[a]



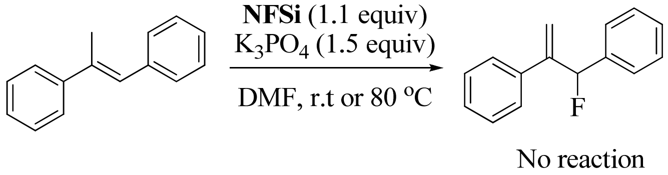
14 → **15**

 4 h **15a** 70% yield	 4 h **15b** 72% yield	 5 h **15c** 56% yield (E/Z = 4.8/ 1)	 5 h **15d** 0% yield
 5 h **15e** 62% yield	 5 h **15f** 58% yield	 5 h **15g** 51% yield	 5 h **15h** 0% yield
 5 h **15i** 0% yield	 5 h **15j** 0% yield	 8 h **15k** 0% yield	 8 h **15l** 42% yield (E/Z = 5.1/ 1)

[a] Conditions: Dicyanoolefins (0.30 mmol), NFSi (0.33 mmol), K_3PO_4 (0.45 mmol), all reactions were performed in DMF protected with N_2. [b] Isolated yield.

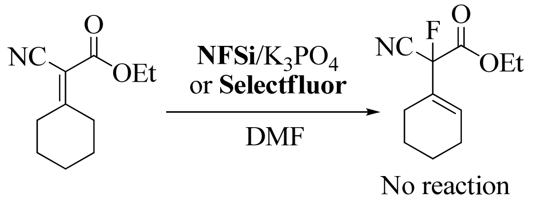
As shown in Table 2.3.2 and Table 2.3.3, most of the fluorinated dicyanoolefins were obtained in moderate to good yields (**15a**, **15c**, **15e-g**, **15l**) using both Selectfuor and NFSI/Basic systems. Some substrates did not give the desired product in both conditions (**15h**, **15j**, **15k**), wherein precipitation was observed in the process of these reactions, suggesting that either the substrates or product is not stable under both two reaction conditions, we suspect that polymerization happened. We can get the desired product 15**i** in 60% yield (**15i**, Table 2.3.2) using Selectfluor, but no fluorinated product was detected using the same substrate in NFSI/Base system. In addition, aliphatic dicyanoolefin bearing *p*-methoxy group gave the desired product in low yield (28%) using Selectfluor as the fluorine source (**15b**, Table 2.3.2). When using NFSI/Base system, desired fluorinated dicyanoolefin was obtained in good yield (72%) (**15b**, Table 2.3.3).

In attempted establish reactivity of NFSI/Base system with aryl alkenes, α-methylstilbene was used as substrate to excute the electrophilic fluorination, however, no aryl allylic fluoride was obtained (Scheme 2.3.5). So for the substrates of alkenes, the fluorinating ablility of NFSI/base is less weak than Slectfluor in DMF.



Scheme 2.3.5 Electrophilic Fluorination Aryl Alkene of with NFSI

Since dicyanoolefin is very similar in reactivity with α-cyano-α-carbonylolefins, ethyl 2-cyano-2-cyclohexylideneacetate was subjected both Selectfluor and the NFSi/Base system. Nevertheless, no reaction was observed under both conditions (Scheme 2.3.6), for more stability of C=C bond of ethyl 2-cyano-2-cyclohexylideneacetate.



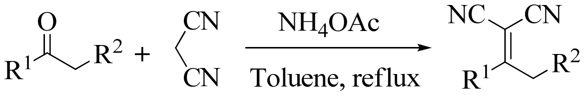
Scheme 2.3.6 Electrophilic Fluorination of α-cyano-α-carbonylolefin with Selectfluor or NFSi/Base System

2.3.2 Conclusion

Fluorinated dicyanoolefins were synthesized using Selectfluor as the electrophilic reagent in DMF. NFSi was also used as the electrophilic reagent to obtain the same fluorinated dicyanoolefins under basic conditions. Both these methods are complementary to one aother.

2.3.3 Experimental Supporting Information

2.3.3.1 General Procedures for the Preparation and of Olefins According to the Literature Procedures[85]:



Malononitrile (10 mmol) and the ketone (11 mmol) were dissolved in 15 mL of toluene containing ammonium acetate (200 mg) and glacial acetic acid (0.8 mL) in a 50 mL flask. By refluxing vigorously, the water formed in the reaction was removed by a Dean and Stark trap placed under the reflux condenser. After the completion of the reaction, the reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was recrystallized from alcohol to give pure products. All the compounds are

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[85] (a) Dong, X.; Chen, Y-C.; Cui, X.; Wang, Q-W.; Zhu, L.; Deng, J-G. *J. Org. Chem.* **2005**, *70*, 3584, 3591. (b) Lu, J.; Liu, F.; Loh, T-P. *Adv. Synth. Catal.* **2008**, *350*, 1781.

known, so the ^{1}H, ^{13}C NMR spectra of the compounds were in accordance with those described in the literature.

2.3.3.1 General Procedures of Synthesis of Fluorinated Dicyanoolefins by Electrophilic Fluorination

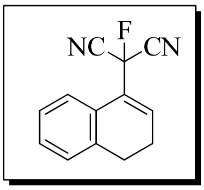
(a) Fluorination with Various Dicyanoolefins using Selectfluor

A solution of aryl dicyanoolefins (0.30 mmol) in dry DMF (2 mL) was treated with Selectfluor (117 mg, 0.33 mmol, dried in oven at 125 °C for 3 h and the reaction mixture stirred at 80 °C. The reaction was monitored by TLC until completion. After approximately 4 h the reaction was complete. The reaction mixture was poured into a separating funnel containing saturated aqueous sodium hydrogen carbonate (10 mL). The product was extracted into EA (3×10 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filter and evaporated in vacuo to afford the crude fluorides, which were purified by flash silica gel column chromatography to afford the desired product.

(b) Fluorination with Various Dicyanoolefins using NFSi/Base system

A solution of aryl dicyanoolefins (0.30 mmol) and K_3PO_4 (95.3 mg, 0.45 mmol) in dry DMF (2 ml) was treated with NFSi (104mg, 0.33mmol) and the reaction mixture stirred at room temperature. The reaction was monitored by TLC until completion. After approximately 4 h the reaction was complete. The reaction mixture was poured into a separating funnel containing saturated aqueous sodium hydrogen carbonate (10 ml). The product was extracted into EA (3×10 ml). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filter and evaporated in vacuo to afford the crude fluorides, which were purified by flash silica gel column chromatography to afford the desired product.

2-(3,4-dihydronaphthalen-1-yl)-2-fluoromalononitrile (15a)



Purified by flash silica gel column chromatography to give the product as pale yellow oil (stand for solid), R_f: 0.43 (hexane: ethyl acetate = 4:1);

^{1}H NMR (300 MHz, CDCl3): 7.50 (dd, *J* = 1.8, 4.5 Hz, 1H), 7.24-7.33(m, 3H), 7.01-7.03 (m, 1H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.50-2.57 (m, 2H) ppm;

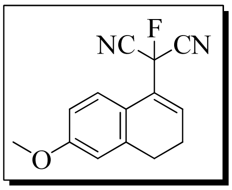
^{13}C NMR (75 MHz, CDCl3): 137.9 (d, *J* = 5.6 Hz), 136.3, 129.4, 128.5, 128.2, 128.0, 127.3 (d, *J* = 29.9 Hz), 123.6 (d, *J* = 2.7 Hz), 110.9 (d, *J* = 27.8 Hz), 80.0 (d, *J* = 187.9 Hz), 26.9. 23.5 ppm;

^{19}F NMR (282.4 MHz, $CDCl_3$): -131.8 ppm;

FTIR (KBr, neat): ν 3063, 3024, 2949, 2893, 2835, 2253, 1720, 1687, 1491, 1452, 1427, 1409, 1240, 1213, 1098 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{13}H_{10}FN_2$ $[M+H]^+$: 213.0828, found: 213.0834.

2-fluoro-2-(6-methoxy-3,4-dihydronaphthalen-1-yl)malononitrile (15b)



Purified by flash silica gel column chromatography to give the product as pale yellow solid, R_f: 0.25 (hexane: ethyl acetate = 4:1)

^{1}H NMR (300 MHz, CDCl3): 7.46 (d, *J* = 8.79 Hz, 1H), 6.89 (dd, *J* = 4.9, 9.9 Hz, 1H), 6.81-6.84 (m, 2H), 3.85 (s, 3 H), 2.84 (t, *J* = 7.83 Hz, 2 H), 2.48-2.57 (m, 2H) ppm;

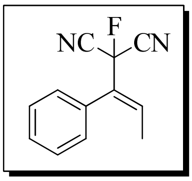
^{13}C NMR (75 MHz, CDCl3): 160.2, 138.5, 135.0 (d, *J* = 7.8 Hz), 127.8 (d, *J* = 21.2), 125.1 (d, *J* = 3.8 Hz), 120.5, 114.8, 111.5, 110.9 (d, *J* = 37.1 Hz), 79.0 (d, *J* = 190.1 Hz), 55.3, 27.5, 23.3 ppm;

^{19}F NMR (282.4 MHz, $CDCl_3$): -131.5 ppm;

FTIR (KBr, neat): ν 2958, 2953, 2837, 2399, 2254, 1609, 1570, 1504, 1429, 1306, 1258, 1215, 1105, 1036 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{14}H_{12}FN_2O$ $[M+H]^+$: 243.0934, found: 243.0943.

(*E*)-2-fluoro-2-(1-phenylprop-1-enyl)malononitrile (15c)



Purified by flash silica gel column chromatography to give the product as colorless oil, R_f: 0.55 (hexane: ethyl acetate = 4:1)

^{1}H NMR (300 MHz, $CDCl_3$): 7.42-7.50 (m, 3H), 6.80-6.84 (m, 2H), 6.84 (dq, *J* = 6.87, 5.19 Hz, 1H), 1.76 (dd, *J* = 6.72, 6.27 Hz, 3 H) ppm;

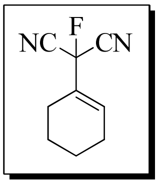
^{13}C NMR (75 MHz, $CDCl_3$): 137.0 (d, *J* = 7.3 Hz), 131.9 (d, *J* = 21.2 Hz), 130.8, 129.6, 129.1, 128.7(d, *J* = 2.3 Hz), 110.6 (d, *J* = 37.4 Hz), 79.8 (d, *J* = 189.6 Hz), 15.3 ppm;

^{19}F NMR (282.4 MHz, $CDCl_3$): -129.9 (*E*), -134.5 (*Z*) ppm;

FTIR (KBr, neat): ν 2958, 2922, 2257, 1655, 1495, 1443, 1261, 1225, 1136, 1092, 1028 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{12}H_{10}FN_2$ $[M+H]^+$: 201.0828, found: 201.0826.

2-cyclohexenyl-2-fluoromalononitrile (15e)



Purified by flash silica gel column chromatography to give the product as colourless oil, R_f: 0.62 (hexane: ethyl acetate = 4:1);

^{1}H NMR (300 MHz, CDCl$_3$): 6.64 (d, *J* = 3.0 Hz, 1H), 2.25-2.303(m, 4H), 1.75-1.81 (m, 2H), 1.64-1.70 (m, 2H) ppm;

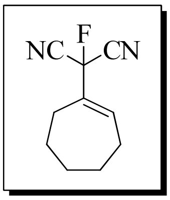
^{13}C NMR (75 MHz, CDCl$_3$): 136.1 (d, *J* = 7.2 Hz), 128.2 (d, *J* = 22.6 Hz), 110.6 (d, *J* = 37.3 Hz), 79.9 (d, *J* = 187.5 Hz), 25.3 (d, *J* = 1.6 Hz). 22.7, 21.5, 20.8 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -135.3 ppm;

FTIR (KBr, neat): ν 2934, 2864, 2255, 1660, 1450, 1446, 1182, 1113, 1028 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_9H_{10}FN_2$ $[M+H]^+$: 165.0828, found: 165.0835.

2-cycloheptenyl-2-fluoromalononitrile (15f)



Purified by flash silica gel column chromatography to give the product as colourless oil, R_f: 0.63 (hexane: ethyl acetate = 4:1);

^{1}H NMR (300 MHz, CDCl$_3$): 6.77 (dd, *J* = 12.2, 6.3 Hz, 1H), 2.42-2.44 (m, 2H), 2.34-2.37 (m, 2H), 1.80-1.86 (m, 2H), 1.55-1.66 (m, 4H) ppm;

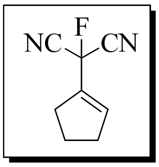
^{13}C NMR (75 MHz, CDCl$_3$): 140.7 (d, *J* = 7.8 Hz), 133.5 (d, *J* = 21.5 Hz), 110.7 (d, *J* = 37.1 Hz), 80.4 (d, *J* = 188.4 Hz), 31.6, 28.4 (d, *J* = 1.6 Hz). 27.9, 26.1 (d, *J* = 1.1 Hz), 25.3 (d, *J* = 2.8 Hz) ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -134.9 ppm;

FTIR (KBr, neat): ν 2873, 2837, 2251, 1663, 1455, 1187, 1033, 867 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{10}H_{11}FN_2$ $[M+H]^+$: 179.0985, found: 179.0977.

2-cyclopentenyl-2-fluoromalononitrile (15g)



Purified by preparative TLC to give the product as colourless oil, R$_f$: 0.55 (hexane: ethyl acetate = 4:1);

^{1}H NMR (400 MHz, CDCl$_3$): 6.57-6.58 (m, 1H), 2.56-2.65(m, 4H), 2.10-2.17(m, 2H) ppm;

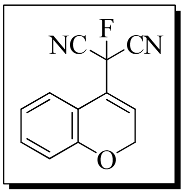
^{13}C NMR (100 MHz, CDCl$_3$): 141.1 (d, *J* = 7.7 Hz), 133.0 (d, *J* = 23.4 Hz), 110.4 (d, *J* = 37.5 Hz), 75.2 (d, *J* = 186.4 Hz), 33.0 (d, *J* = 2.4 Hz). 30.2, 23.3 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -134.5 ppm;

FTIR (KBr, neat): ν 2960, 2920, 2849, 2253, 1641, 1171, 1098, 1028 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_8H_8FN_2$ $[M+H]^+$: 151.0672, found: 151.0678.

2-(2H-chromen-4-yl)-2-fluoromalononitrile (15i)



Purified by flash silica gel column chromatography to give the product as yellow solid, R_f: 0.52 (hexane: ethyl acetate = 4:1);

^{1}H NMR (400 MHz, CDCl$_3$): 7.41 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.64(dd, *J* = 8.3, 4.1 Hz, 1H), 4.93 (dd, *J* = 6.3, 4.0, 2H) ppm;

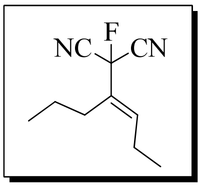
^{13}C NMR (100 MHz, CDCl$_3$): 154.1, 131.8, 128.4 (d, *J* = 7.5 Hz), 125.6 (d, *J* = 22.4 Hz), 123.8 (d, *J* = 3.1 Hz), 122.2, 117.2, 116.1, 110.1 (d, *J* = 36.4 Hz), 77.2 (d, *J* = 186.8 Hz), 64.3 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -136.7 ppm;

FTIR (KBr, neat): ν 3018, 2399, 2255, 1627, 1609, 1516, 1491, 1458, 1215, 1138, 1101, 1055 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{12}H_8FN_2O$ $[M+H]^+$: 215.0621, found: 215.0623.

(E)-2-fluoro-2-(hept-3-en-4-yl)malononitrile (15l)



Purified by column chromatography over silica gel (hexane: ethyl acetate = 4:1, Rf = 0.47) to give the product as colorless oil;

^{1}H NMR (300 MHz, CDCl$_3$): 6.35 (dt, *J* = 7.26, 5.34 Hz, 1H), 2.19-2.37 (m, 4H), 1.53-1.61 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.32 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): 141.7 (d, *J* = 7.9 Hz), 129.2 (d, *J* = 21.3 Hz), 111.0 (d, *J* = 37.3 Hz), 80.8 (d, *J* = 188.3 Hz), 29.2, 22.7, 22.0 (d, *J* = 9.3 Hz), 14.1, 13.0 (d, *J* = 3.07 Hz) ppm;

^{19}F NMR (282.4 MHz, $CDCl_3$): -132.1(*E*), -140.4(*Z*) ppm;

FTIR (KBr, neat): ν 2968, 2938, 2878, 2253, 1655, 1460, 1381, 1199, 1138, 1107, 1064, 1024 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{10}H_{14}FN_2$ $[M+H]^+$: 181.1141, found: 181.1139.

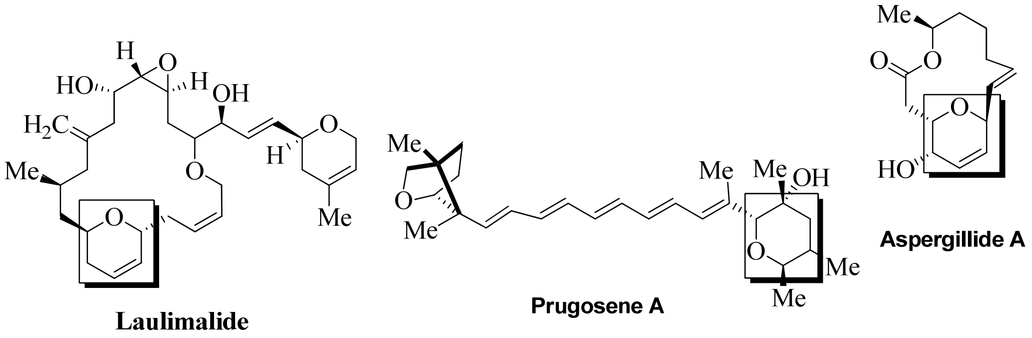
CHAPTER 3

Highly Stereocontrolled Synthesis of Fluorinated 2,6-trans Dihydropyrans via Prins Cyclization

3.1 Introduction

Organofluorine compounds play important roles in medicinal, agrochemical, and material sciences. This is because the introduction of fluorine atoms into organic molecules significantly alters their biological activity, metabolism, solubility, hydrophobicity and bulk properties.[86]

It is well known that 2,6-substituted tetrahydropyrans are common features of large number of natural products and biologically active compounds such as Laulimalide, Aspergillide A, Prugosene A *et al.* and their analogues (Scheme 3.1).[87] Therefore, many strategies for their synthesis have been reported.[88] Among them, the Prins cyclization involving reaction of a homoallylic alcohol with an aldehyde is one of the most attractive methods.[89]



Scheme 3.1 Representative Examples of 2,6-Substituted THPs

In 1955, Hanschke firstly reported the selective synthesis of tetrahydropyran (THP) rings through a Prins cyclyzation reaction by combining

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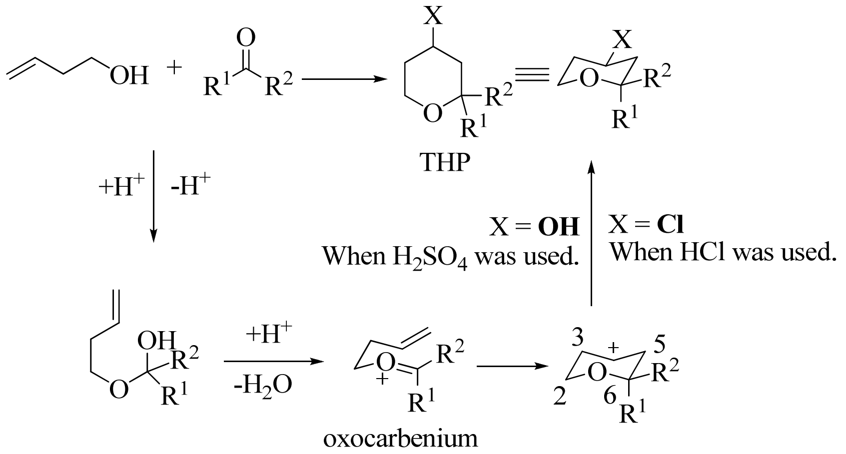
[86] (a) For an important early review on the subject, see: Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; (b) Special Issue on "Fluorine in the Life Sciences", *ChemBioChem* **2004**, *5*, 557; (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

[87] (a) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1988**, *53*, 3644; (b) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225; (c) Lang, G.; Wiese, J.; Schmaljohann, R.; Imhoff, J. F. *Tetrahedron* **2007**, *63*, 11844.

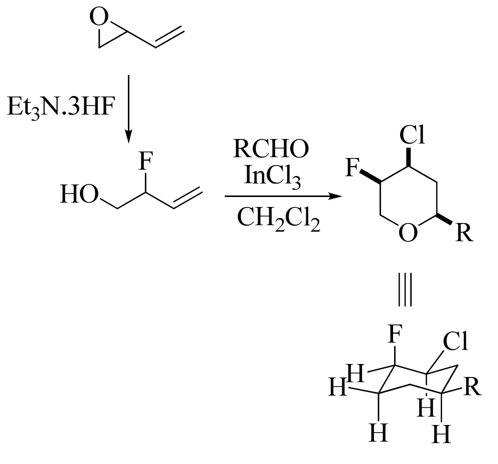
[88] (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772; (b) Pospísil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516; (c) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862; (d) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.

[89] (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577; (b) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291; (c) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387; (d) Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun.* **2004**, 2456; (e) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491; (f) Liu. F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063.

3-buten-1-ol with a variety of aldehydes or ketones in the presence of acid (Scheme 3.2).[90] The mechanism involves the condensation of the alcohol onto the activated aldehyde to give an oxocarbenium intermediate. This intermediate is then attacked by the olefin to give a tetrahydropyranal carbocation, which exists in a chair conformation with the hydrogen adjacent to the carbocation in a pseudo-axial position.



Scheme 3.2 The First Report and Mechanism of The synthesis of THP Rings by The Prins Cyclization Reaction.



Scheme 3.3 Prins Reaction Involving the 2-Fluorobut-3-en-1-ol

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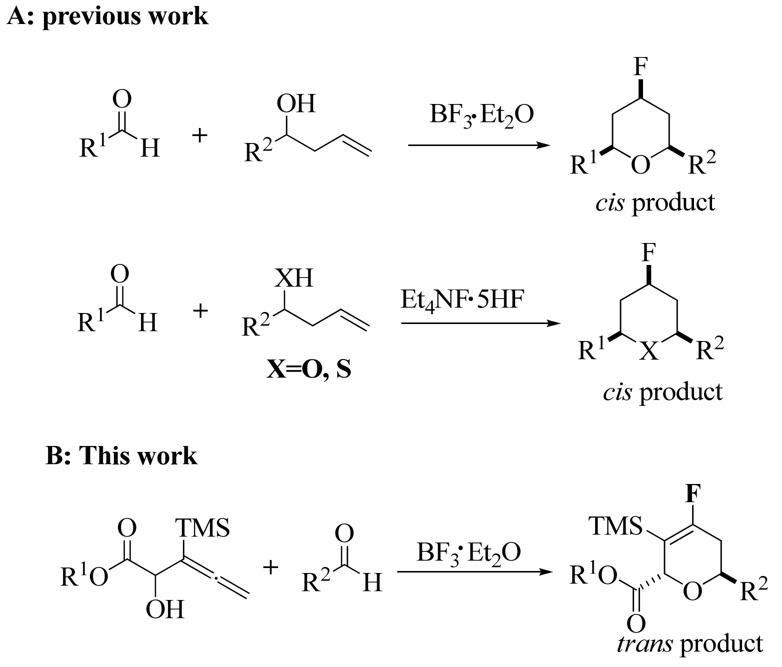
[90] Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.

Moreover, several groups have described access to the *trans* pyran skeleton by direct Prins-type cyclization, with control of the *trans* stereochemistry by using α-hydroxy esters or *via* 1,3-diaxial interactions.[91]

However, few methods for the synthesis of fluorinated pyranyl motifs have been explored.[92] In the presence of $InCl_3$, Dobbs et al. described a Prins cyclization using 2-fluorobut-3-en-1-ol as the substrate with various aldehydes (Scheme 3.3).[93] This generated 4-chloro-5-fluoropyrans in good yield and high diastereoisomeric selectivity where chloride ion is the nucleophile. It is noteworthy that the resultant pyrans always have the fluorine in an axial position.



Scheme 3.4 Synthesis of Fluorinated Pyranyl Motifs

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[91] (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426; (b) Roush, W. R.; Dilley, G. T. *Synlett* **2001**, 955; (c) Markó, I. E.; Dobbs, A.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1977**, *38*, 2899.

[92] (a) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876; (b) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471; (c) Dobbs, A. P.; Pivevi, L.; Penny, M. J.; Martinovic, S.; Lley, J.; Stephenson, P. T. *Chem. Commun.* **2006**, 3134; (d) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R..; Hughes, R. A.; King, C. D. T.; Simpson, J. R.; Smith, W.; Willis, C. L. *Chem. Commun.* **2001**, 835; (e) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

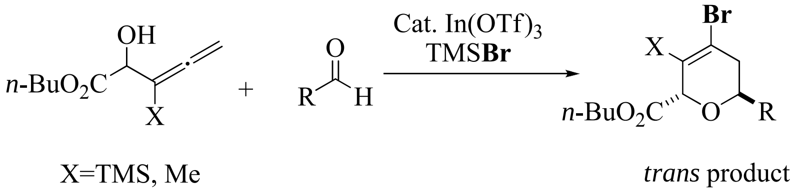
[93] Dobbs, A. P.; Pivnevi, L.; Penny, M. J.; Martinović, S.; Iley J. N. and Stephenson, P. T. *Chem. Commun.* **2006**, 3134.

Among these methods, $BF_3{\bullet}Et_2O$ and $Et_4NF{\bullet}5HF$ have been demonstrated to be both good catalysts and fluorine sources to achieve Prins cyclization of homoallylic alcohols to fluorinated pyranyl motifs (Scheme 3.4A).[86a,b] In particular, all reports involving Prins cyclization almost exclusively led to the fluorinated 2,6-*cis* pyranyl motifs. In comparison, the diastereocontrolled formation of fluorinated 2,6-*trans* pyranyl motifs is still elusive. Therefore, development of a more efficient and highly diastereoselective synthesis of fluorinated 2,6-*trans* pyranyls is still highly desirable for the exploration of new pharmaceuticals.

In this thesis, we report the development of an efficient method for the synthesis of fluorinated 2,6-*trans* dihydropyrans using allenic alcohols as substrates (Scheme 3.4B). The reactions proceeded smoothly in the presence of $BF_3{\bullet}Et_2O$ to afford the fluorinated 2,6-*trans* dihydropyrans in moderate to good yields with excellent diastereoselectivities.

3.2 Results and Discussion

Recently, we described a highly diastereocontrolled synthesis of 2,6-*trans* pyranyl motifs using allenic alcohols (Scheme 3.5).[94]



Scheme 3.5 Synthesis of 2,6-*trans* Pyranyl Motifs Using Allenic Alcohols

Encouraged by this work, we embarked on the synthesis of fluorinated 2,6-*trans* pyranyl motifs *via* the Prins cyclization by using different Lewis acids

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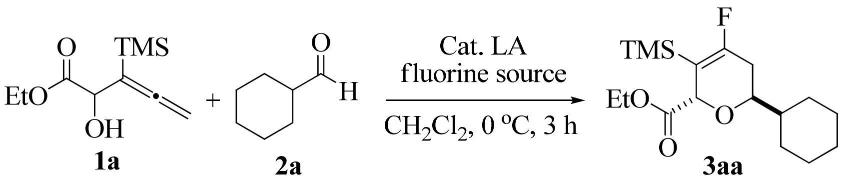
[94] Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741-1743.

(LA) as catalysts and various fluorine sources. After several trials, fluorinated 2,6-*trans* pyranyl motifs were obtained successfully in good yields and with excellent diastereoselectivities mediated by BF_3•Et_2O using allenic alcohols and aldehydes as substrates (Table 3.1, entry 4). It can be seen from Table 1 that Lewis acids such as InF_3, $In(OTf)_3$, and fluorine sources such as InF_3, NaF and Et_3N•3HF were inactive in this system. Further experiments showed that BF_3•Et_2O was the most efficient choice where it not only acts as an efficient Lewis acid, but also serves as the source of fluorine concurrently.

Table 3.1
Lewis Acid Catalyzed Fluorination by Prins Cyclization of Allenic Alcohol **1a** with Aldehyde **2a**[a]



1a **2a** **3aa**

2,6-*trans*[b]

Entry	LA	Fluorine source	Yield (%)[c]	dr (*trans*/*cis*)[d]
1	InF_3	InF_3	0	-
2	$In(OTf)_3$	NaF	0	-
3	$In(OTf)_3$	$Et_3N\cdot 3HF$	0	-
4	$BF_3\cdot Et_2O$	$BF_3\cdot Et_2O$	84	91:9

[a] Reactions were performed with **1a** (0.3 mmol, dissolved in 1 mL of CH_2Cl_2), aldehyde (0.36 mmol), LA (0.03 mmol) and fluorine source (0.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C.

[b] Stereochemistry was assigned by NOESY experiments.

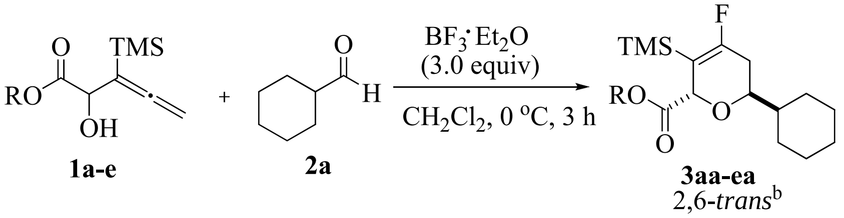
[c] Isolated yield based on allenic alcohol.

[d] The *trans*/*cis* ratios were determined by ^{19}F NMR spectroscopy of spectroscopy the crude reaction mixture.

With the optimal conditions in hand, we next investigated the reactions of trimethylsilyl allenic alcohols bearing different ester groups with cyclohexanecarboxaldehyde in the presence of BF_3•Et_2O (3.0 equiv). The results are summarized in Table 3.2. In all cases, the expected fluorinated 2,6-*trans* dihydropyrans were obtained in good yields and excellent diastereoselectivities (Table 3.2, entries 1-4). The highest diastereoselectivity was obtained when a trimethylsilanyl allenic alcohol with an isopropyl ester (**1c**) was used as the substrate (Table 3.2, entry 3). However, the desired product was not obtained when the trimethylsilyl allenic alcohol contained carboxylic acid group was used as the substrate (Table 3.2, entry 5).

Table 3.2.

Prins Cyclization of Various Allenes with Aldehyde **2a**[a]



Entry	R	Product	Yield (%)[c]	dr (*trans*/*cis*)[d]
1	ethyl	**3aa**	84	91:9
2	methyl	**3ba**	83	89:11
3	isopropyl	**3ca**	85	93:7
4	*n*-butyl	**3da**	85	91:9
5	H	**3ea**	0	-

[a] Reactions were performed with allenic alcohol (0.3 mmol, dissolved in 1 mL of CH_2Cl_2), aldehyde (0.36 mmol), $BF_3{\cdot}Et_2O$ (0.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C.

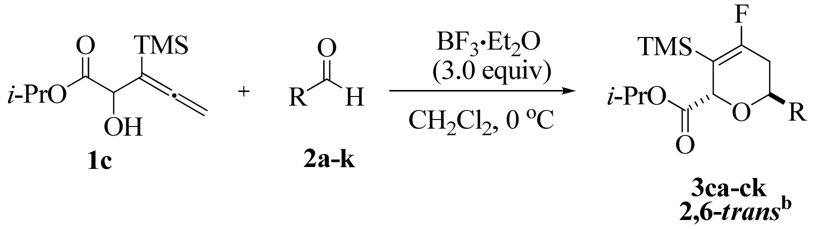
[b] Stereochemistry was assigned by NOESY experiments.

[c] Isolated yield based on allenic alcohol.

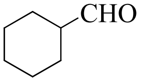
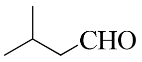
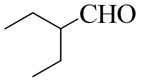
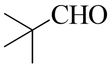
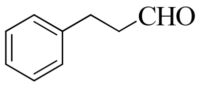
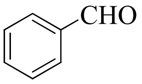
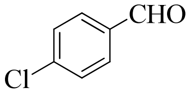
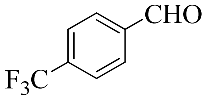
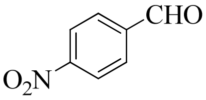
[d] The *trans*/*cis* ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

Next, we explored the scope of the reactions using trimethylsilyl allenic alcohols **1c** and different aldehydes as substrates under the typical conditions. The results are summarized in Table 3.3. To our delight, the Prins cyclization proceeded smoothly to afford the desired products in excellent diastereoselectivities (up to 94:6 dr). In addition, both aliphatic and aromatic aldehydes bearing chloro, trifluoromethyl and *p*-NO_2 groups gave the desired fluorinated dihydropyrans in moderate to good yields (Table 3.3, entries 1-11).

Table 3.3
Prins Cyclization of Trimethylsilyl Allenic Alcohol **1c** with Various Aldehydes[a]



1c **2a-k** **3ca-ck**

Entry	Aldehyde	Time (h)	Product	Yield (%)[c]	dr (*trans*/*cis*)[d]
1		3	**3ca**	85	93:7
2	*n*-$C_8H_{17}CHO$	3	**3cb**	82	92:8
3		3	**3cc**	80	94:6
4		3	**3cd**	78	93:7
5		3	**3ce**	77	93:7
6	n-C_4H_9CHO	3	**3cf**	83	92:8
7		3	**3cg**	78	89:11
8		6	**3ch**	51	93:7
9		6	**3ci**	53	94:6
10		6	**3cj**	68	94:6
11		10	**3ck**	43	91:9

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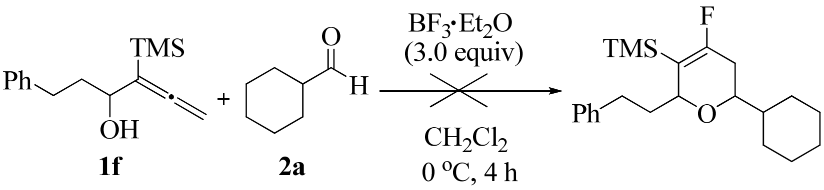
[a] For detailed reaction conditions, see Table 1, footnote a.
[b] Stereochemistry was assigned by NOESY experiments.
[c] Isolated yield based on allenic alcohol.
[d] The *trans*/*cis* ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

We also used a trimethylsilyl allenic alcohol bearing $PhCH_2CH_2$ group to carry this reaction, but no *cis* or *trans* fluorinated product was generated as indicated by ^{19}F NMR spectroscopy (Scheme 3.6). Only some intractable products were observed by TLC analysis. Hence, the allenic alcohol possessing an ester moiety plays a very important role in this reaction.



Scheme 3.6 Prins Cyclization of **1f** Bearing a $PhCH_2CH_2$ Group

The relative sterochemistries of the major products were confirmed by NOESY experiments, H-H interreaction of the two protons at 2,6 position which showed the main ismer have no this interreaction. Therefore, the 2,6-substituted functional groups in the products were in *trans*-configuration. The relative stereochemistry of the cyclization product **3ce** (Table 3.3, entry 5) was further confirmed by single crystal X-ray analysis (CCDC: 722707) (Figure 3.1).

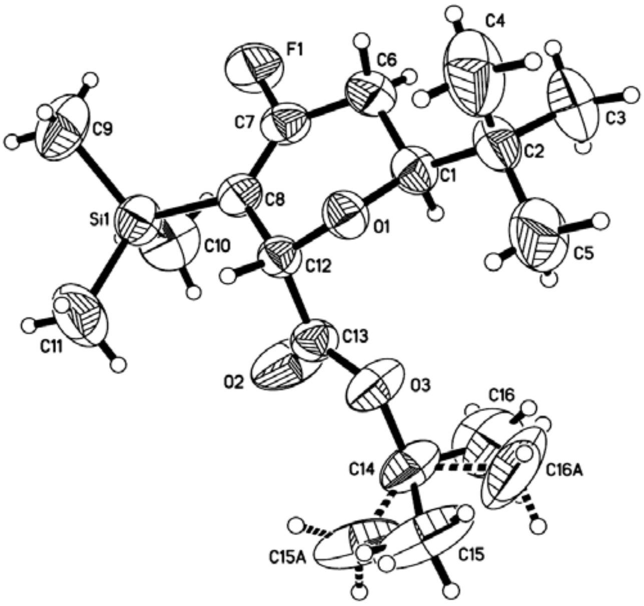
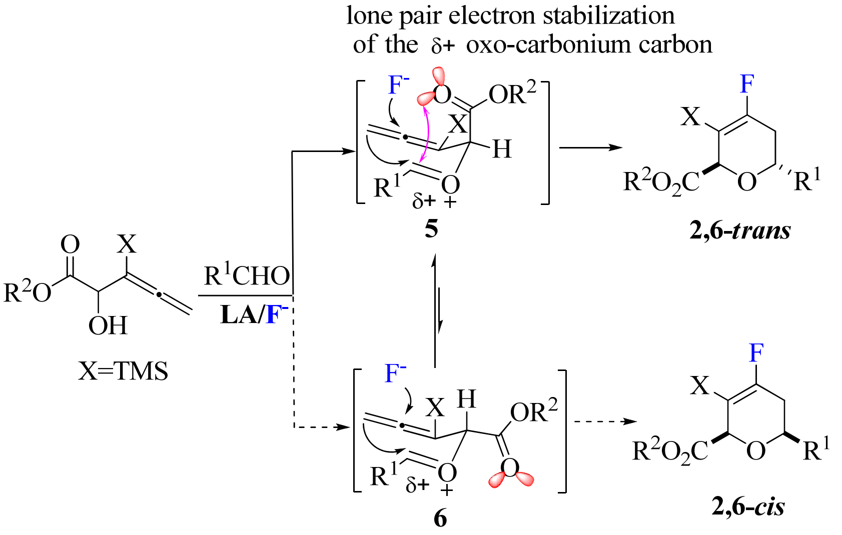


Figure 1. ORTEP Diagram of **3ce**.

Here the lone pairs of the ester group adjacent to the allenic alcohol moiety are important as they stabilize the δ^+ on the oxo-carbenium carbon,[95] thereby, forcing the carbonyl group to adopt an axial orientation, which offers stereoelectronic induction to form the desired transition state **5** and suppresses generation of the undesirable transition state **6** (Scheme 3.7). Moreover, in the transition state **6**, the potential allylic $A^{1,2}$ strains between the TMS group on the pseudo axial position and hydrogen atom attached to the carbonyl group has been considered, the interaction between these two groups made this transition state more disfavarable. In addition, the carbonyl group is a polar group, in consideration of anomiric effect, the electronic factor also made transition state **5** more favarable**.** As a consequence, transition state **5** gives the desired fluorinated 2,6-*trans* dihydropyran, selectively.



Scheme 3.7 Proposed Prins Cyclization Pathway

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[95] For the role of lone pair of ester groups in the stabilization of oxo-carbeniums in asymmetric synthesis, see: (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am.Chem. Soc.* **2002**, *124*, 10692, and references therein; (b) Loh, T. P.; Wang, R. B.; Sim, K. Y. *Tetrahedron Lett.* **1996**, *37*, 2989; (c) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am.Chem. Soc.* **2005**, *127*, 5322; (d) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521; (e) Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503.

3.3 Conclusion

In summary, we have demonstrated an efficient $BF_3•Et_2O$-promoted Prins cyclization for synthesis of fluorinated 2,6-*trans* dihydropyrans in moderate to good yields with excellent diastereoselectivities by using allenic alcohols and various aldehydes as substrates. This report provides a new method for the synthesis of biologically active fluorinated 2,6-*cis* pyranyl motifs. Futher application of this method to the synthesis of other fluorinated compounds is currently in progress in our lab.

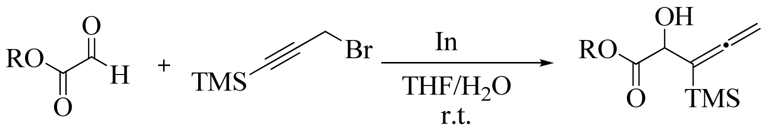
3.4 Experimental Supporting Information

3.4.1 General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification except for CH_2Cl_2 which was freshly distilled from CaH_2. All aldehydes were purified by distillation or flash chromatography.

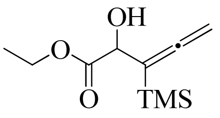
Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized under UV or by potassium permanganate stain. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^{1}H-NMR spectra were performed on a Bruker Advance 300 MHz or 500 MHz NMR spectrometer and reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ=7.26, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C–NMR spectras were recorded on Bruker Advance 75 MHz or 125 MHz spectrometer and reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Conversion of the addition product was determined by ^1H-NMR analysis of the crude product. IR spectras were recorded on a Bio-Rad FTS 165 FTIR spectrometer and were reported in frequency of absorption (cm^{-1}). High Resolution Mass Spectral (HRMS) analysis was performed on Waters Q-TofPermies Mass Spectrometer.

3.4.2 Preparation of Trimethylsilane Allenic Alcohol Bearing Ester Group[96]



To a suspension of indium power (1.15 g, 10 mmol, 2.0 equiv) in H_2O/THF (5:1, 10 mL) was added the glyoxylate (5 mmol, 1.0 equiv) followed by trimethylsilyl propargyl bromide (1.91 g, 10 mmol, 2.0 equiv). The mixture was stirred vigorously overnight at room temperature. Standard work up and purification by flash silica gel column chromatography gave desired product.

Ethyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (1a)



1a

Purified by flash silica gel column chromatography to give the product as a pale yellow oil (38% yield); R_f: 0.16 (hexane: ethyl acetate = 10:1);

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[96] Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042.

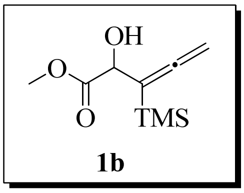
^{1}H NMR (400 MHz, CDCl$_3$) : 4.66 (d, *J* = 8.0 Hz, 1H), 4.53-4.61 (m, 2H), 4.18-4.29 (m, 2H), 2.93 (d, *J* = 8.0 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.16 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl$_3$): 208.9, 173.5, 96.5, 72.1, 70.4, 61.7, 14.2, -1.1 ppm;

FTIR (KBr, neat): ν 3466, 2960, 2900, 1930, 1730, 1639, 1447, 1248, 1207, 1082, 839 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{10}H_{18}O_3SiNa$ [M+Na]$^+$: 237.0923, Found: 237.0923.

Methyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (1b)



1b

Purified by flash silica gel column chromatography to give the product as a pale yellow oil (30% yield:); R$_f$: 0.24 (hexane: ethyl acetate = 4:1);

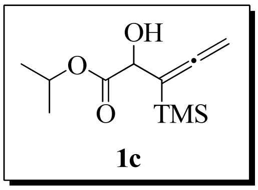
^{1}H NMR (400 MHz, CDCl3): 4.70 (d, *J* = 8.1 Hz, 1H), 4.55-4.62 (m, 2H), 3.77 (s, 3H), 2.90 (d, *J* = 8.1 Hz, 1H), 0.15 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl3): 209.0, 173.9, 96.5, 72.1, 70.6, 52.3, -1.1 ppm;

FTIR (KBr, neat): ν 3467, 2955, 2899, 1932, 1737, 1638, 1439, 1248, 1213, 1082, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_9H_{16}O_3SiNa$ [M+Na]$^+$: 223.0766, found: 223.0768.

Isopropyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (1c)



1c

Purified by flash silica gel column chromatography to give the product as a colourless oil (48% yield); R_f: 0.20 (hexane: ethyl acetate = 10:1);

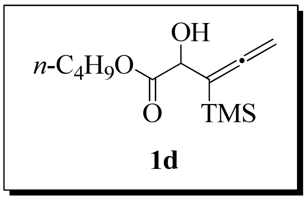
^{1}H NMR (400 MHz, CDCl$_3$): 5.04-5.15 (m, 1H), 4.61 (d, *J* = 8.1 Hz, 1H), 4.52-4.59 (m, 2H), 2.93 (d, *J* = 8.1 Hz, 1H), 1.27 (dd, *J* = 6.2, 4.0 Hz, 6H), 0.16 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl$_3$): 208.9, 194.9, 173.0, 96.5, 72.0, 69.7, 21.9, 21.8, -1.0 ppm;

FTIR (KBr, neat): ν 3468, 2982, 2899, 1933, 1720, 1643, 1375, 1248, 1213, 1107, 837 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{11}H_{20}O_3SiNa$ $[M+Na]^+$: 251.1079, found: 251.1079.

n-Butyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (1d)



1d

Purified by flash silica gel column chromatography to give the product as a colourless oil (55% yield); R_f: 0.42 (hexane: ethyl acetate = 4:1);

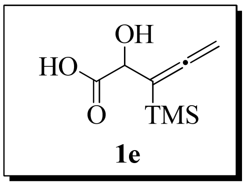
^{1}H NMR (400 MHz, CDCl3): 4.68 (dt, *J* = 2.1, 8.1 Hz, 1H), 4.53-4.60 (m, 2H), 4.14-4.24 (m, 2H), 2.91 (d, *J* = 8.1 Hz, 1H), 1.61-1.68 (m, 2H), 1.36-1.42 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.16 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl3): 209.0, 173.6, 96.5, 72.0, 70.5, 65.5, 30.6, 19.0, 13.6, -1.0 ppm;

FTIR (KBr, neat): ν 3469, 2961, 2874, 1932, 1728, 1639, 1466, 1273, 1248, 1082, 839 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{12}H_{22}NaO_3Si$ $[M+Na]^+$: 265.1236, found: 265.1238.

2-Hydroxy-3-(trimethylsilyl)penta-3,4-dienoic acid (1e)



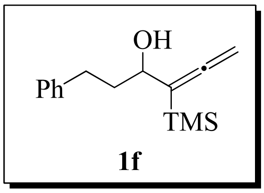
1e

Purified by flash silica gel column chromatography to give the product as a white solid (7% yield); R_f: 0.19 (hexane: ethyl acetate = 1:1);

^{1}H NMR (400 MHz, CDCl3): 4.75 (s, 1H), 4.60-4.65 (m, 2H), 0.17 (s, 9H) ppm;

^{13}C NMR (100 MHz, CDCl3): 209.1, 177.4, 96.1, 72.6, 70.3, -1.1 ppm.

1-Phenyl-4-(trimethylsilyl)hexa-4,5-dien-3-ol (1f)



1f

Purified by flash silica gel column chromatography to give the product as a white solid (82% yield); R_f: 0.39 (hexane: ethyl acetate = 4:1);

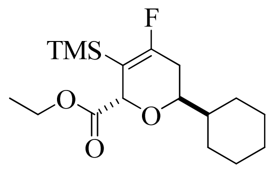
^{1}H NMR (300 MHz, CDCl3): 7.29-7.34 (m, 2H), 7.19-7.24 (m, 3H), 4.56-4.65 (m, 2H), 4.23 (s, 1H), 2.68-2.89 (m, 2H), 1.88-2.08 (m, 2H), 1.83 (d, *J* = 5.6 Hz, 1H), 0.19 (s, 9H) ppm;

^{13}C NMR (75.4 MHz, $CDCl_3$): 207.3, 142.1, 128.5, 128.4, 125.8, 100.6, 72.1, 70.0, 39.7, 32.1, -0.8 ppm.

3.4.3 General Procedure for Prins Cyclization Reactions of Allenic Alcohols and Aldehydes

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $BF_3 \bullet Et_2O$ (128 mg, 0.90 mmol, 3.0 equiv) in 2 mL anhydrous CH_2Cl_2. The mixture was allowed to cool to 0 ºC prior to the addition of cyclohexanecarboxaldehyde (40.4 mg, 0.36 mmol, 1.2 equiv) over a period of 5 minutes, then the mixture was stirred for 10 min. Next, a solution of isopropyl 2-hydroxy-3-methylpenta-3,4-dienoate (68.5 mg, 0.3 mmol, 1.0 equiv) dissolved in 1 mL anhydrous CH_2Cl_2 was added over a period of 15 min. The reaction was stirred at 0 ºC for 3 hours before the mixture was quenched with saturated $NaHCO_3$ aqueous solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography to afford fluorinated dihydropyrans 3**aa** (90.6 mg) as a colorless oil.

(2,6-*Trans*)-Ethyl 6-cyclohexyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3aa)



3aa

Purified by flash silica gel column chromatography to give the product as white solid (84% yield); dr = 91:9 (*trans*/*cis*); R_f: 0.43 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, $CDCl_3$): 4.79 (d, *J* = 2.5 Hz, 1H), 4.11-4.27 (m, 2H), 3.62-3.67 (m, 1H), 2.18-2.26 (m, 1H), 2.02-2.10 (m, 1H), 1.98 (d, *J* = 12.8 Hz, 1H), 1.63-1.75 (m, 4H), 1.39-1.47 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.13-1.26 (m, 3H), 1.01-1.08 (m, 2H), 0.15 (s, 9H) ppm;

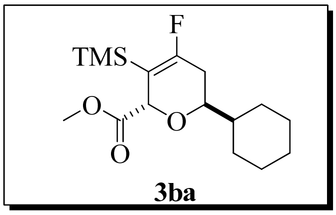
^{13}C NMR (100 MHz, $CDCl_3$): 171.2 (d, *J* = 5.6 Hz), 164.0 (d, *J* = 257.4 Hz), 108.4 (d, *J* = 25.7 Hz), 75.0 (d, *J* = 7.9 Hz), 74.4 (d, *J* = 14.0 Hz), 61.1, 42.4 (d, *J* = 2.2 Hz), 29.8 (d, *J* = 23.9 Hz), 28.8, 28.0, 26.5, 25.9, 25.8, 14.2, -1.0 ppm;

^{19}F NMR (282.4 MHz, $CDCl_3$): -79.9 (*trans*), -77.9 (*cis*) ppm;

FTIR (KBr, Nujol): ν 3437, 2934, 2852, 1732, 1668, 1458, 1240, 1177, 1109, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{17}H_{29}O_3FSiNa$ $[M+Na]^+$: 351.1768, found: 351.1768.

(2,6-*Trans*)-methyl 6-cyclohexyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ba)



3ba

Purified by flash silica gel column chromatography to give the product as a colorless oil (83% yield); dr = 89:11 (*trans*/*cis*); R_f: 0.42 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 4.83 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.63-3.68 (m, 1H), 1.95-2.29 (m, 3H), 1.64-1.75 (m, 4H), 0.97-1.49 (m, 6H), 0.15 (s, 9H) ppm;

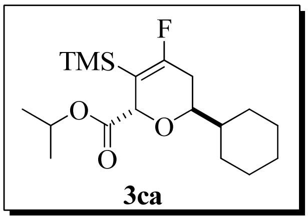
^{13}C NMR (100 MHz, CDCl$_3$): 171.7 (d, *J* = 5.5 Hz), 164.1 (d, *J* = 257.7 Hz), 108.4 (d, *J* = 25.6 Hz), 74.9 (d, *J* = 7.8 Hz), 51.8, 42.4 (d, *J* = 2.3 Hz), 29.7 (d, *J* = 24.0 Hz), 28.7, 27.8, 26.4, 25.9, 25.7, 14.2, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -77.8 (*trans*), -79.7 (*cis*) ppm;

FTIR (KBr, neat): ν 3446, 2928, 2852, 1740, 1668, 1450, 1314, 1248, 1177, 1121, 1105, 843 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{16}H_{27}O_3FSiNa$ [M+Na]$^+$: 337.1611, found: 337.1611.

(2,6-*Trans*)-isopropyl 6-cyclohexyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ca)



3ca

Purified by flash silica gel column chromatography to give the product as white solid (85% yield); dr = 93:7 (*trans*/*cis*); R_f: 0.46 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 5.02-5.09 (m, 1H), 4.75-4.76 (m, 1H), 3.59-3.64 (m, 1H), 2.19-2.27 (m, 2H), 1.98-2.11 (m, 1H), 1.63-1.75 (m, 4H), 1.39-1.46 (m, 1H), 1.28 (dd, *J* = 2.3, 6.2 Hz, 6H), 1.17-1.24 (m, 3H), 0.96-1.08 (m, 2H), 0.15 (s, 9H) ppm;

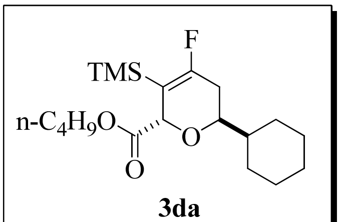
^{13}C NMR (100 MHz, CDCl$_3$): 170.7 (d, *J* = 5.2 Hz), 164.1 (d, *J* = 257.1 Hz), 108.5 (d, *J* = 25.3 Hz), 75.0 (d, *J* = 7.9 Hz), 74.7 (d, *J* = 13.9 Hz), 68.9, 42.5 (d, *J* = 2.3 Hz), 30.8, 30.0 (d, *J* = 24.0 Hz), 28.9, 28.1, 26.5, 26.0, 25.8, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -80.2 (*trans*),-78.0 (*cis*) ppm;

FTIR (KBr, Nujol): ν 3424, 2924, 2852, 1722, 1668, 1452, 1242, 1177, 1101, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{18}H_{31}O_3FSiNa$ $[M+Na]^+$: 365.1924, found: 365.1924.

(2,6-*Trans*)-butyl 6-cyclohexyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3da)



3da

Purified by flash silica gel column chromatography to give the product as white solid (85% yield); dr = 91:9 (*trans*/*cis*); R_f: 0.40 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 4.79-4.80 (m, 1H), 4.05-4.21 (m, 2H), 3.63-3.68 (m, 1H), 1.96-2.27 (m, 3H), 1.61-1.75 (m, 6H), 1.35-1.45 (m, 3H), 1.13-1.27 (m, 3H), 0.99-1.07 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.15 (s, 9H) ppm;

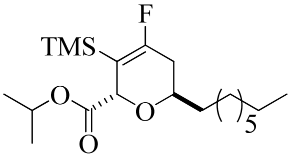
^{13}C NMR (100 MHz, CDCl$_3$): 171.4 (d, *J* = 5.2 Hz), 164.1 (d, *J* = 257.3 Hz), 108.5 (d, *J* = 25.4 Hz), 75.0 (d, *J* = 7.9 Hz), 74.5 (d, *J* = 13.9 Hz), 65.1, 42.5 (d, *J* = 2.3 Hz), 30.6, 29.8 (d, *J* = 24.0 Hz), 28.8, 28.0, 26.5, 26.0, 25.8, 19.1, 13.6, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -79.9 (*trans*), -77.9 (*cis*) ppm;

FTIR (KBr, neat): ν 3448, 2928, 2853, 1732, 1668, 1450, 1248, 1177, 1121, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{19}H_{33}O_3FSiNa$ [M+Na]$^+$: 379.2081, found: 379.2069.

(2,6-*Trans*)-isopropyl 4-fluoro-6-octyl-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cb)



3cb

Purified by flash silica gel column chromatography to give the product as colorless oil (82% yield); dr = (*trans*/*cis*) 92:8; R$_f$: 0.47 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 5.01-5.10 (m, 1H), 4.76 (d, *J* = 3.7 Hz, 1H), 3.84-3.91 (m, 1H), 2.06-2.21 (m, 2H), 1.56-1.64 (m, 1H), 1.42-1.52 (m, 2H), 1.26-1.28 (m, 17H), 0.86 (t, *J* = 6.6 Hz, 3H), 0.15 (s, 9H) ppm;

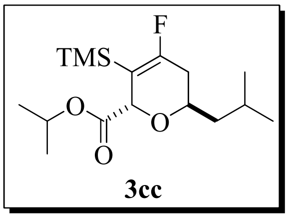
^{13}C NMR (100 MHz, CDCl$_3$): 170.7 (d, *J* = 5.4 Hz), 163.7 (d, *J* = 257.2 Hz), 108.6 (d, *J* = 25.3 Hz), 74.7 (d, *J* = 13.9 Hz), 71.0 (d, *J* = 8.2 Hz), 68.9, 35.8 (d, *J* = 2.3 Hz), 32.4 (d, *J* = 23.7 Hz), 31.9, 29.6, 29.5, 25.3, 22.6, 21.8, 21.8, 14.1, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -80.6 (*trans*), -78.5 (*cis*) ppm;

FTIR (KBr, neat): ν 3435, 2928, 2856, 1730, 1668, 1466, 1248, 1179, 1105, 843 cm-1;

HRMS (ESI): m/z Calcd. for $C_{20}H_{37}O_3FSiNa$ $[M+Na]^+$:395.2394, found: 395.2392.

(2,6-*Trans*)-isopropyl 4-fluoro-6-isobutyl-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cc)



3cc

Purified by flash silica gel column chromatography to give the product as colorless oil (80% yield); dr = 94:6 (*trans*/*cis*); R$_f$: 0.46 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 5.03-5.09 (m, 1H), 4.76 (d, *J* = 3.7 Hz, 1H), 3.96-4.03 (m, 1H), 2.05-2.19 (m, 2H), 1.79-1.90 (m, 1H), 1.51-1.58 (m, 1H), 1.23-1.29 (m, 7H), 0.92 (t, *J* = 6.0 Hz, 6H), 0.15 (s, 9H) ppm;

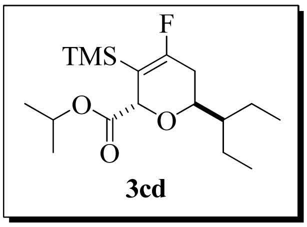
^{13}C NMR (100 MHz, CDCl$_3$): 170.7 (d, *J* = 5.2 Hz), 163.6 (d, *J* = 257.3Hz), 108.5 (d, *J* = 25.2 Hz), 74.7 (d, *J* = 13.9 Hz), 69.2 (d, *J* = 8.4 Hz), 68.9, 45.2 (d, *J* = 2.4 Hz), 32.8 (d, *J* = 23.7 Hz), 24.4, 23.2, 22.3, 21.8, 21.7, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -80.6 (*trans*),-78.6 (*cis*) ppm;

FTIR (KBr, neat): ν 3443, 2957, 2900, 1728, 1668, 1468, 1248, 1179, 1105, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{16}H_{29}O_3FSiNa$ [M+Na]$_+$: 339.1768, found: 339.1765.

(2,6-*Trans*)-isopropyl 4-fluoro-6-(pentan-3-yl)-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cd)



3cd

Purified by flash silica gel column chromatography to give the product as colorless oil (78% yield); dr = 93:7 (*trans*/*cis*); R$_f$: 0.46 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 5.01-5.10 (m, 1H), 4.76 (d, *J* = 3.4 Hz, 1H), 3.83-3.88 (m, 1H), 2.22-2.29 (m, 1H), 2.02-2.10 (m, 1H), 1.22-1.57 (m, 11H), 0.86-0.90 (m, 6H), 0.15 (s, 9H) ppm;

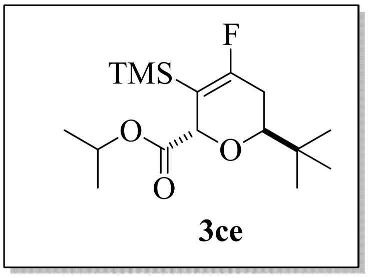
^{13}C NMR (100 MHz, CDCl$_3$): 170.7 (d, *J* = 5.2 Hz), 164.1 (d, *J* = 256.9Hz), 108.5 (d, *J* = 25.3 Hz), 74.7 (d, *J* = 13.9 Hz), 72.3 (d, *J* = 7.9 Hz), 68.9, 45.5 (d, *J* = 2.4 Hz), 29.9 (d, *J* = 23.9 Hz), 21.8, 21.8, 20.9, 20.8, 11.3, 11.0, -1.0 ppm;

19F NMR (282.4 MHz, CDCl$_3$): -80.1 (*trans*), -77.9 (*cis*) ppm;

FTIR (KBr, neat): ν 3439, 2966, 2877, 1728, 1670, 1466, 1375, 1248, 1180, 1103, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{17}H_{31}O_3FSiNa$ $[M+Na]^+$: 353.1924, found: 353.1922.

(2,6-*Trans*)-isopropyl 6-tert-butyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ce)



3ce

Purified by flash silica gel column chromatography to give the product as white solid (77% yield); dr = 94:6 (*trans*/*cis*); R_f: 0.43 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, $CDCl_3$): 5.02-5.10 (m, 1H), 4.78 (d, *J* = 2.8 Hz, 1H), 3.53 (dd, *J* = 3.6, 7.2 Hz, 1H), 2.23-2.30 (m, 1H), 1.97-2.04 (m, 1H), 1.27 (dd, *J* = 3.6, 6.4 Hz, 6H), 0.92 (s, 9H), 0.15 (s, 9H) ppm;

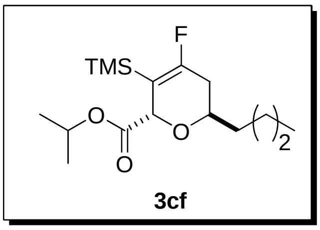
^{13}C NMR (100 MHz, $CDCl_3$): 170.7 (d, *J* = 5.5 Hz), 164.3 (d, *J* = 256.9 Hz), 108.3 (d, *J* = 25.3 Hz), 77.9 (d, *J* = 7.7 Hz), 74.9 (d, *J* = 14.0 Hz), 68.8, 33.7 (d, *J* = 2.4 Hz), 27.3 (d, *J* = 24.1 Hz), 25.5 (d, *J* = 7.4 Hz), 21.8, 21.8, -1.0 (d, *J* = 1.3 Hz) ppm;

^{19}F NMR (282.4 M Hz, $CDCl_3$): -79.8 (*trans*), -77.5 (*cis*) ppm;

FTIR (KBr, Nujol): ν 3437, 2959, 2856, 1730, 1670, 1460, 1375, 1248, 1179, 1105, 845 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{16}H_{29}O_3FSiNa$ $[M+Na]^+$: 339.1768, found: 339.1768.

(2,6-*Trans*)-isopropyl 6-butyl-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cf)



3cf

Purified by flash silica gel column chromatography to give the product as colorless oil (83% yield); dr = 92:8 (*trans*/*cis*); R_f: 0.41 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 5.02-5.11 (m, 1H), 4.77 (d, J = 3.6 Hz, 1H), 3.85-3.92 (m, 1H), 2.07-2.22 (m, 2H), 1.55-1.64 (m, 1H), 1.45-1.53 (m, 2H), 1.31-1.39 (m, 3H), 1.28 (dd, *J* = 2.5, 6.3 Hz, 6H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.15 (s, 9H) ppm;

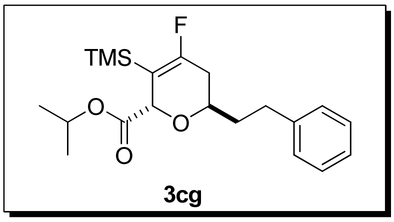
^{13}C NMR (100 MHz, CDCl$_3$): 170.7 (d, *J* = 5.3 Hz), 163.6 (d, *J* = 257.2 Hz), 108.6 (d, *J* = 25.2 Hz), 74.7 (d, *J* = 13.8 Hz), 70.9 (d, *J* = 8.3 Hz), 68.9, 35.5 (d, *J* = 2.5 Hz), 32.4 (d, *J* = 23.7 Hz), 27.4, 22.6, 21.8, 21.8, 14.0, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -80.6 (*trans*), -78.5 (*cis*) ppm;

FTIR (KBr, neat): ν 3439, 2958, 2936, 1728, 1668, 1465, 1248, 1178, 1103, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{16}H_{29}O_3FSiNa$ $[M+Na]^+$: 339.1768, found: 339.1768.

(2,6-*Trans*)-isopropyl 4-fluoro-6-phenethyl-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cg)



3cg

Purified by flash silica gel column chromatography to give the product as colorless oil (78% yield); dr = (*trans*/*cis*) 89:11; R_f: 0.30 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, $CDCl_3$): 7.16-7.30 (m, 5H), 5.02-5.12 (m, 1H), 4.81 (d, *J* = 3.1 Hz, 1H), 3.94-4.00 (m, 1H), 2.85-2.93 (m, 1H), 2.64-2.70 (m, 1H), 2.10-2.26 (m, 2H), 1.78-1.97 (m, 2H), 1.27 (dd, *J* = 2.3, 6.2 Hz, 6H), 0.15 (s, 9H) ppm;

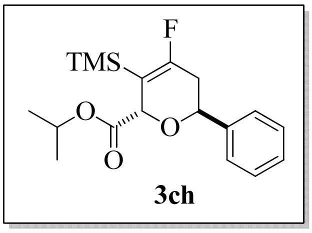
^{13}C NMR (100 MHz, $CDCl_3$): 170.6 (d, *J* = 5.4 Hz), 163.4 (d, *J* = 257.2 Hz), 141.8, 128.4, 128.3, 125.9, 108.7 (d, *J* = 25.6 Hz), 74.7 (d, *J* = 13.8 Hz), 70.4 (d, *J* = 8.3 Hz), 69.0, 37.6 (d, *J* = 2.4 Hz), 32.3 (d, *J* = 24.1 Hz), 31.6, 21.8, 21.8, -1.0 ppm;

19F NMR (282.4 MHz, $CDCl_3$): -80.7 (*trans*), -78.7 (*cis*) ppm;

FTIR (KBr, neat): ν 3437, 2980, 2900, 1730, 1668, 1454, 1248, 1179, 1105, 843 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{16}H_{29}O_3FSiNa$ $[M+Na]^+$: 387.1768, found: 387.1774.

(2,6-*Trans*)-isopropyl 4-fluoro-6-phenyl-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ch)



3ch

Purified by flash silica gel column chromatography to give the product as colorless oil (51% yield); dr = 93:7 (*trans*/*cis*); R_f: 0.30 (hexane: diethyl ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 7.30-7.41 (m, 5H), 5.04-5.14 (m, 2H), 4.94 (d, *J* = 3.6 Hz, 1H), 2.56-2.64 (m, 1H), 2.39-2.46 (m, 1H), 1.30 (t, *J* = 6.2 Hz, 6H), 0.15 (s, 9H) ppm;

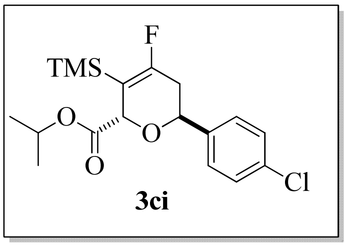
^{13}C NMR (100 MHz, CDCl$_3$): 170.6 (d, *J* = 5.4 Hz), 163.4 (d, *J* = 257.2 Hz), 141.8, 128.4, 128.3, 125.9, 108.7 (d, *J* = 25.6 Hz), 74.7 (d, *J* = 13.8 Hz), 70.4 (d, *J* = 8.3 Hz), 69.0, 37.6 (d, *J* = 2.4 Hz), 32.3 (d, *J* = 24.1 Hz), 31.6, 21.8, 21.8, -1.0 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -80.0 (*trans*), -78.1 (*cis*) ppm;

FTIR (KBr, neat): ν 3441, 2980, 2902, 1728, 1667, 1454, 1248, 1170, 1103, 1069, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{18}H_{25}O_3FSiNa$ [M+Na]$^+$: 359.1455, found: 359.1460.

(2,6-*Trans*)-isopropyl 6-(4-chlorophenyl)-4-fluoro-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ci)



3ci

Purified by flash silica gel column chromatography to give the product as colorless oil (53% yield); dr = 94:6 (*trans*/*cis*); R_f: 0.53 (hexane: ethyl acetate = 4:1);

^{1}H NMR (400 MHz, $CDCl_3$): 7.31-7.36 (m, 4H), 5.04-5.12 (m, 2H), 4.92 (d, *J* = 3.6 Hz, 1H), 2.37-2.56 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 6H), 0.22 (s, 9H) ppm;

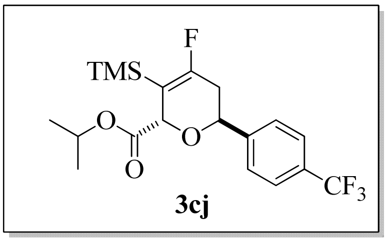
^{13}C NMR (100M Hz, $CDCl_3$): 170.5 (d, *J* = 5.4 Hz), 163.1 (d, *J* = 257.8 Hz), 139.2, 133.8, 128.7, 127.5, 108.8 (d, *J* = 25.3 Hz), 74.8 (d, *J* = 13.8 Hz), 71.7 (d, *J* = 8.7 Hz), 69.3, 33.4 (d, *J* = 24.8 Hz), 21.8 , 21.8, -0.9 ppm;

^{19}F NMR (282.4 M Hz, $CDCl_3$): -80.1 (*trans*), -78.2 (*cis*) ppm;

FTIR (KBr, neat): ν 3439, 2980, 2900, 1732, 1667, 1492, 1372, 1248, 1188, 1170, 1105, 842 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{18}H_{24}O_3FClSiNa$ $[M+Na]^+$: 393.1065, found: 393.1065.

(2,6-*Trans*)-isopropyl 4-fluoro-6-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3cj)



3cj

Purified by flash silica gel column chromatography to give the product as colorless oil (68% yield); dr = 94:6 (*trans*/*cis*); R_f: 0.35 (hexane: diether ether = 10:1);

^{1}H NMR (400 MHz, CDCl$_3$): 7.63 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 5.06-5.19 (m, 2H), 4.95 (d, *J* = 3.9 Hz, 1H), 2.42-2.56 (m, 2H), 1.29 (dd, *J* = 6.3, 8.8 Hz, 6H), 0.23 (s, 9H) ppm;

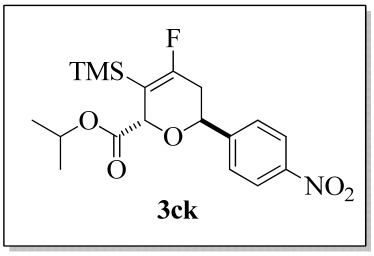
^{13}C NMR (100 MHz, CDCl$_3$): 170.4 (d, *J* = 5.4 Hz), 163.1 (d, *J* = 257.8 Hz), 144.7, 130.2 (q, *J* = 32.3 Hz), 126.3, 125.5 (d, *J* = 7.4 Hz), 124.1 (d, *J* = 270.0 Hz), 108.9 (d, *J* = 25.3Hz), 74.9 (d, *J* = 13.7 Hz), 71.7 (d, *J* = 8.9 Hz), 69.4, 33.4 (d, *J* = 25.1 Hz), 21.8, 21.8, -0.9 ppm;

^{19}F NMR (282.4 MHz, CDCl$_3$): -62.6 (CF3), -80.2 (*trans*), -78.3 (*cis*) ppm;

FTIR (KBr, neat): ν 3439, 2981, 2903, 1732, 1666, 1492, 1375, 1325, 1249, 1169, 1126, 1107, 1066, 841 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{19}H_{24}O_3F_4SiNa$ $[M+Na]^+$: 427.1329, found: 427.1324.

(2,6-*Trans*)-isopropyl 4-fluoro-6-(4-nitrophenyl)-3-(trimethylsilyl)-5,6-dihydro-*2H*-pyran-2-carboxylate (3ck)



3ck

Purified by flash silica gel column chromatography to give the product as white solid (43% yield); dr = 91:9 (*trans*/*cis*); R_f: 0.46 (hexane: ethyl acetate = 4:1);

^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 5.21-5.25 (m, 1H), 5.05-5.13 (m, 1H), 4.95 (d, *J* = 3.9 Hz, 1H), 2.42-2.54 (m, 2H), 1.28 (dd, *J* = 6.3, 9.3 Hz, 6H), 0.22 (d, *J* = 0.96 Hz, 9H) ppm;

^{13}C NMR (100M Hz, $CDCl_3$): 170.3 (d, *J* = 5.2 Hz), 162.5 (d, *J* = 257.9 Hz), 148.0 (d, *J* = 2.7 Hz), 147.5, 126.6, 123.8, 109.0 (d, J = 25.7 Hz), 74.7 (d, *J* = 13.6 Hz), 71.2 (d, *J* = 8.9 Hz), 69.5, 33.3 (d, *J* = 25.6 Hz), 21.8, -0.9 ppm;

^{19}F NMR (282.4 M Hz, $CDCl_3$): -80.2 (*trans*), -78.3 (*cis*) ppm;

FTIR (KBr, Nujol): ν 3439, 2954, 2852, 1728, 1659, 1528, 1363, 1249, 1221, 1173, 1103, 1076, 847 cm^{-1};

HRMS (ESI): m/z Calcd. for $C_{18}H_{24}O_3FNSiNa$ $[M+Na]^+$: 404.1310, found: 404.1305.

CHAPTER 4

Pd-Catalyzed Coupling of Polyfluoroarenes and Polyfluorobenzoic Acids with Simple Arenes: Efficient Entry to Fluorobiphenyls

4.1 Introduction

The development of new reactions capable of catalytically transforming the inert C–H bonds of organic molecules into useful functional groups is an area of research which has attracted tremendous attention. Among them, the decarboxylative coupling[97] and the coupling of two C–H bonds[98] to form a C–C bond are attractive methods as it can provide practical methods for the construction of complex molecules. However, the oxidative arylation of electron-deficient arenes by simple arenes is difficult because of their poor coordination with Pd.[99]

Recently, polyfluoroarenes have been shown to be useful substrates for C–H functionalization in the presence of transition metals. Therefore, many groups have contributed in the use polyfluorearenes for coupling reactions.

In 2006, Fagnou's group developed a Pd-catalyzed intermolecular direct arylation of polyfluorobenzenes with aryl halides (Scheme 4.1a).[100] Two years later, Daugulis *et al.* performed a Cu-catalyzed arylation and alkenylation of

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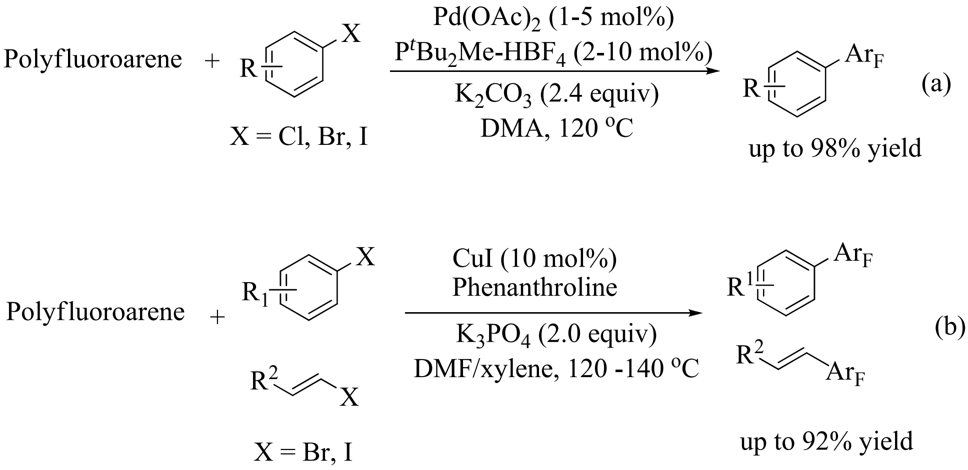
[97] (a) Cornella, J.; Lu, P. F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506; (b) Zhang, F. Z.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768; (c) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem.-Eur. J.* **2010**, *16*, 5876; (d) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564; (e) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194; (f) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

[98] (a) Stuart, D. R.; Fagnou, K.*Science* **2007**, *316*, 1172; (b) Qin, C.; Lu, W. *J.Org. Chem.* **2008**, *73*, 7424; (c) Kobayashi, O.; Urajuchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679; (d) Liu, W.; Cao, H.; Lei, A. *Angew. Chem.,Int. Ed.* **2010**, *49*, 2004; (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115; (f) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Chem. Soc.* **2010**, *132*, 1822; (g) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207; (h) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137; (i) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am.Chem. Soc.* **2009**, *131*, 1668.

[99] (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072; (b) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874.

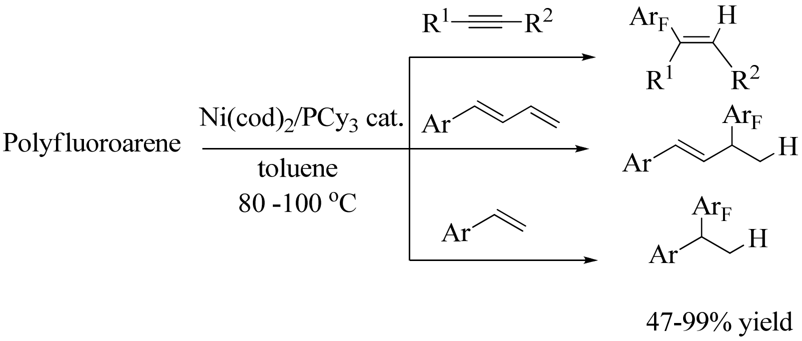
[100] (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754; (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097; (c) René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.

polyfluorobenzenes (Scheme 4.1b).[101] In 2009, Su *et al.* investigated the oxidative direct arylation of polyfluorobenzenes with arylboronic acids.[102]



Scheme 4.1 Direct Arylation of Polyfluorobenzenes with Aryl Halides

In addition, examples of C–H functionalization of polyfluoroarenes for direct alkylation have been well studied. In 2008, Hiyama *et al.* reported nickel-catalyzed alkenylation and alkylation of fluoroarenes *via* activation of C–H bond,[103] where the desired products were obtained in excellent regio- and stereoselectivities (Scheme 4.2).



Scheme 4.2 Nickel-Catalyzed Alkenylation and Alkylation of Fluoroarenes

In 2010, Su *et al.* reported a copper-catalyzed direct oxidative cross-coupling of electron-deficient polyfluoroarenes with terminal alkynes using O_2

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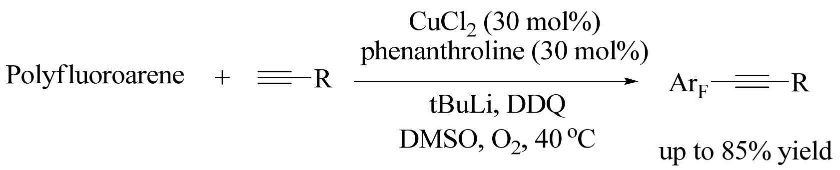
[101] (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128; (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185; (c) Do, H.-Q.; Daugulis, O. *Chem. Commun.* **2009**, 6433.

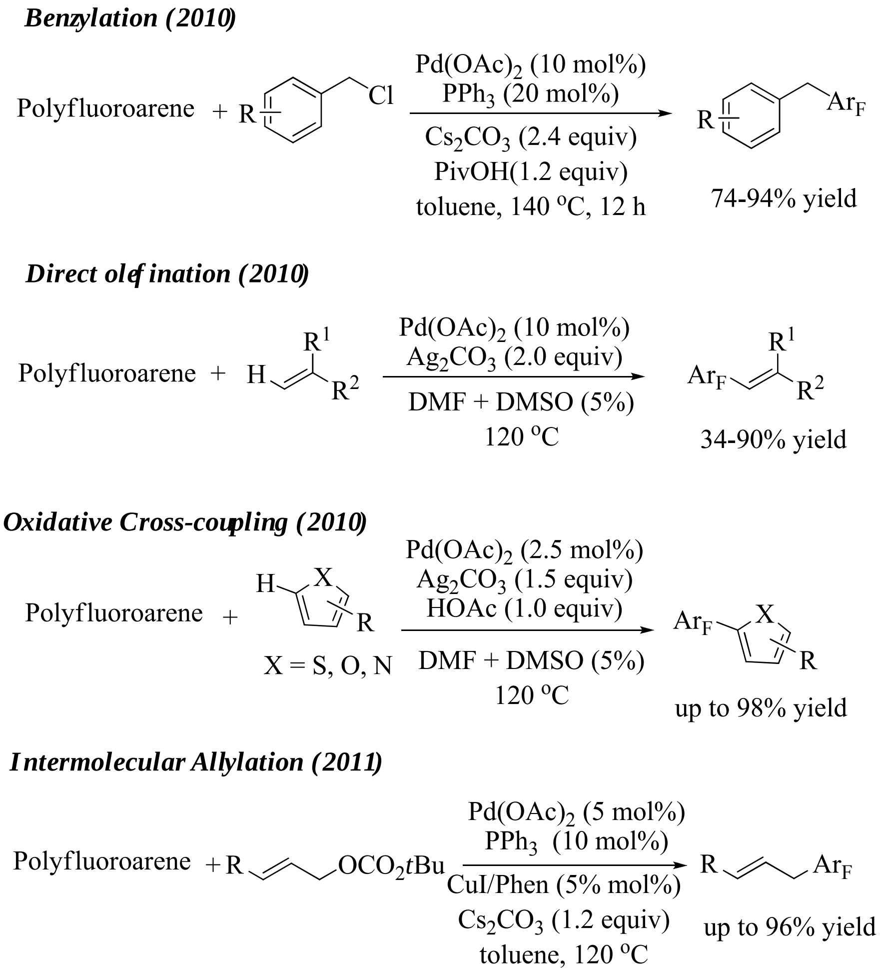
[102] Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346.

[103] Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170.

as an oxidant (Scheme 4.3).[104] This reaction proceeds under mild conditions and tolerates a number of functional groups.



Scheme 4.3 Cu Catalyzed Oxidative Cross-Coupling of Polyfluoroarenes With Terminal Alkynes



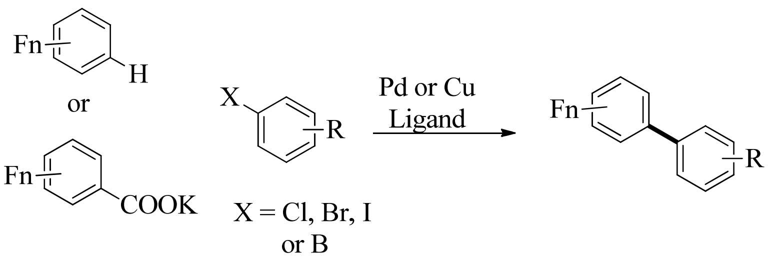
Scheme 4.4 Benzylation, Direct Olefination, Oxidative Cross-coupling of Aromatic Heterocycles, and Intermolecular Allylation with Polyfluoroarenes reported by Zhang et al

---

[104] (a) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522.

It is worth to note that very recently Zhang *et al.* developed straightforward protocols for benzylation, direct olefination, oxidative cross-coupling of aromatic heterocycles, and intermolecular allylation with polyfluoroarenes (Scheme 4.4). [105]

Typical method



Scheme 4.5 Typical Arylation of Polyfluoroarenes and Polyfluorobenzoic Acids

Synthesis of fluorobiphenyls *via* Pd or Cu-catalyzed direct C–H bond functionalization of polyfluoroarenes with ArX, or arylboronic acids have been reported (Scheme 4.5). In addition, representative examples include decarboxylative coupling of benzoic acids with aryl halides or triflates with carefully optimized Pd/Cu catalytic systems by Goossen *et al*, [106] and the Pd/Ag decarboxylative Heck-type of olefination and biaryl coupling of aromatic carboxylic acids by Meyers.[107] Recently Liu and co-workers reported that both Cu and Pd catalysts could catalyze the decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides and bromides. [108] We envisage that using

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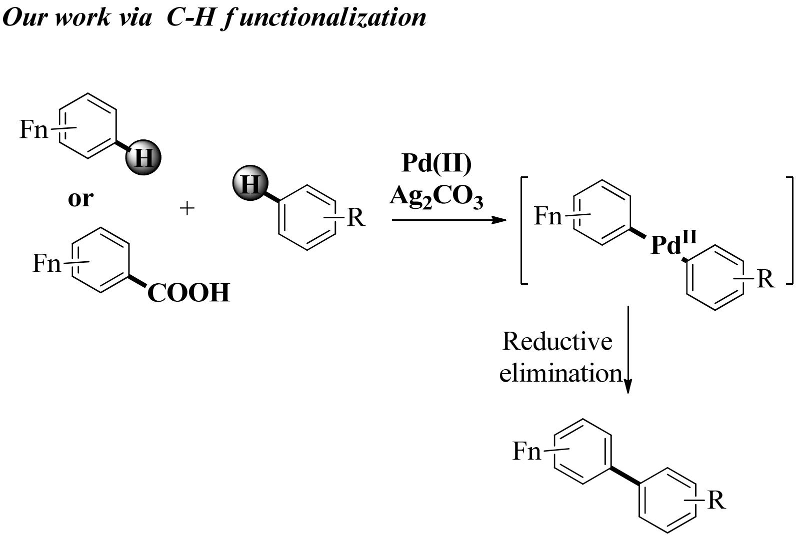
[105] (a) Fan, S.; He, C-Y.; Zhang, X. *Chem. Commun.* **2010**, *46*, 4926; (b) Zhang, X.; Fan, S.; He, C. Y.; Wan, X.; Min, Q. Q.; Yang, J.; Jiang, Z. X. *J. Am. Chem, Soc. 2010*, *132*, 4506;. (c) He, C-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850; (d) Fan, S.; Chen, F. Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918.

[106] (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662; (b) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103; (c) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (d) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248.

[107] (a) Tanaka, D.; Romeril, A. S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323; (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, 6, 433; (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

[108] (a) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350; (b) Shang, R.; Xu, Q.; Jiang, Y-Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1003.

the same reaction conditions, decarboxylation of polyfluorobenzoic acid may lead to the same palladium complex, thus affording the same product when coupled with simple arenes (Scheme 4.6).



Scheme 4.6 Arylation of Polyfluoroarenes and Polyfluorobenzoic Acids *via* C–H Functionalization

Synthesis of organofluorine compounds by C–F bond formation is very efficient. As shown in chapter 2, we reported the methods of direct electrophilic fluorination of alkenes. On the other hand, we focus on synthesis of more useful fluorinated targets using organofluorine substrates. As part of our ongoing research on the development of efficient methods for the construction of C–C bonds, we became interested in the direct cross-coupling of polyfluoroarenes or polyfluorobenzoic acids with simple arenes without using prefunctionalized substrates. From the point of view of atom-economy, the carbon-carbon bond formation obtained *via* coupling of the two C–H bonds to form C–C bond (*i.e.*, the approach of oxidative cross-coupling) would provide one of the most straightforward and efficient methods in organic synthesis. Herein we describe the method for direct Pd-catalyzed the direct cross couplings of electron-deficient polyfluoroarenes with simple arenes *via* two C–H bonds functionalization.[109] Using a similar catalytic system, we discovered a ligand-free, low catalyst loading (5 mol%) Pd-catalyzed decarboxylative cross coupling reaction of electron-deficient polyfluorobenzoic acids with simple arenes *via* C–H bonding functionalization. These straightforward protocols provide new and efficient methods for the synthesis of fluorobiphenyls.

4.2 Results and Discussion

First, we optimized the arylation of polyfluoroarenes with simple arenes. The electron-deficient pentafluorobenzene (**1a**) and *p*-xylene (**2a**) were choosen as model substrates. As summarized in Table 4.1, the reaction was carried out using **1a** (1.0 equiv), **2a** (about 25.0 equiv), Ag_2CO_3 (2.0 equiv), and $Pd(OAc)_2$ (10 mol %) with DMSO (10%) at 120 ^oC. The desired crossing-coupling product **3a** was obtained in excellent yield (Table 4.1, entry 9). At the same time, a small amount of side-products **4a** and **5a** due to homo-coupling and oxidation of arene were observed. Other Pd sources and oxidants were also examined, and it is notable that $Pd(OAc)_2$, and Ag_2CO_3 with 20% DMSO proved to be the best choice in terms of reaction efficiency (Table 4.1, entry 28). The addition of DMSO is very important, and use of other solvents such as DMF, NMP and dioxane led to a lower yield of **3a** (Table **1**, entry 6-8). Presumably, DMSO functions as a ligand to activate the Pd catalyst and prevents the formation of palladium black.[110] The catalyst loading of $Pd(OAc)_2$ could be further lowered to 7.5 mol% to give the desired products in good yields (Table **1**, entry 12).

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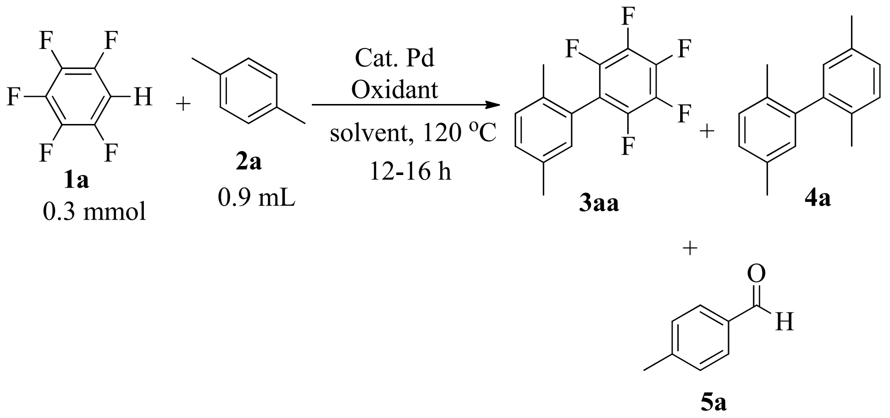
[109] While this manuscript was in preparation, a report on Pd(OAc)2 catalyzed arylation perfluorobenzenes with simple arenes using Pd/Cu with base and acid catalytic system was reported : Wei Y.; Su, W. *J. Am. Chem. Soc.* **2010,** *132*, 16377.

[110] Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348, and references therein.

Table 4.1.

Pd Sources Screening for Oxidative Arylation of Pentafluorobenzene **1a** with p-xylene **2a** [a]



Entry	Pd (mol%)	Oxidant	Additive	Yield (**3aa**, %)[b]
1	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	23
2	$PdCl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	25
3	$Pd(CH_3CN)Cl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	15
4	$Pd(PhCN)Cl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	0
5	$Pd(acac)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	6
6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMF (10%)	30
7	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	NMP (10%)	21
8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	dioxane (10%)	18
9	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	85
10	$Pd(OAc)_2$ (10)	None or +1 equiv K_2CO_3	DMSO (10%)	0
11	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1.0 equiv)	DMSO (10%)	48
12	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1.5 equiv)	0.1 mL DMSO (10%)	68
13	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.5 equiv)	DMSO (10%)	88
14	$Pd(OAc)_2$ (10)	2.0 equiv Ag_2CO_3 + 1 equiv HOAc	DMSO (10%)	88
15	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2.0 equiv)	DMSO (10%)	19
16	$Pd(OAc)_2$ (10)	AgOAc (2.0 equiv)	DMSO (10%)	35
17	$Pd(OAc)_2$ (10)	1.0 equiv AgOAc + 1.0 equiv Ag_2CO_3	DMSO (10%)	73
18	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	None	24

19	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (5%)	82
20	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (15%)	84
21	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	87
22	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (25%)	81
23	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (30%)	39
24	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (50%)	15
25	none	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	0
26	$Pd(OAc)_2$ (2.5)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	31
27	$Pd(OAc)_2$ (5)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	68
28	***$Pd(OAc)_2$*** ***(7.5)***	***Ag_2CO_3*** ***(2.0 equiv)***	***DMSO*** ***(20%)***	***88***
29	$Pd(OAc)_2$ (12.5)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	84
30[c]	$Pd(OAc)_2$ (7.5)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	19
31[d]	$Pd(OAc)_2$ (7.5)	Ag_2CO_3 (2.0 equiv)	DMSO (20%)	85

[a] Reactions were performed in sealed tube under air with pentafluorobenzene (0.3 mmol)

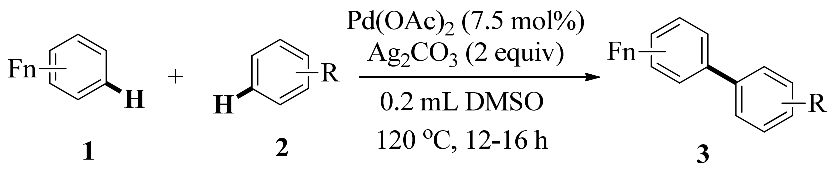
[b] Isolated yield based on pentafluorobenzene.

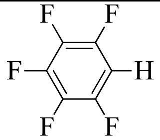
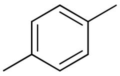
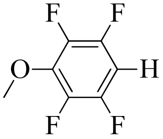
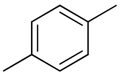
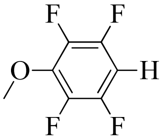
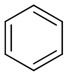
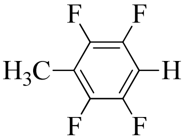
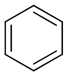
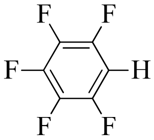
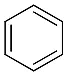
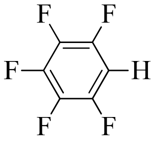
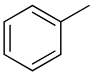
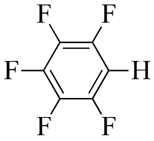
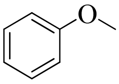
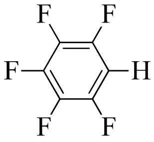
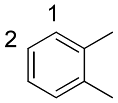
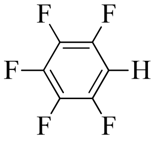
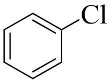
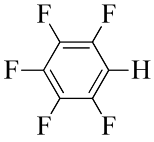
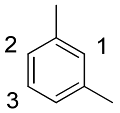
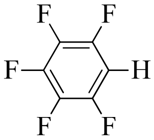
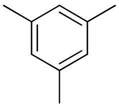
[c] The reaction was carried out at 110 °C for 16 h.

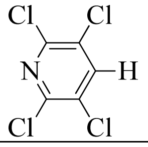
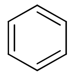
[d] The reaction was carried out at 130 °C for 12 h.

With these optimized conditions in hand (Table 4.1, entry 28), we proceeded to explore the scope of the direct arylation of polyfluoarenes with simple arenes. The results were summarized in Table 4.2. To our delight, moderate to good yields of the desired product were obtained for these reactions (Table 2，entries 1-9), except in the case of mesitylene (Table 2，entry 10), which was deactivated by strong steric effect. When perchloropyridine was used to carry out this reaction, the desired arylation product was obtained in 39% yield (Table 4.2, entry 12).

Table 4.2.
Decarboxylative Arylation of Polyfluorobenzenes **1** with Various Simple Arenes **2** [a]



Entry	Polyfluorobenzenes	Arene	Product	Yield (%)[b]
1			**3a**	88
2			**3b**	84
3			**3c**	85
4			**3d**	86
5			**3e**	78
6[d]			**3f**	81[c] *o*:*p*:*m* = 2:2:1
7			**3g**	53 *p*:*o* = 7:1
8			**3h**	86 *1*:*2* = 1:9.2
9			**3i**	89 *m*: *p*:*o* = 1.5:1:1
10			**3j**	76 *1*:*2*:*3* = 0:5:2
11			**3k**	0

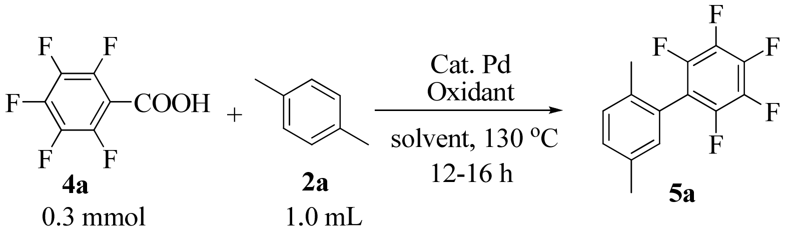
12			**3l**	39

[a] Reactions were performed in sealed tube under air with polyfluorobenzene **1** (0.3 mmol) and simple arenes **2** (0.9 ml). [b] Isolated yield based on polyfluorobenzene. [c] Yield determined as a mixture of isomers, and the ratio of isomers was calculated by GC–MS or/and ^{19}F NMR. [d] 10 mol% $Pd(Ac)_2$ was used.

Based on the condition of direct arylation of polyfluoroarenes with simple arenes, as summarized in Table 4.3, we optimized the arylation of pentafluorobenzonic acids with simple arenes. The electron-deficient pentafluorobenzonic acid (**4a**) and *p*-xylene (**2a**) were choosen as model substrates. The reaction was carried out under the optimized conditions: **4a** (1.0 equiv), **2a** (1 ml, about 25.0 equiv), Ag_2CO_3 (2.0 equiv), and $Pd(OAc)_2$ (5 mol %) with DMSO (10%) at 130 °C for 12-16 h. The desired crossing-coupling product **5a** was obtained with excellent yield (Table 4.3, entry 12).

Table 4.3

Decarboxylative Arylation of Pentafluorobenzoic Acid **4a** with *p*-xylene **2a** [a]



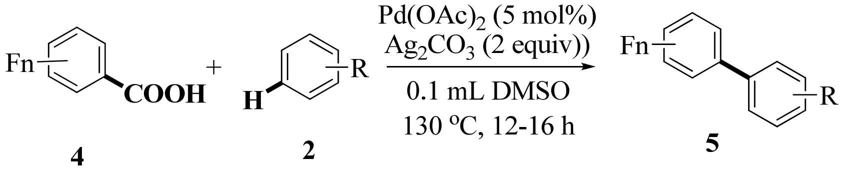
Entry	Pd (mol%)	Oxidant	Solvent	Yield of **3ca** (%)[b]
1	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	88
2	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	44
3	$PdCl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	5
4	$Pd(CH_3CN)Cl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	53
5	$Pd(PhCN)Cl_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	0
6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	DMF (10%)	32
7	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	Dioxane (10%)	36

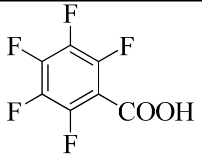
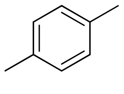
8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0 equiv)	NMP (10%)	34
9	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2.0 equiv)	DMSO (10%)	19
10	$Pd(OAc)_2$ (10)	AgOAc (2.0 equiv)	DMSO (10%)	41
11	$Pd(OAc)_2$ (7.5)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	88
12	***$Pd(OAc)_2$*** ***(5)***	***Ag_2CO_3*** ***(2.0 equiv)***	***DMSO*** ***(10%)***	***89***
13	$Pd(OAc)_2$ (2.5)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	54
14[c]	$Pd(OAc)_2$ (7.5)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	74
15[d]	$Pd(OAc)_2$ (7.5)	Ag_2CO_3 (2.0 equiv)	DMSO (10%)	84

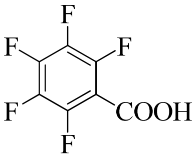
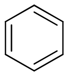
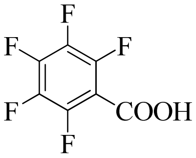
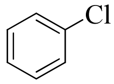
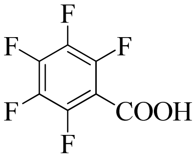
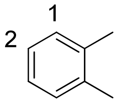
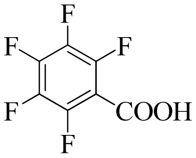
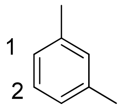
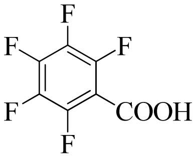
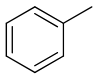
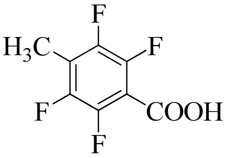
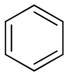
[a] Reactions were performed in sealed tube under air with pentafluorobenzoic acid **1a** (0.3 mmol) and *p*-xylene **2a** (25 equiv); [b] Isolated yield based on pentafluorobenzoic acid; [c] The reaction was carried out at 120 °C for 16 h; [d] The reaction was carried out at 140 °C for 12 h.

Next we proceeded to explore the scope of the decarboxylative arylation of electron-dificeint polyfluorobenzoic acids with various simple arenes using the similar optimized conditions (2.0 equiv Ag_2CO_3, 5 mol% $Pd(OAc)_2$ with 10% DMSO in simple arenes at 130 °C, for more detailed optimization study, please refer to Table 4.3). The results were summarized in Table 4.4. To our delight, moderate to good yields of the desired products were obtained for these decarboxylative arylations (Table 4.4, entries 1-7).

Table 4.4
Decarboxylative Arylation of Polyfluorobenzoic Acid **3a** with Various Simple Arenes **2**.[a]



Entry	Polyfluorobenzoic acid	Arene	Product	Yield (%)[b]
1			**5a**	89

2			**5b**	84
3			**5c**	65 *o*:*m*:*p* = 1:1.5:1
4			**5d**	79 *2*:*1*= 6.3:1
5			**5e**	80 *1*:*2*= 2.2:1
6			**5f**	70[c] *o*: *m*: *p*=2:1:2
7			**5e**	61

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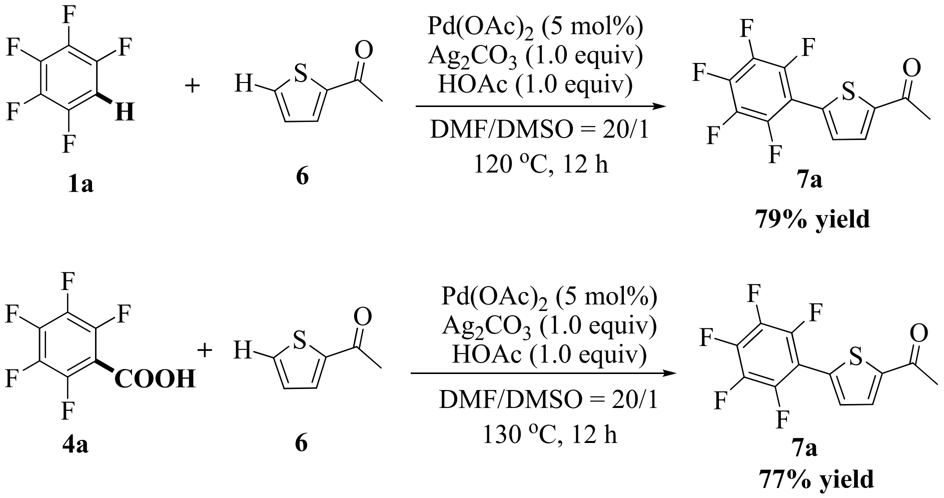
[a] Reactions were performed in sealed tube under air with polyfluorobenzoic acid **4** (0.3 mmol) and simple arenes **2** (0.9 mL). [b] Isolated yield based on polyfluorobenzoic acids. [c] Yield determined as a mixture of isomers, and the ratio of isomers was calculated by GC–MS or/and ^{19}F NMR.

Aromatic heterocycle **6** was also subjected to the reaction (Scheme 4.3). We are happy to find that the desired cross-coupling product was obtained both using pentafluorobenzene and pentafluorobenzonic acid in good yield.



Scheme 4.3 Arylation of Pentafluoroarenes and Pentafluorobenzoic Acids with Aromatic Heterocycles

A mechanism similar to the one proposed by Larrosa[97a] could be operative here. Since both our decarboxylative coupling as well as direct C–H/C–H coupling operate under the same conditions, the catalytic cycles are proposed to be interwined (scheme **2**). Firstly, the palladium inserted into the benzene ring *via* an electrophilic palladation (**I** to **II**) process. This reversible process was first reported in 1965 by Van Helden and later again by Sasson.[111] Decarboxylation using metal carbonates was well-established in the literature,[112] so a silver species facilitated the decarboxylative activation step (**IV** to **V**). In these processes, **II** and **V** could lead to two side products **VI** and **VII**. From the direct arylation of polyfluoroarenes with simple arenes, **VI** could be easily recycled *via* oxidative arylation process with simple arene to afford the same product **3a** (Scheme 4.3, Catalytic cycle **A**). Transmetallation of Ar-Pd species **II** with silver species intermediates **V** would then afford the palladium intermediate **III**, which

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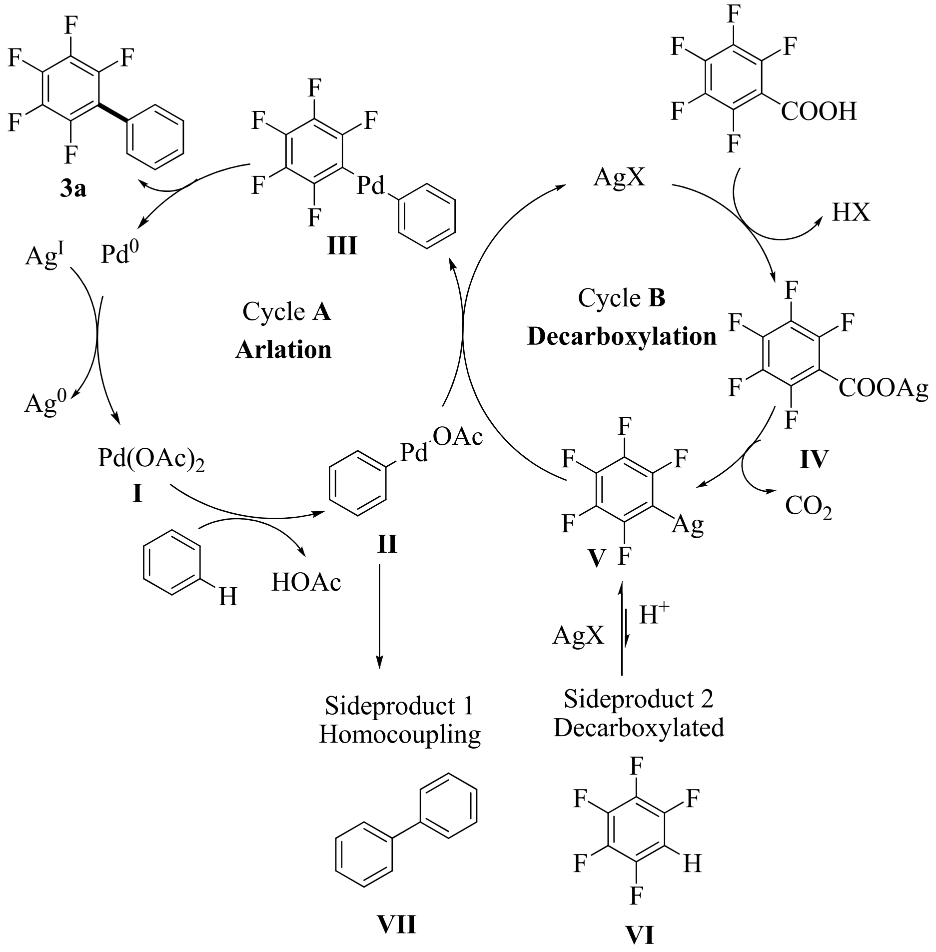
[111] (a) van Helden, R.; Verberg, G. *Recl. TraV. Chim. Pays-Bas* **1965**, *84*, 1263; (b) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *J. Org. Chem.* **2000**, *65*, 3107.

[112] For a recent review, see: Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

could produce the coupled product **3a** through reductive elimination. Finally, oxidation of Pd^0 to Pd^{II} (**I**), also performed by the silver salt, completed the arylation cycle.



Scheme 4.3 Proposed Mechanisms

4.3 Conclusion

In conclusion, we have developed an efficient method for the direct two C–H/C–H arylation that allows the intermolecular coupling of electron-poor polyfluorobenzenes with simple arenes Using similar conditions of Pd/Ag bimetallic catalytic system, we discover the first example of decarboxylative arylation of electron-deficient polyfluorobenzoic acids with simple arenes *via* C–H bond functionalization. Our method uses low catalytic loading of palladium (7.5 mol% or 5 mol%) based on a Pd/Ag bimetallic system without the need to use acid or base. These two processes lead to the same intermediate (Scheme **2**, **III**), providing the desired coupling products in moderate to good yields. Both these methods are complementary to one aother. These straightforward protocols provide new and efficient methods for the synthesis of fluorobiphenyls under simple and mild conditions.

4.4 Experimental Supporting Information

4.4.1 General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification except for CH_2Cl_2 was freshly distilled from CaH_2.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Columns were typically packed as slurry and equilibrated with hexane prior to use.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Liquid samples were examined as film between NaCl or KBr salt plates. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Advance 300, 400 and 500 NMR spectrometers. Chemical shifts ^{1}H NMR spectra are reported as in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-*d* (*J* = 7.264, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); dddd (doublet of doublets of doublets of doublets); dt (doublet of triplets); m (multiplets) and etc. The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as d in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-*d* (*J* = 77.03, triplet).

High resolution mass spectral analysis (HRMS) was performed on Water Q-TOF Premier mass spectrometer (Thermo Electron Corporation).

X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter.

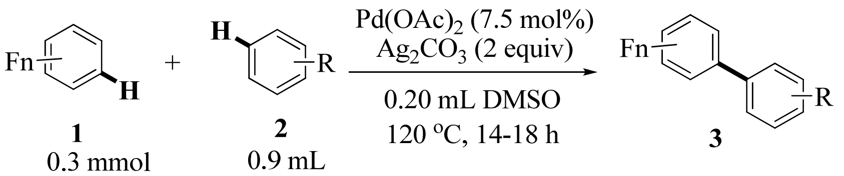
4.4.2.1 Conditions Screening for Oxidative Arylation of Pentafluorobenzene 1a with *p*-xylene 2a

To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added Pd Source (0~12.5 mol%) and oxidant under air, followed by additive with pentafluorobenzene **1a** (50.5 mg, 0.3 mmol), DMSO and *p*-xylene **2a** (0.9 mL) were then added subsequently. The sealed tube was screw capped and heated for 12-16 h (oil bath). After completed, the reaction was cooled to room temperature, then the mixture was diluted with 5 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo at 60 °C. The residue was purified with silica gel chromatography (Hexane) to provide pure product **3a**.

4.4.2.2 Conditions Screening for Decarboxylative Arylation of Pentafluorobenzoic Acid 4a with p-xylene 2a

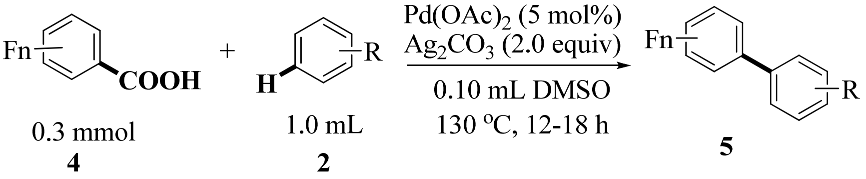
To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added Pd Source (0~10mol%) and Oxidant under air, followed by additive with pentafluorobenzoic **4** (63.6 mg, 0.3 mmol), DMSO (0.1 mL) and *p*-xylene **2a** (0.9 mL) were then added subsequently. The sealed tube was screw capped and heated for 14 h (oil bath). After completed, the reaction was cooled to room temperature, then the mixture was diluted with 5 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo at 60 °C. The residue was purified with silica gel chromatography (Hexane) to provide pure product **5a**.

4.4.3.1 General Procedure for Direct Oxidative Arylation of Polyfluoroarenes 1 with unactivated arenes 2.



To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added $Pd(OAc)_2$ (10 mol%) and Ag_2CO_3 (164 mg, 0.6 mmol, 2.0 equiv) under air, DMSO (0.20 mL),and polyfluoroarenes **1** (0.3 mmol) and simple arenes **2** (0.9 mL) were added subsequently. The sealed tube was screwcapped and heated to 120 °C (oil bath), and stirring for 14-16 h, After completed, the reaction was cooled to room temperature, then the mixture was diluted with 5 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. in vacuo. The residue was purified with silica gel chromatography to provide pure product.

4.4.3.2 General Procedure for Direct Oxidative Arylation of Polyfluorobenzoic Acids 4 with Unactivated arenes 2.

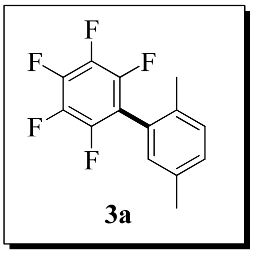


To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added $Pd(OAc)_2$ (5 mol%) and Ag_2CO_3 (164 mg, 0.6 mmol, 2.0 equiv) under air, DMSO (0.10 mL), and polyfluorobenzoic acids **4** (0.3 mmol) and simple arenes **2** (0.9 mL) were added subsequently. The sealed tube was screwcapped and heated to 130 ^{o}C (oil bath), and stirring for 12-16 h, After completed, the reaction was cooled to room temperature, then the mixture was diluted with 5 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. in vacuo. The residue was purified with silica gel chromatography to provide pure product.

All the compounds except **3b** and **3c** are known, so the ^{1}H, ^{13}C and ^{19}F NMR spectra of the compounds were in accordance with those described in the literature.[113,114,115] Each of the *o*-, *m*-, and *p*- isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.

Experimental data (select the several isolated pure product)

2,3,4,5,6-pentafluoro-2',5'-dimethylbiphenyl



3a

Purified by flash silica gel column chromatography to give the product as white solid (88% yield); R_f: 0.58 (hexane);

^{1}H NMR (400 MHz, CDCl3): δ 7.19-7.26 (m, 2H), 7.02 (s, 1H), 2.37 (s, 3H), 2.15 (s, 3H);

13C NMR (100 MHz, CDCl3): δ 145.3-145.2 (m), 142.9-142.8 (m), 142.8-142.7 (m), 139.3 -139.0 (m), 136.4-136.3 (m), 135.6, 134.2, 131.1, 130.4, 130.4, 126.6, 115.8 - 115.4 (m);

^{19}F NMR (282.4 MHz, CDCl3): δ -140.7 (dd, *J* = 23.6, 8.6 Hz, 2F), -155.7 (t, *J* = 21.8 Hz, 1F), -162.5 - 162.4 (m, 2F).

2,3,5,6-tetrafluoro-4-methoxy-2',5'-dimethylbiphenyl

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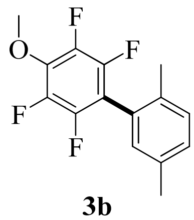
[113] Kamigata, N.; Yoshikawa, M.; Shimizu, T. *J. Fluorine Chem.* **1998**, *87*, 91.

[114] Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*,3346..

[115] Wei Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377.



3b

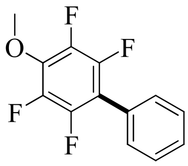
Purified by flash silica gel column chromatography to give the product standing for white solid (84% yield), R_f: 0.50 (hexane);

^{1}H NMR (400 MHz, CDCl$_3$): 2.18 (s, 3H), 2.38 (s, 3H), 4.14 (s, 3H), 7.04 (s, 1H), 7.19 (d, 1H, *J* = 7.9 Hz) and 7.24 (d, 1H, *J* = 7.9 Hz);

^{13}C NMR (100 MHz, CDCl3): 145.4(m), 143.0 142.3 (dm), 139.8 (m), 137.6 (m), 135.4, 134.3, 131.2, 130.2, 130.1, 126.5, 114.0 (t, . *J* = 19.1Hz);

^{19}F NMR (282 MHz, CDCl3): δ -142.5 (dd, *J* = 22.3 Hz, 8.6 Hz, 2F), -158.4 (dd, *J* = 22.3 Hz, 8.6 Hz, 2F).

2,3,5,6-tetrafluoro-4-methoxybiphenyl



3c

Purified by flash silica gel column chromatography to give the product standing for white solid (85% yield, R_f: 0.50 (hexane);

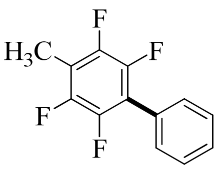
^{1}H NMR (400 MHz, CDCl$_3$): 4.15 (s, 3H), 7.47-7.54 (m, 5H;

^{13}C NMR (100 MHz, CDCl3): 145.5 (m), 143.2, 143.1 (dm), 142.4 (m), 140.1 (m), 130.2, 130.2, 128.9,128.6, 127.3, 114.2 (t, . *J* = 17.1Hz) ;

^{19}F NMR (282 MHz, CDCl3): δ -145.2 (dd, *J* = 22.0 Hz, 8.8 Hz, 2F), -158.3 (dd, *J* = 22.1 Hz, 8.9 Hz, 2F);

HRMS (ESI): m/z Calcd. for $C_{13}H_8F_4O$ $[M+H]^+$: 257.0590, found: 257.0590.

2,3,4,5,6-pentafluorobiphenyl



3d

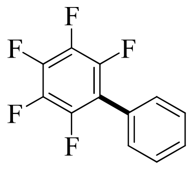
Purified by flash silica gel column chromatography to give the product as white solid (86% yield), R_f: 0.58 (hexane);

^{1}H NMR (400 MHz, CDCl3): δ 7.50-7.48 (m, 5H), 2.34 (t, *J* = 2.1Hz, 3H);

13C NMR (100 MHz, CDCl3): δ 146.7-146.4 (m), 145.0-144.7 (m), 144.2-144.0 (m), 142.5 -142.2 (m), 130.1, 128.9, 128.5, 127.8, 118.1 - 117.8 (m), 115.3115.0 (m), 7.54;

^{19}F NMR (282.4 MHz, CDCl3): δ -144.2 (dd, *J* = 22.3, 12.4 Hz, 2F), -145.7 (dd, *J* = 22.2, 12.5, Hz, 2F).

2,3,4,5,6-pentafluorobiphenyl



3e

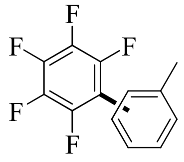
Purified by flash silica gel column chromatography to give the product as white solid(84% yield), R_f: 0.62 (hexane);

^{1}H NMR (400 MHz, CDCl3): δ 7.56-7.53 (m, 1H), 7.51-7.50(m, 2H), 7.45-7.43 (m, 1H);

13C NMR (100 MHz, CDCl3): δ 145.6-145.4 (m), 143.0-142.8 (m), 141.8-

141.5 (m), 139.2 -138.9 (m), 136.7-136.3 (m), 130.2, 129.3, 128.7, 126.4, 116.1 - 115.8 (m);

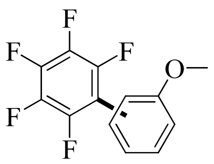
^{19}F NMR (282.4 MHz, CDCl3): δ -143.3 (dd, *J* = 22.3, 8.3 Hz, 2F), -155.8 (t, *J* = 22.8 Hz, 1F), -162.3 - 162.4 (m, 2F).



3f

o:*p*:*m* = 2:2:1

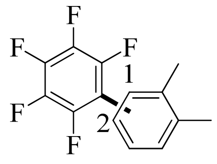
Purified by flash silica gel column chromatography to give the product as white solid (81% yield), R_f: 0.56 (hexane). The ^{1}H, ^{13}C and ^{19}F NMR spectra were in accordance with those described in the literature.[64,65] The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.



3g

p:*o* =7:1

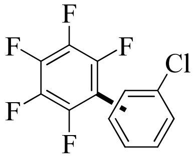
Purified by flash silica gel column chromatography to give the product as white solid(53% yield), R_f: 0.31 (hexane). The ^{1}H, ^{13}C and ^{19}F NMR spectra were in accordance with those described in the literature.[64,65] The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.



3h

2:1 = 9.2:1

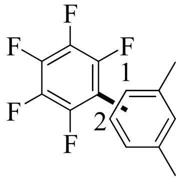
Purified by flash silica gel column chromatography to give the product standing for white solid (86% yield), R_f: 0.56 (hexane). The ^{1}H, ^{13}C and ^{19}F NMR spectra were in accordance with those described in the literature.[63] The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.



3i

o:*p*:*m* = 1:1.4:1

Purified by flash silica gel column chromatography to give the product standing for white solid (72% yield, R_f: 0.52 (hexane). The ^{1}H, ^{13}C and ^{19}F NMR spectra were in accordance with those described in the literature.[65] The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.

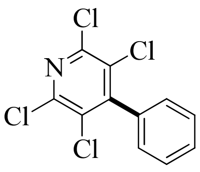


3j

1:*2* = 2.4:1

Purified by flash silica gel column chromatography to give the product as the white solid (76% yield), R$_f$: 0.56 (hexane). The ^{1}H, ^{13}C and ^{19}F NMR spectra were in accordance with those described in the literature.[65] The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.

2,3,5,6-tetrachloro-4-phenylpyridine

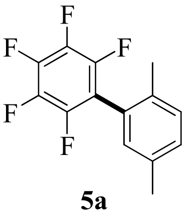


3l

Purified by flash silica gel column chromatography to give the product as white solid (39% yield); R$_f$: 0.35 (hexane/ Ethyl Acetate = 4:1).

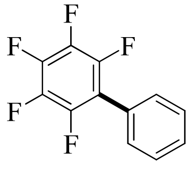
^{1}H NMR (300 MHz, CDCl3): δ 7.51-7.53 (m, 3H), 7.21-7.23 (m, 3H);

^{13}C NMR (75.4 MHz, CDCl3): δ 151.8, 146.4, 135.1, 129.9, 129.5, 128, 8, 128.1.



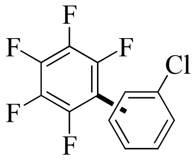
5a

Purified by flash silica gel column chromatography to give the product as white solid (89% yield); R_f: 0.58 (hexane).



5b

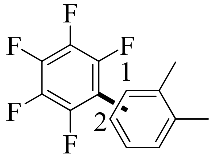
Purified by flash silica gel column chromatography to give the product as white solid(82% yield).



5c

o:*p*:*m* = 1:1.5:1

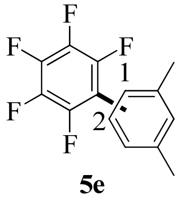
Purified by flash silica gel column chromatography to give the product standing for white solid (65% yield, R_f: 0.52 (hexane). The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.



5d

2:*1* = 6.3:1

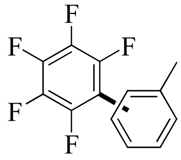
Purified by flash silica gel column chromatography to give the product standing for white solid (79% yield), R_f: 0.56 (hexane).The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}H NMR and/or GC/MS.



5e

1:*2* = 2.2:1

Purified by flash silica gel column chromatography to give the product as the white solid (80% yield), R_f: 0.56 (hexane).The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.

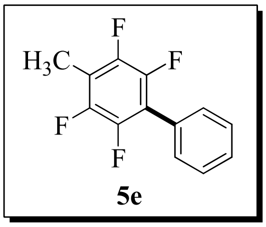


5f

o:*p*:*m* = 2:2:1

Purified by flash silica gel column chromatography to give the product as white solid(70% yield), R_f: 0.56 (hexane). The mixture of isomers of polyfluorophenylated products could not be always isolated by column chromatography, Therefore, the structure and ratio of the isomers were determined by using ^{19}F NMR and/or GC/MS.

2,3,4,5,6-pentafluorobiphenyl



5e

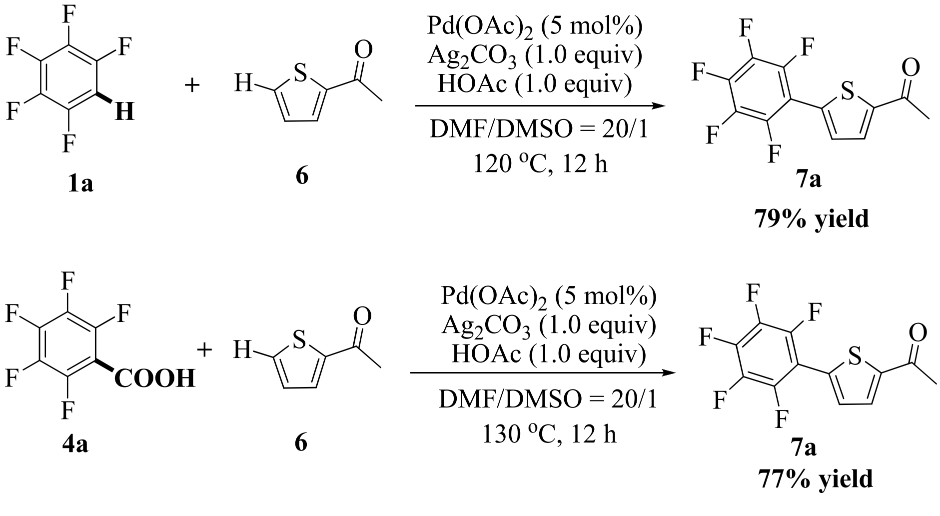
Purified by flash silica gel column chromatography to give the product as white solid (86% yield), R_f: 0.58 (hexane);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 5H), 2.34 (t, *J* = 2.1Hz, 3H);

13C NMR (100 MHz, $CDCl_3$): δ 146.7-146.4 (m), 145.0-144.7 (m), 144.2-144.0 (m), 142.5 -142.2 (m), 130.1, 128.9, 128.5, 127.8, 118.1 - 117.8 (m), 115.3115.0 (m), 7.54;

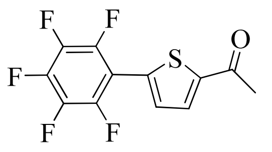
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -144.2 (dd, *J* = 22.3, 12.4 Hz, 2F), -145.7 (dd, *J* = 22.2, 12.5, Hz, 2F).

4.4.3.3 Procedure for Arylation of Pentafluoroarenes and Pentafluorobenzoic Acids with Aromatic Heterocycles 6.



To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added $Pd(OAc)_2$ (5 mol%) and Ag_2CO_3 (164 mg, 0.6 mmol, 2.0 equiv) under air, followed by DMF (1.0 mL), DMSO (50 μL), and HOAc (18 μL, 0.3 mmol, 1 equiv) with stirring. Heterocycles **6** (0.3 mmol) and pentafluoroarene **1a** or pentafluorobenzoic acid **4a** (0.45 mmol) were added subsequently. The sealed tube was screwcapped and heated (oil bath), and stirring for 12 h. After completed, the reaction was cooled to room temperature, then the mixture was diluted with 5 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. in vacuo. The residue was purified with silica gel chromatography to provide pure product.

1-(5-(perfluorophenyl)thiophen-2-yl)ethanone



7a

Purified by flash silica gel column chromatography to give the product as white to light yellow solid, R_f: 0.60 (Hexane /Ethyl Acetate = 4:1).

^{1}H NMR (300 MHz, CDCl3): δ 7.71 (d, *J* = 4.21 Hz, 1H), 7.50 (d, *J* = 4.22 Hz, 1H), 2.60 (s, 3H);

^{13}C NMR (75 MHz, CDCl3): δ 190.5, 145.9, 144.2 (dm, J = 249.1 Hz), 140.7 (dm, *J* = 256.5 Hz), 138.2 (dm, J = 253.4 Hz), 133.9, 131.8, 130.9 (t, *J* = 4.9 Hz), 109.1 (m), 26.7;

^{19}F NMR (282.4 MHz, CDCl3): δ -139.1 (dd, J = 22.0 Hz, 5.9 Hz, 2F), -153.5 (t, J = 20.8 Hz, 1F), -161.4, -161.6 (m, 2F).

LIST OF PUBLICATION

1. **Hai-Qing Luo** and Teck-Peng Loh*. Synthesis of Aryl Allylic Fluorides by Direct Electrophilic Fluorination of Alkenes. *Tetrahedron Lett.* **2009**, *50*, 1554-1556.

2. **Hai-Qing Luo**, Xu-Hong, Hu and Teck-Peng Loh*. Highly Stereo-controlled Synthesis of Fluorinated 2,6-trans Dihydropyrans *via* Prins Cyclization. *Tetrahedron Lett.* **2010**, *51*, 1041-1043.

3. **Hai-Qing Luo**, Teck-Peng Loh*. Pd-Catalyzed Coupling of Polyfluoroarenes and Polyfluorobenzoic Acids with Simple Arenes: Efficient Entry to Fluorobiphenyls. **2011**, *Prepared for publication*.

4. **Hai-Qing Luo**, Teck-Peng Loh*. Synthesis of Fluorinated Dicyanoolefins by Electrophilic Fluorination. **2011**, *Prepared for publication*.

5. **Hai-Qing Luo**, Teck-Peng Loh*. AgF Mediated Homo-Coupling Reaction of Trialkoxy Aryl Silanes”. **2011**, *Prepared for publication*.