EXPLORATORY STUDY ON THE CHEMISTRY OF BROMODIFLUOROMETHYL PHENYL SULFIDE

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
(ORGANIC CHEMISTRY)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2013

Thesis
entitled

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was submitted to the Faculty of Graduate Studies, Mahidol University
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ACKNOWLEDGEMENTS

I would like to express my deepest and sincere gratitude to my supervisor, Professor Dr. Vichai Reutrakul, for his kind supervision, valuable guidance and encouragement throughout this work.

Moreover, I feel very thankful and grateful to Prof. Dr. Manat Pohmakotr and Asst. Prof. Dr. Jaray Jaratjaroonphong for their kindness, valuable discussions and comments on this thesis. Special thanks go to Asst. Prof. Dr. Chutima Kuhakarn for her hard proof-reading through all of my thesis and any of her advice.

My appreciation is also extended to the staff of the Department of Chemistry, Faculty of Science, Mahidol University, Mrs. Patcharin Poochaiwatananon, Miss Amporn Srisuthipruth, and Mrs. Suttiporn Pikulthong for recording spectral data as well as elemental analyses. I would like to express to all of my friends and colleagues, especially the members in laboratory room C505 for their kind helpfulness and the best wonderful relationship.

The financial support was provided by the Center of Excellence for Innovation in Chemistry (PERCH-CIC) and Teaching Assistant program of the Faculty of Science, Mahidol University.

Finally, I wish to express my deepest gratitude to my family for giving me love, care, support, understanding and encouragement.

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EXPLORATORY STUDY ON THE CHEMISTRY OF BROMODIFLUOROMETHYL PHENYL SULFIDE

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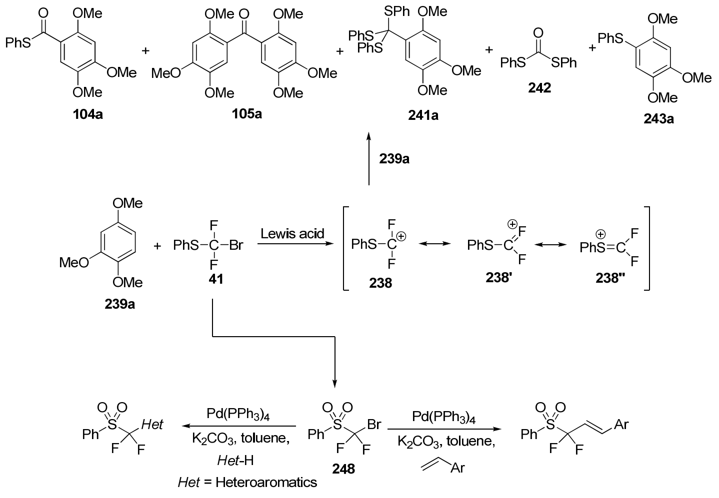
ABSTRACT

The Friedel–Crafts alkylation of activated aromatic compound (**239a**) with bromodifluoromethyl phenyl sulfide (**41**) provided corresponding thioester **104a**, benzophenone **105a**, orthothioester **241a**, *S,S*-diphenyl carbonodithioate (**242**), and phenyl(2,4,5-trimethoxyphenyl)sulfane (**243a**) via 1,1-difluoro-1-phenylsufanyl methyl carbocation intermediates. The formation of the products depends on the reaction conditions employed.

We have also demonstrated the reactivity of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) toward a palladium-catalyzed reaction with suitable coupling partners, including styrene derivatives, vinyl ethers, and heteroaromatics, resulting in successful synthesis of α-alkenyl- and α-heteroaryl-substituted α,α-difluoromethyl phenyl sulfones.



KEY WORDS: FLUOROCARBOCATIONS/ FLUOROALKYLATIONS/ HECK REACTION

181 pages

การศึกษาคุณสมบัติทางเคมีของ โบรโมไดฟลูออโรเมทิล เฟนิล ซัลไฟด์

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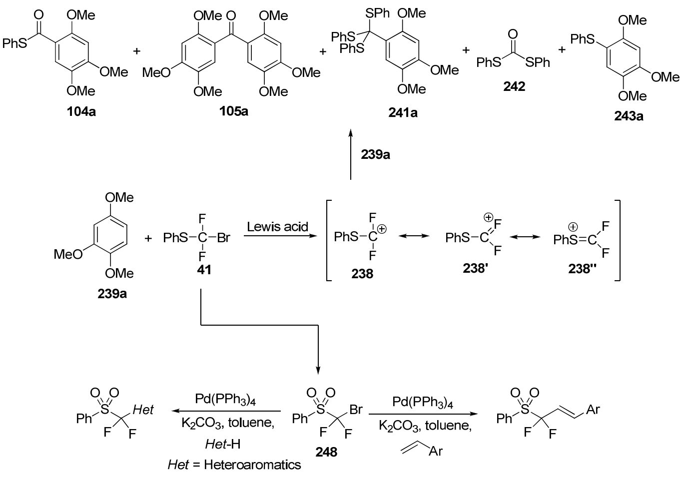
บทคัดย่อ

ปฏิกิริยาฟรีเดล—คราฟ อัลคิลเลชันของ 1,2,4-ไตรเมทอกซีเบนซีน (**239a**) กับโบรโมไดฟลูออโรเมทิลเฟนิลซัลไฟด์ (**41**) โดยผ่านตัวกลาง 1,1-ไดฟลูออโร-1-เฟนิลซัลฟานิลเมทิล คาร์โบแคตไอออน (**238**) ทำให้ได้ผลิตภัณฑ์หลายชนิดได้แก่ ไทโอเอสเทอร์ **104a**, เบนโซฟีโนน **105a**, ออร์โธไทโอเอสเทอร์ **241a**, *S,S*-ไดเฟนิลคาร์โบโนไดไทโอเอท (**242**) และ เฟนิล(2,4,5-ไตรเมทอกซีเฟนิล)ซัลแฟน(**243a**) ซึ่งชนิดของผลิตภัณฑ์ที่ได้รับขึ้นอยู่กับสภาวะในการทำปฏิกิริยา

นอกจากนี้เรายังได้แสดงให้เห็นว่า การทำปฏิกิริยาของ [(โบรโมไดฟลูออโรเมทิล)ซัลโฟนิล]เบนซีน กับ อนุพันธ์ของสไตรีน, ไวนิลอีเทอร์, และ เฮเทอโรอะโรมาติก สามารถทำได้ โดยใช้ตัวเร่งปฏิกิริยาพาลลาเดียม ทำให้ประสบผลสำเร็จในการสังเคราะห์สารประกอบประเภท α-แอลคีนิล และ α-เฮเทอโรเอริล ที่เชื่อมต่ออยู่กันหมู่ฟังก์ชัน α,α-ไดฟลูออโรเมทิลเฟนิลซัลโฟน



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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
amu	atomic mass unit
aq.	aqueous
Ar	aryl
Å	bond length unit (angstrom)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
[BMIM]	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
br s	broad singlet
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
BuLi	butyl lithium
cat.	catalyst
$CDCl_3$	deuterochloroform
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
Cp	cyclopentadienyl
Cbz	carboxybenzyl
Cy	cyclohexyl
δ	chemical shift relative to TMS
°C	degree Celsius
cm^{-1}	reciprocal centimeter (wave number unit)
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
d	doublet

LIST OF ABBREVIATIONS (cont.)

dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DABAL-Me_3	bis(trimethylalminum)-1,4-diazadicyclo[2.2.2]octane adduct
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
ee.	enantiomeric excess
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram
h	hour(s)
h*v*	photolysis
HRMS	high resolution mass spectrometry
HPLC	high-performance liquid chromatography
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
Hz	hertz
HNTf$_2$	bistrifluoromethylsulfonimide acid
Het	heteroaromatic
HMPA	hexamethylphosphoramide
HFIP	1,1,1,3,3,3-hexafluoroisopropanol

LIST OF ABBREVIATIONS (cont.)

HMDS	1,1,1,3,3,3-hexamethyldisilazane
IR	infrared radiation
J	coupling constant (Hz)
Ln	ligand
Lg	leaving group
Li	lithium
m	multiplet
min	minute(s)
mg	milligram
mL	milliliter
mmol	millimole
m.p.	melting point
m/z	a value of mass divided by charge
M	molar
M^+	molecular ion
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
MW	microwave
NMR	nuclear magnetic resonance
Nu	nucleophile
NMP	*N*-methylpyrrolidinone
[O]	oxidation
%	percent
PG	protecting group
Ph	phenyl
Pr	propyl group

LIST OF ABBREVIATIONS (cont.)

1,10-phen	1,10-phenanthroline
i-Pr	isopropyl
$P(Cy)_3$	tricyclohexylphosphine
$P(o\text{-Tol})_3$	tri(*o*-tolyl)phosphine
$P(2\text{-furyl})_3$	tri(2-furyl)phosphine
$P(Bu)_3$	tributylphosphine
ppm	part per million
q	quartet
quint	quintet
rt	room temperature (°C)
s	singlet
SiO_2	silica gel
SSA	silica-supported sulfuric acid
t	triplet
td	triplet of doublets
tr	trace
Temp	temperature
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tf_2O	trifluoromethanesulfonic anhydride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TLC	thin layer chromatography
TMS	trimethylsilyl
p-Tol	*para*-tolyl
Ts	toluenesulfinate
ν_{max}	maximum absorption frequencies
X	halide group

LIST OF ABBREVIATIONS (cont.)

XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl
°	angle unit (degree)

THE RELEVANCY OF THE RESEARCH WORK TO THAILAND

The research work is a part of the basic research on the development of synthetic method for pharmaceutical purposes. The research work will be further the goal of developing for new synthetic methodologies and demonstrate its value in a real-world application. The research effect is an example of an attempt to invent a new synthetic method for the synthesis of useful compounds for the well-being of people with a help of science and technology.

CHAPTER I

INTRODUCTION

1.1 Fluorine chemistry

1.1.1 Effect of fluorine on physical properties

Fluorine atom is the second smallest substituent after hydrogen as measured by van der waals radius (1.47 Å versus 1.20 Å for hydrogen).[1] The substitution of fluorine for hydrogen results in minimal change of steric requirement of the molecules. Therefore, replacement of hydrogen atom by fluorine atom in biological molecules causes a relatively small steric perturbation but leads to major changes in lipophilicity, polarity factor and physical properties.[2-4] The carbon-fluorine bond length is 1.39 Å and the carbon-oxygen bond length is 1.43 Å. Fluorine can function as a hydrogen bond acceptor and it becomes easy to understand why replacement of hydroxyl by fluorine often allows biological properties to be retained. Fluorine is the most electronegative element (4 versus 3.5 for oxygen) and it alters the electron density, basicity and acidity of neighboring groups, dipole moments within the molecule and the overall reactivity and stability of neighboring functional groups.

1.1.2 Electronic effects in fluorocarbon systems[1,5]

Understanding of the influence of carbon-fluorine bonds on reaction mechanism is still rather qualitative. In addition to effects arising from different electronegativities, the effect of the electrons of fluorine that are not involved in δ bonds must be taken into consideration. A further complication is that the relative importance of these effects seems to be very dependent on the center to which the fluorine is attached.

1.1.2.1 Positively charged species

- Inductive electron withdrawing effect of fluorine would tend to destabilize α-carbocation (Figure 1.1).

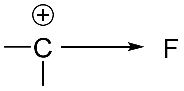

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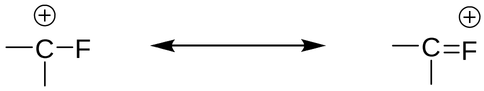
Figure 1.1

- Mesomeric interaction of an unshared pair electron of a fluorine atom with the empty orbital on carbon, if operating, would lead to stabilization (Figure 1.2).



1a **1b**

Figure 1.2

Later study showed that fluorine directly attached to a carbocation centre is clearly a stabilizing influence, but the effect of fluorine substituted more remote from the centre is strongly destabilizing. In the case of a α-cation **1**, fluorine stabilized such species by lone pair electron donation rather than the inductive effect working in the opposite way while their strong electron-withdrawing nature plays a key role in the destabilization of β-cation **2** (Figure 1.3).

α-cation **1** β-cation **2**

Figure 1.3

1.1.2.2 Negatively charged species

- Inductive electron withdrawing effect of fluorine would lead to stabilization.

- Repulsion between adjacent electron pairs would lead to destabilizing.

It becomes apparent that fluorine not directly attached to the carbanionic carbon is strongly stabilizing, but, when directly attached, it has either moderate stabilizing effect compared with hydrogen, or definitely destabilizes, depending on the stereochemistry of the carbanion. The α-anion **3** is definitely destabilized by the electrostatic repulsion. Moreover, negative hyperconjugation also works as the dominant factor for the stabilization of β-anion **4** (Figure 1.4).

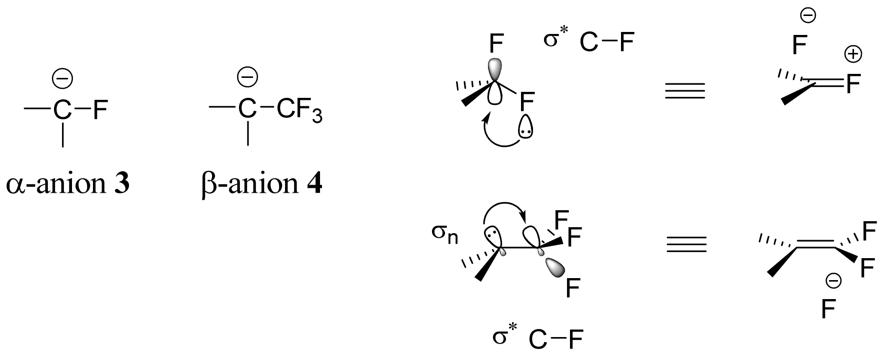


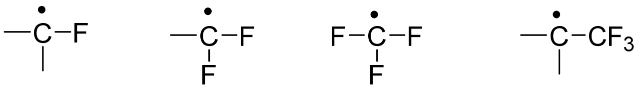
Figure 1.4

1.1.2.3 Free radical

- Inductive electron withdrawing effect of fluorine will affect the polar characteristics and reactivity of a radical.

- All substituents replacing hydrogen appear to lower the potential energy of a free radical and this may be represented as resonance stabilization.

Unlike the planar methyl carbocation, the introduction of a fluorine atom to the carbon radical gives rise to partial pyramidalization, thus **7** becomes almost tetrahedral in shape with a significant inversion barrier. Because such deviation from planarity causes less effective resonance stabilization by lone pairs, **5** is more stable than any other fluorine-containing methyl radical. Thus, the stability order is **5** > **6** > **7**. The β-fluorinated radical like **8** is inductively destabilized (Figure 1.5).



5 **6** **7** **8**

Figure 1.5

1.1.3 Fluoroalkylation methodology

Since fluorine has significantly interesting unique properties, it has come to be recognized as a key element in materials science: in heat-transfer agents, liquid crystal, dyes, surfactants, plastics, elastomers, membranes, and other materials. Furthermore, many fluorine-containing biologically active agents are finding applications as pharmaceutical and agrochemicals. For instance, compound **9**[6] containing a difluoroketone as its core unit is a highly potent HIV proteinase inhibitor, compound **10**[7] was found to effect platelet aggregation, compound **11**[8] was found to inhibit hydroxylation process during vitamin D_3 metabolism and trifluoromethyl-containing molecules such as Prozac **12**[9d] (antidepressant) and Celebrex **13**[9d] (anti-inflammatory) are commercially available pharmaceuticals (Figure 1.6).

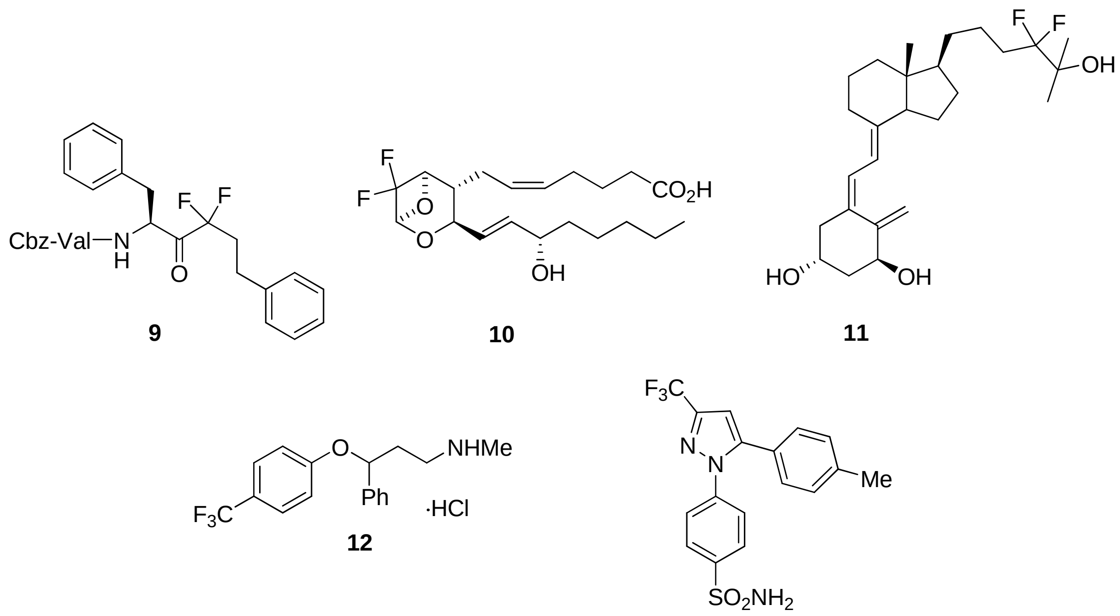
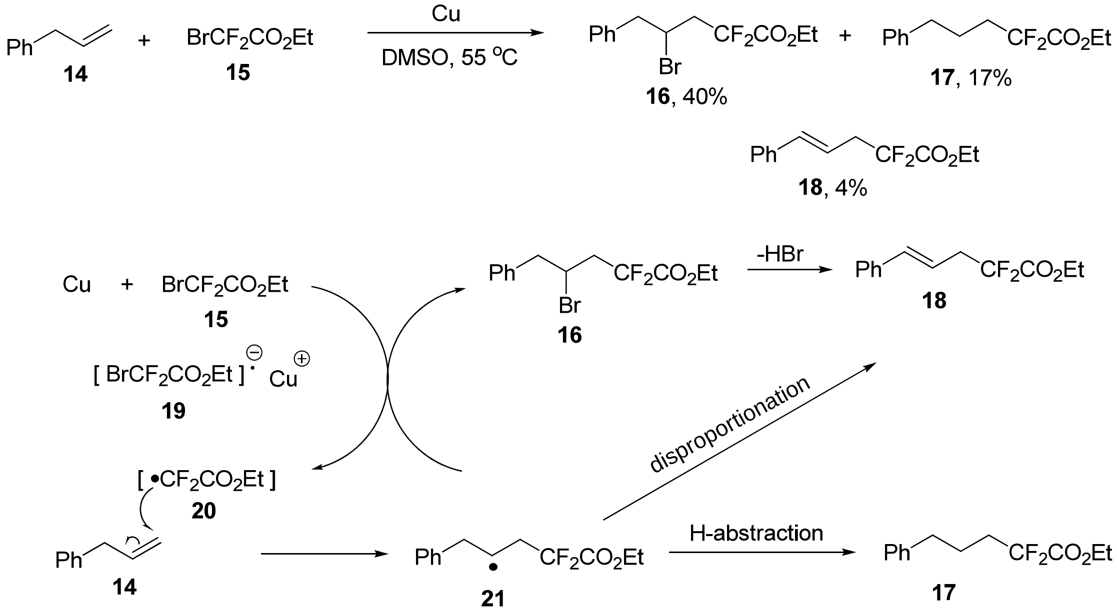


Figure 1.6

Therefore, progress in synthetic fluorine chemistry has been critical to the development of these fields and has led to the invention of many novel fluorinated molecules as future drugs and materials. As a result of the electronic effects of fluorine substituents, fluorinated substrates and reagents often exhibit unusual and unique chemical properties, which often make them incompatible with established synthetic methods. Thus, the problem of how to control the unusual properties of compounds with fluorine substituents deserves much attention, so as to promote the design of facile, efficient, and environmentally benign methods for the synthesis of valuable organofluorine targets. For this reason, methods for introducing a fluorine atom, CF_2 and CF_3 units into an organic compound have been investigated energetically.[9] Radical,[10] carbene,[11] carbanion,[12] fluorocarbocation[13] and transition metal-mediated fluoroalkylation[14] reactions involving readily available sources of *gem*-difluorinated compounds have been reported. These reactive intermediates have extended the scope of fluorine research considerably.

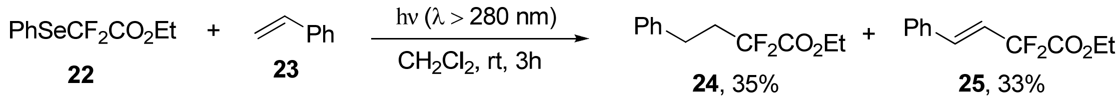
1.1.3.1 Radical and electrophilic fluoroalkylation pathway

For the synthesis of various difluoromethylene compounds, the Reformatsky reaction of halodifluoroacetates is commonly used as CF_2-synthon approach[15a,15b] via radical addition of α,α-difluoro-α-haloesters to olefins. According to this strategy, Kumadaki and co-workers reported the introduction of CF_2COOR group into olefins by using radical reaction.[15c] Bromodifluoroacetate (**15**) was treated with copper powder in the presence of allyl benzene (**14**) as a substrate to give radical addition products **16** (40%), **17** (17%), and **18** (4%). A speculative mechanism for formation of these compounds is shown in Scheme 1.1.



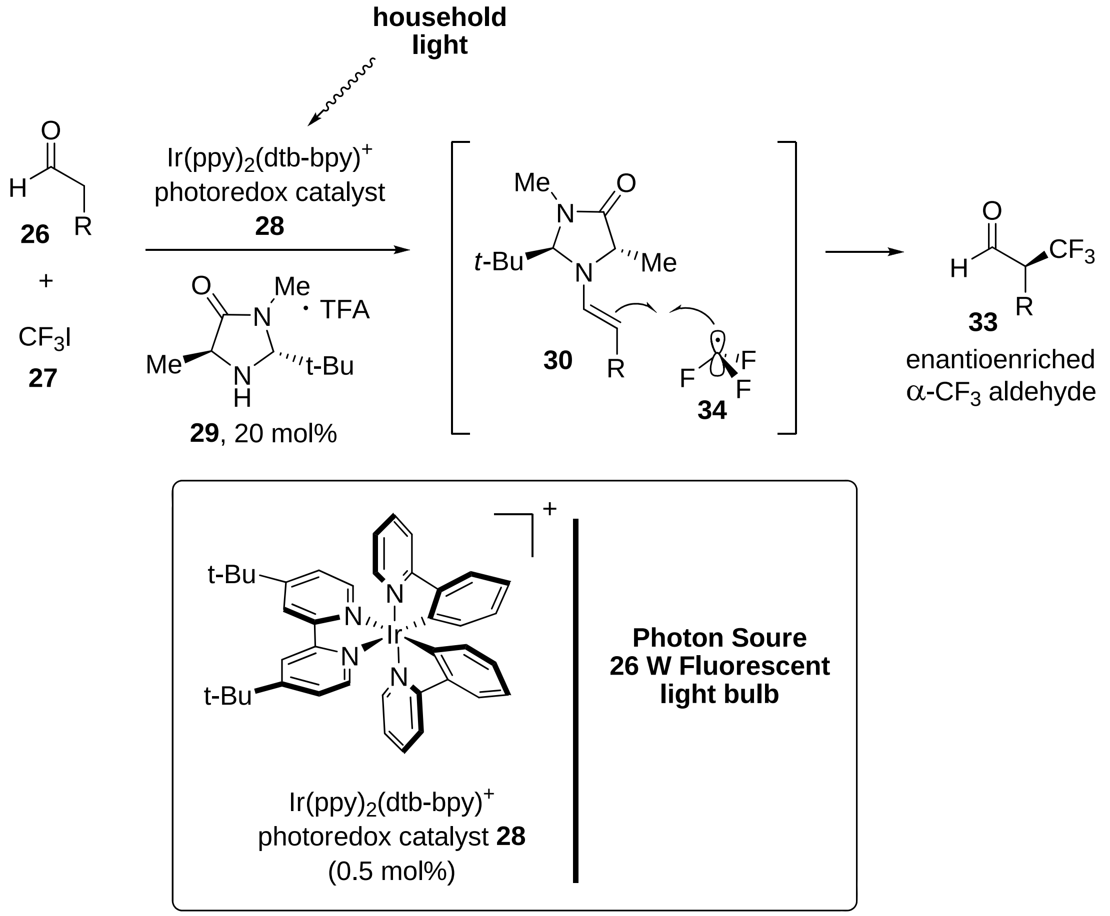
Scheme 1.1

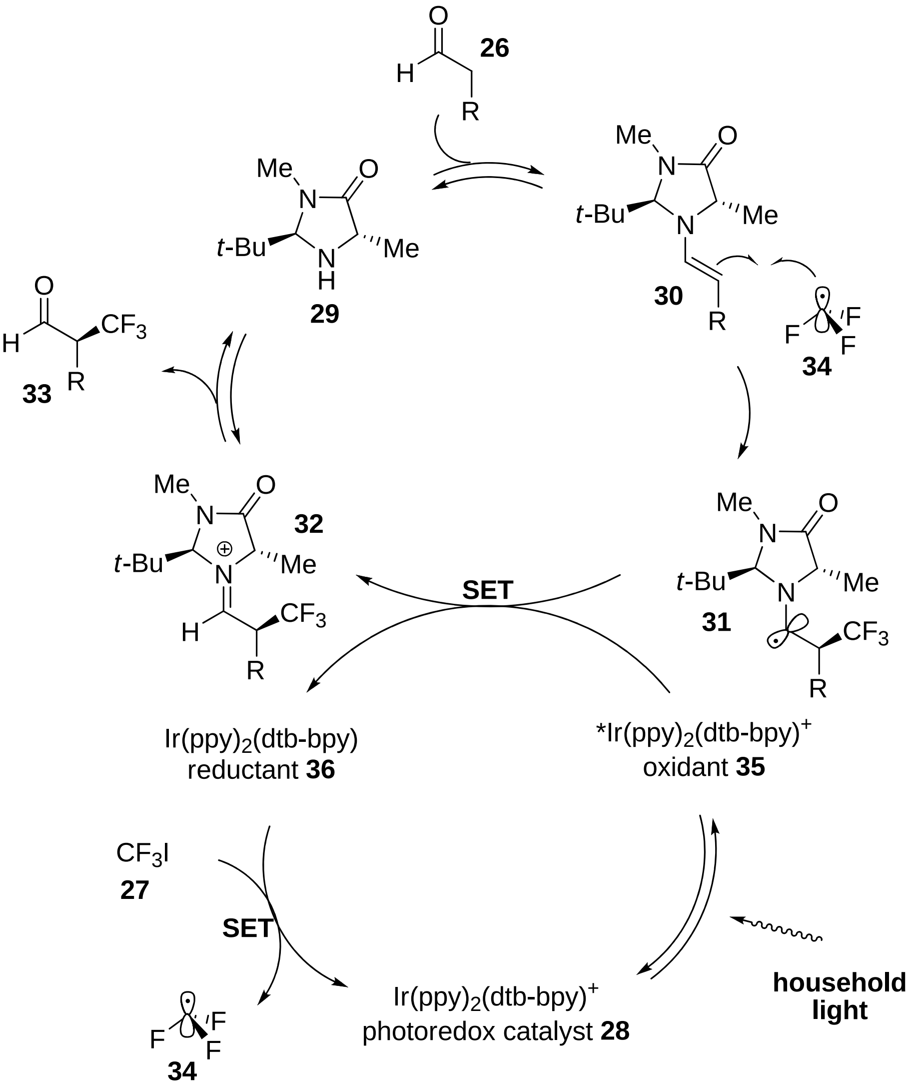
In 2004, Fuchigami and co-workers reported the dissociation of the C–Se bond of α,α-difluoroacetate **22** using UV light in the presence of styrene (**23**).[16] Upon photolysis of **22** and **23** using 100 W high-pressure of mercury-vapour lamp through Pyrex filter, compounds **24** and **25** were obtained in 35% and 33% yields, respectively (Scheme 1.2).



Scheme 1.2

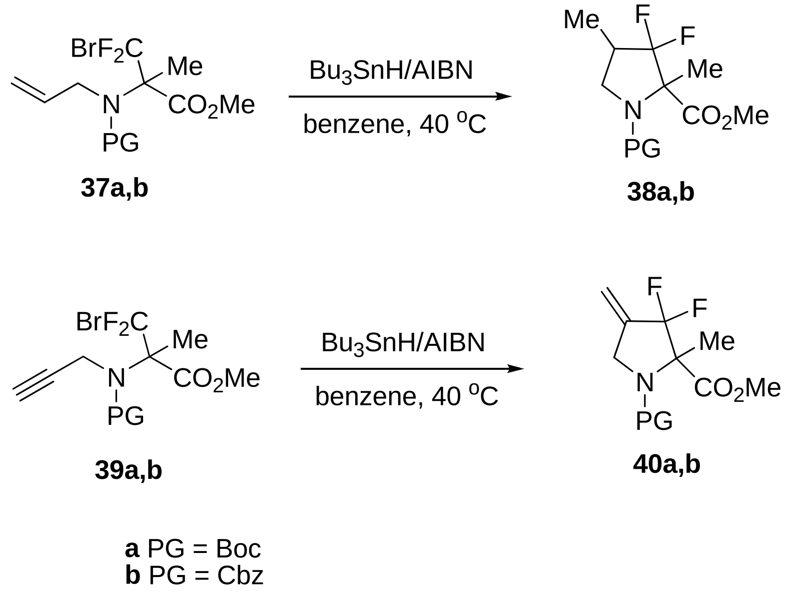
Enantioselective α-trifluoromethylation of aldehydes via photoredox organocatalysis was reported by MacMillan and co-workers[17] in which the reaction mechanism was proposed as followed; the electron-rich iridium system, Ir(ppy)$_2$(dtb-bpy) **36**, would participate in single electron transfer (SET) with trifluoromethyl iodide to render the electrophilic radical **34** followed by trapping with chiral enamine **30** to form the α-amino radical **31**. The iminium ion was formed by giving an electron of the α-amino radical intermediate to *Ir(ppy)$_2$(dtb-bpy)$^+$ **35** excited state and then rapid hydrolysis of iminium reconstituted the organocatalyst **29** while rendering the optically enriched α-CF$_3$ aldehydes **33** in high yields and *ee* value (up to 99%) (Scheme 1.3).





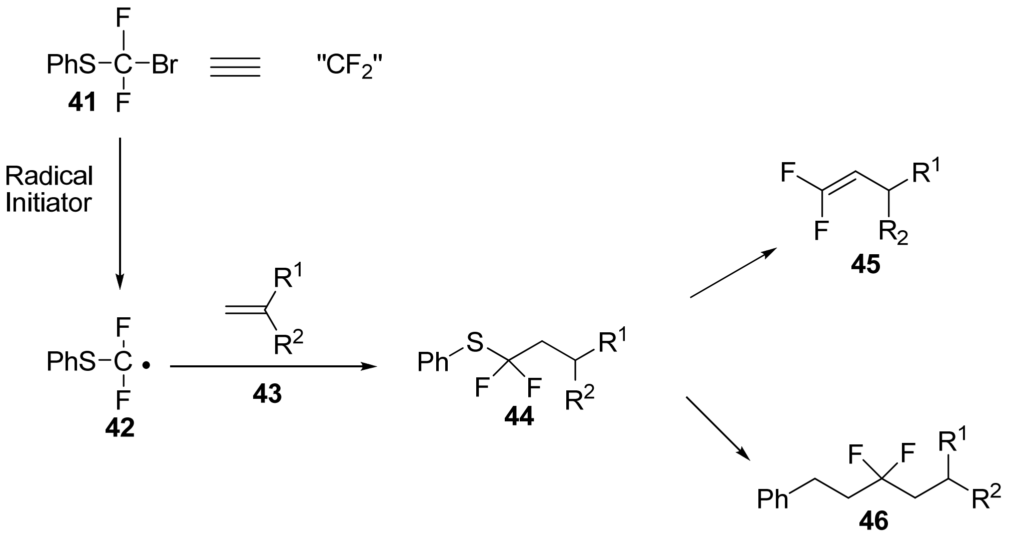
Scheme 1.3

An intramolecular free radical ring closure of compounds **37**, and **39** proceeded at 40 °C in benzene within 3-4 h in the presence of 1.1 equiv of Bu_3SnH and 15 mol% of AIBN to give the corresponding cyclized products **38**, and **40** respectively, in acceptable yields (40–45%) (Scheme 1.4). This reaction was reported by Osipov and Burger in 2000.[10g]



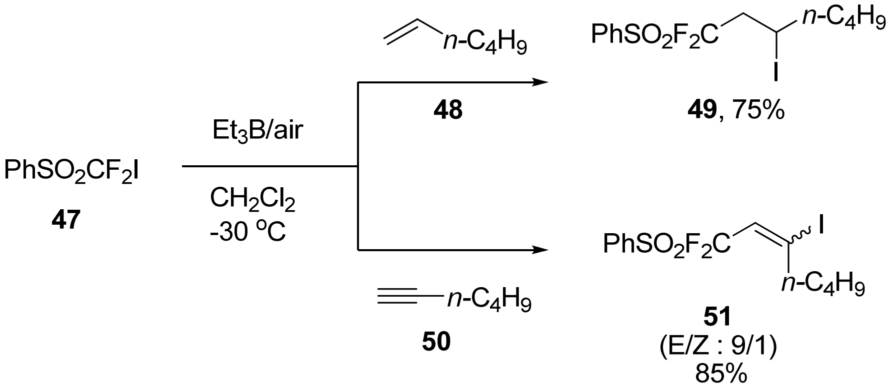
Scheme 1.4

In 2004, our group reported the use of bromodifluoromethyl phenyl sulfide (**41**) as "CF_2" building block via the carbon-carbon bond formation between the difluorophenylsulfanylmethyl radical (**42**) and olefins (**43**) (Scheme 1.5).[101] the primarily formed adduct **44** can be further transformed to *gem*-difluoroalkenes **45** and compounds containing mid-chain difluoromethylenes **46**.



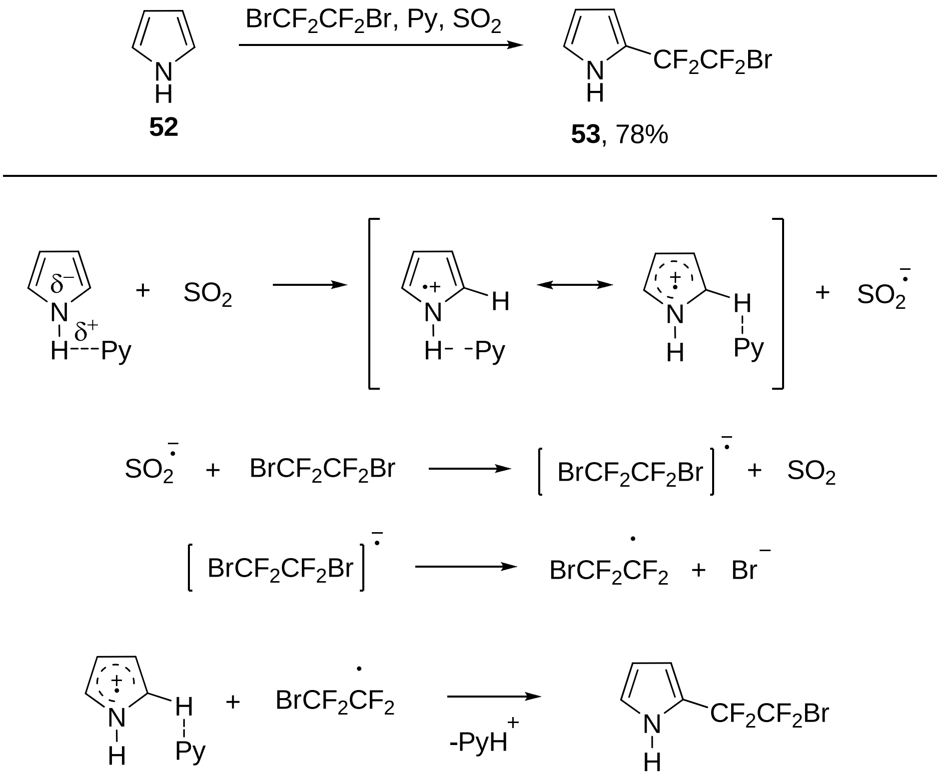
Scheme 1.5

In 2007 and 2009, Hu and co-workers reported free radical (phenylsulfonyl)difluoromethylation of alkenes[10n] and alkynes[10o] with $PhSO_2CF_2I$ reagent by using Et_3B/air as an radical initiator to give *gem*-difluoroalkylation products **49** and **51**, respectively, in good yields (Scheme 1.6).



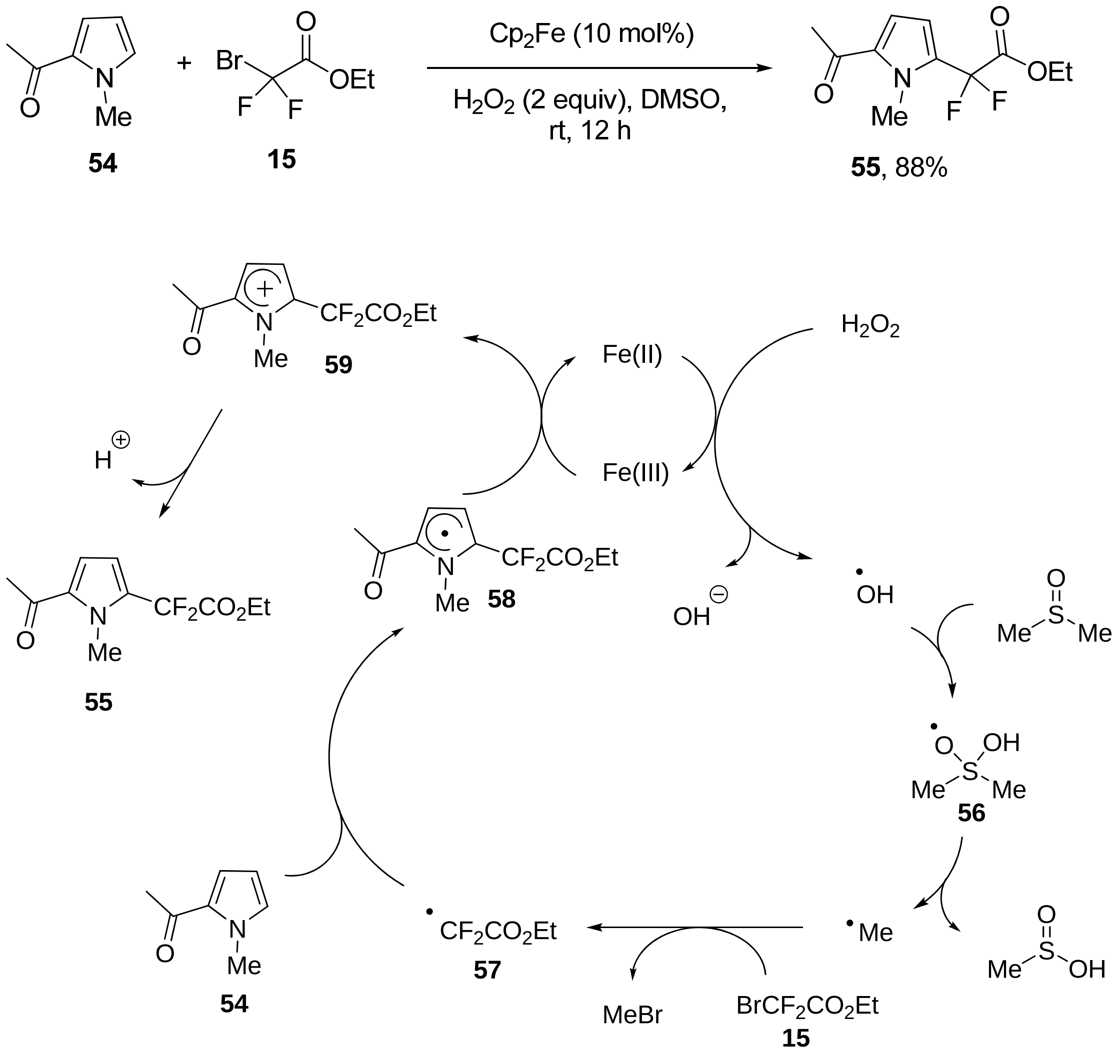
Scheme 1.6

The homogeneous catalytic fluoroalkylation of pyrrole (**52**) with Freon $BrCF_2CF_2Br$ using a nitrous base–sulfur dioxide system was reported by Kiprinova and co-workers. In this system, sulfur dioxide plays the key role in the fluoroalkylation of pyrrole as an electron transfer mediator facilitating the reaction to occur. The ion-radical mechanism of the processes was proposed as shown in Scheme 1.7.[18]



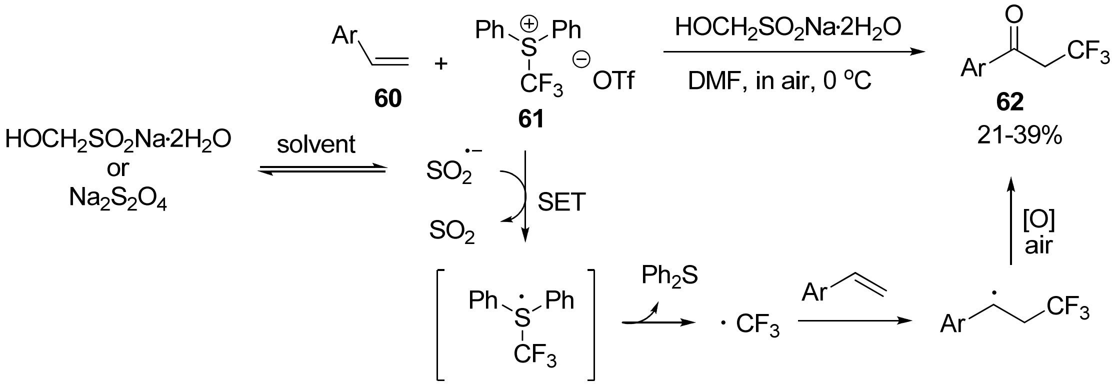
Scheme 1.7

In 2011, Ohtsuka and Yamakawa[10p] reported direct ethoxycarbonyldifluoromethylation of aromatic compounds with ethyl 2-bromo-2,2-difluoroacetate (**15**) using a combination of Cp_2Fe and H_2O_2 in DMSO. Example of this transformation and the proposed reaction mechanism are shown in Scheme 1.8. Thus, (i) Fe(II) reduces H_2O_2 to a hydroxyl radical, (ii) the hydroxyl radical is rapidly trapped by DMSO solvent to from a radical adduct **56**, (iii) a methyl radical is generated from **56**, (iv) the reaction of $BrCF_2CO_2Et$ **15** and the methyl radical releases a CF_2CO_2Et radical **57**, (v) the CF_2CO_2Et radical adds to the 2-position of 2-acetyl-1-methylpyrrole (**54**) to form a radical species **58** and (vi) Fe(III) oxidize **58** to **55** and is reduced to Fe(II).



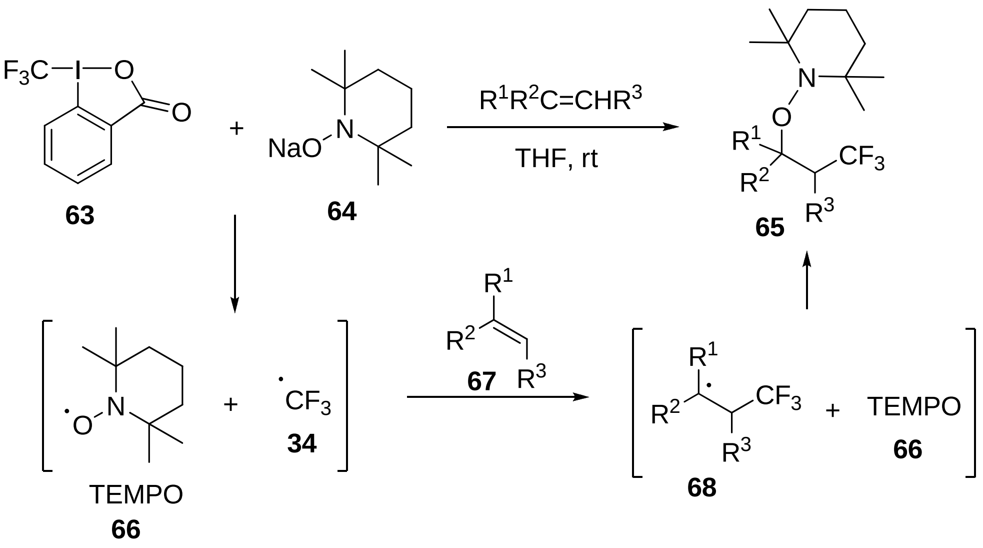
Scheme 1.8

Xiao and co-workers[19] have reported the first example of the generation of the CF_3 radical from a *S*-(trifluoromethyl)diarylsulfonium salt initiated by $Na_2S_2O_4$ or $HOCH_2SO_2Na$. The radical was trapped by styrenes to give, after oxidation, α-trifluoromethylacetophenones (Scheme 1.9). In this case, *S*-(trifluoromethyl)diarylsulfonium salts behaved more like a "pseudo halide" instead of electrophilic reagents "CF_3^+".



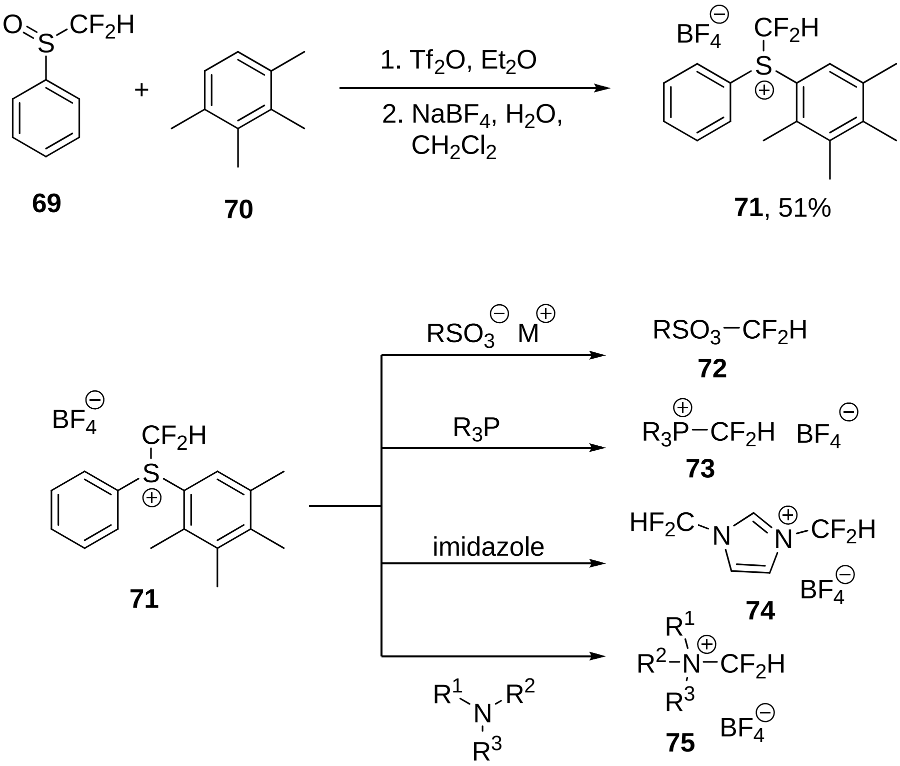
Scheme 1.9

In 2012, Li and Studer[20] discovered trifluoromethyl-aminoxylation of alkenes initiated by a single-electron-transfer (SET) reagent, sodium aminoalkoxide **64** (TEMPONa). Sodium aminoalkoxide **64** (TEMPONa) was used for reduction of hypervalent-iodine-CF_3 to generate the CF_3 radical **34** along with the corresponding persistent TEMPO radical **66** (2,2,6,6,-tetramethylpiperidine-*N*-oxyl) and *o*-$IC_6H_4CO_2Na$. Addition of the CF_3 radical **34** to an alkene **67** and subsequent selective trapping steered by TEMPO **66** should eventually provide the corresponding trifluoromethylated product **65** in moderate to good yields (Scheme 1.10).



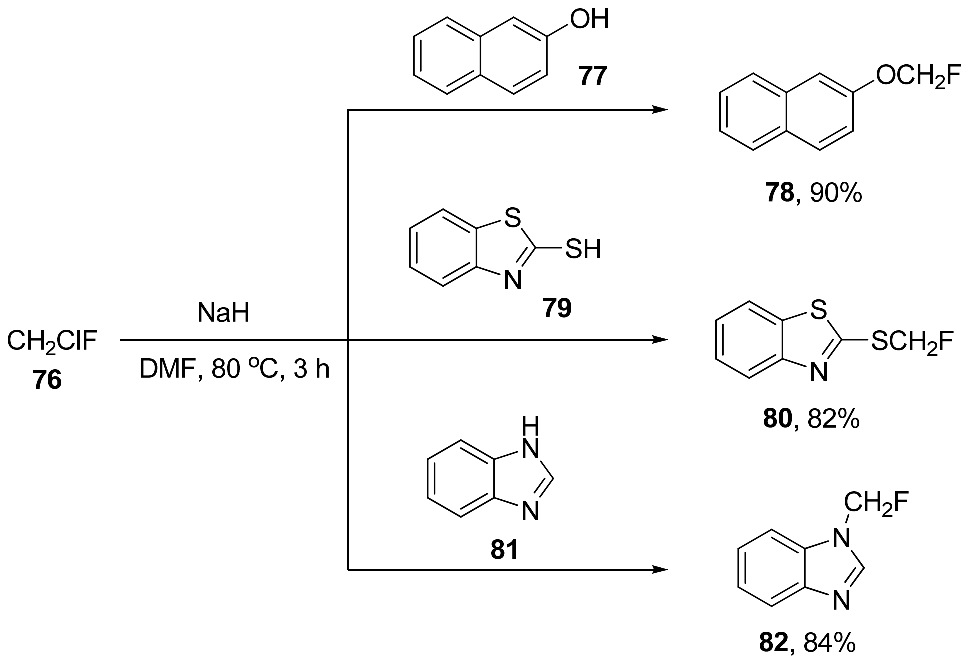
Scheme 1.10

In search for electrophilic fluoroalkylation, *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate (**71**) was firstly synthesized and used as a powerful electrophilic difluoromethylating agent by Prakash and co-workers[9b,21a] in 2007. The application of this reagent was demonstrated as an effective electrophilic difluoromethylating agent for the selective introduction of a "CF_2H" group into a variety of nucleophiles, such as sulfonic acids, tertiary amines, imidazole derivatives, and phosphines (Scheme 1.11).



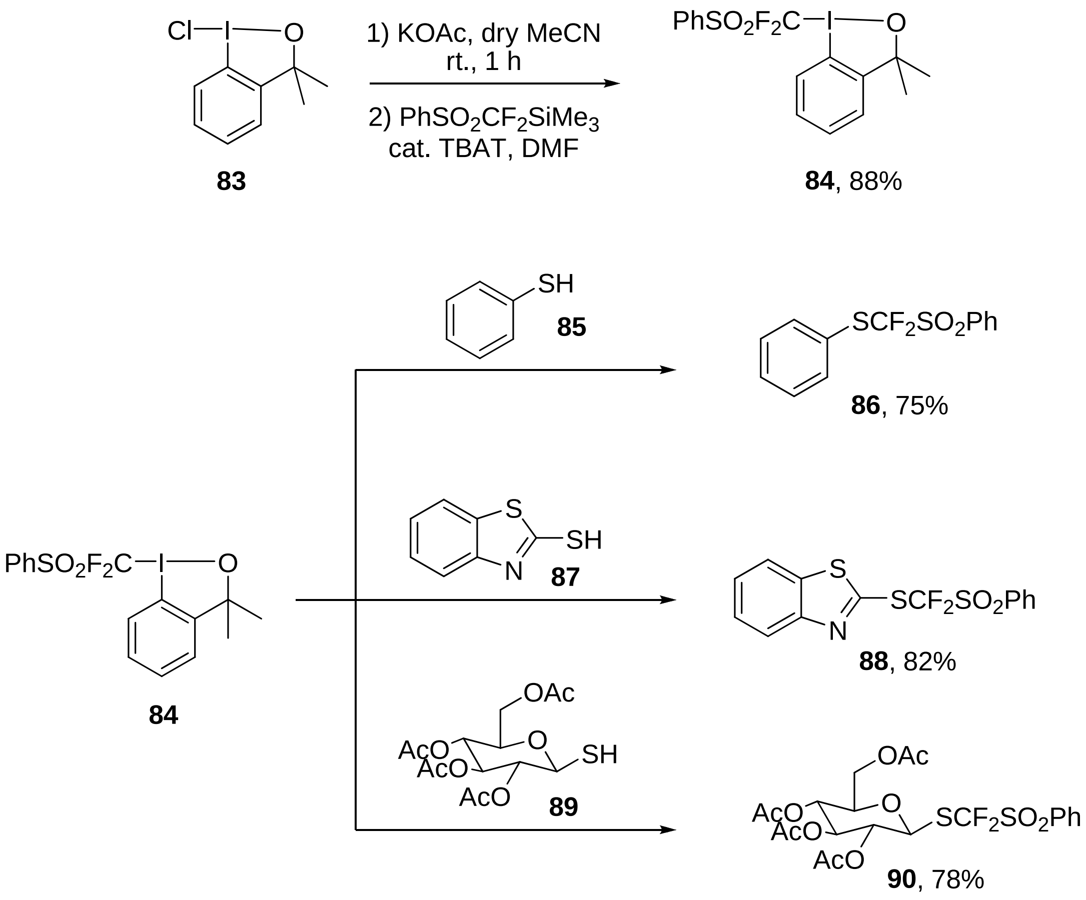
Scheme 1.11

The electrophilic monofluoromethylation was firstly reported by Olah and Pavlath[22a-b] by using FCH_2OH as monofluoromethylating agent.[22] Thereafter, several reagents including CH_2FCl,[22c-d] CH_2FBr,[22e] CH_2FI,[22f] and $CHFOSO_2R$[22g] were reported for the electrophilic monofluoromethylation of oxygen-, sulfur-, nitrogen-, and carbon-nucleophiles but these reactions suffered from reproducibility of obtained products and some limitations. To overcome this problem, Hu an co-workers[22h] developed an efficient electrophilic monofluoromethylation using inexpensive and readily available chlorofluoromethane (CH_2FCl) as electrophilic monofluoromethylating agent for a variety of *O*-, *S*-, and *N*-nucleophiles. The isolated monofluoromathylated products were obtained in good yields with good purity (Scheme 1.12).



Scheme 1.12

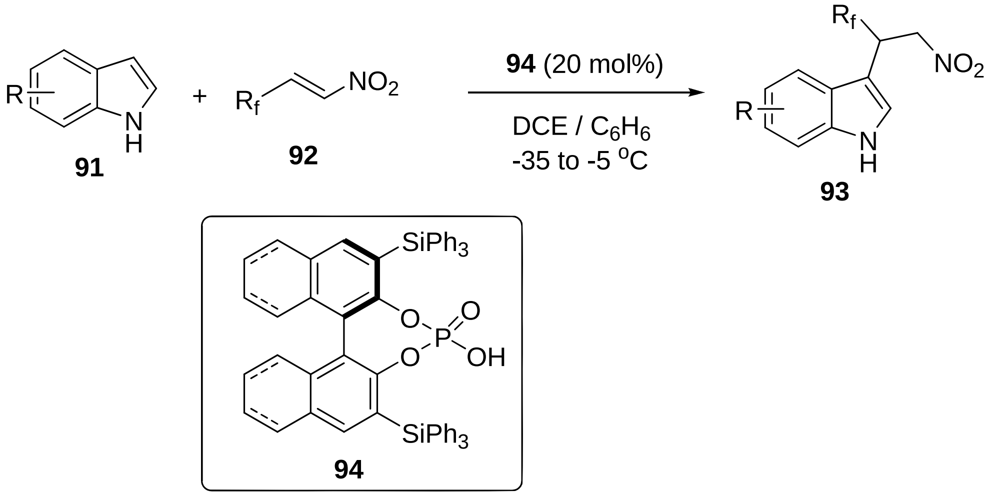
In 2008, Hu and co-workers[21b] successfully prepared a hypervalent iodine(III)-CF_2SO_2Ph (**84**) from $PhSO_2CF_2SiMe_3$. The fluorine-containing hypervalent iodine(III) **84** was found to be more stable than the known Togni's hypervalent iodine(III)-CF_3 compound. After searching for its synthetic application, they found that the hypervalent iodine(III)-CF_2SO_2Ph reagent (**84**) can be used as electrophilic (phenylsulfonyl)difluoromethylation for thiols and other *S*-nucleophiles under mild reaction conditions (Scheme 1.13).



Scheme 1.13

Recently, Xiao and co-workers[23] reported an enantioselective Friedel–Crafts fluoroalkylation of indoles **91** with fluoroalkylated nitroalkenes **92**, catalyzed by chiral phosphoric acid **94**. 20 Mol% of chiral phosphoric acid **94** provided a good results in both product yields and *ee* value (Table 1.1).

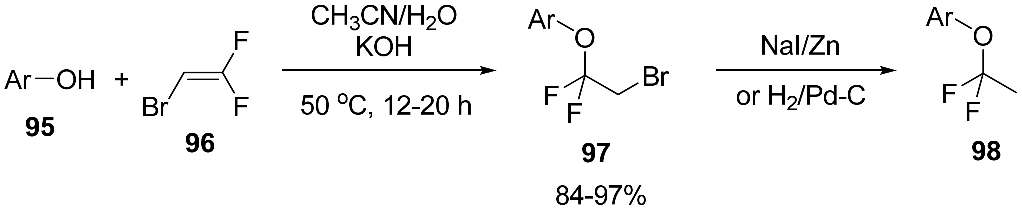
Table 1.1 Asymmetric Friedel–Crafts reaction of indoles with fluoroalkylated nitroalkenes, catalyzed by chiral phosphoric acid[a]



Entry	R	R_f	Time [d]	Yield (%)[b] 93	ee (%)[c]
1	H	CF_3	5	**93**a, 93	85
2	H	CF_2Cl	3.5	**93b**, 92	77
3	H	CF_2Br	4.5	**93c**, 89	84
4	H	CF_2H	6	**93d**, 98	82
5	H	$PhCF_2$	9	**93e**, 78	79
6	H	$4\text{-}MeOC_6H_4CF_2$	10	**93f**, 70	75
7	4-Cl	CF_3	5	**93g**, trace	-
8	5-MeO	CF_3	4	**93h**, 97	86
9	6-Me	CF_3	3	**93i**, 90	89
10	4-MeO	CF_2Br	6	**93j**, 88	76
11	5-MeO	CF_2Br	2.5	**93k**, 98	87
12	6-Me	CF_2Br	2.5	**93l**, 90	89

[a]Reaction conditions: 1 (0.2 mmol), 2 (0.4 mmol) and catalyst **94** (20 mol%) in DCE/C_6H_6 (1.2 mL/1.2 mL) at -5 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

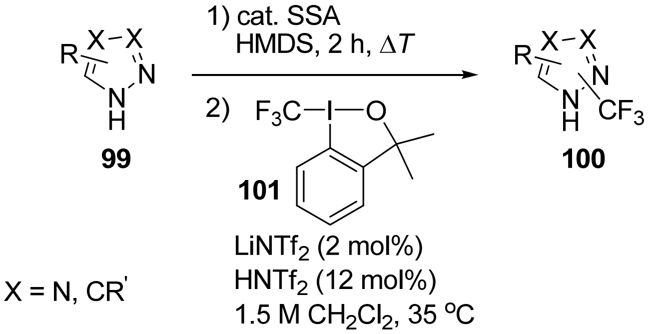
In order to find an efficient, scaleable and environmentally safe way to replace an aryl ethoxy group with the α,α-difluoroethoxy group to reduce the extent of oxidative metabolism α to oxygen, Humphrey and co-workers[24] disclosed an efficient electrophilic difluoroethylation of aryl and heteroaryl alcohols by using a commercial 2-bromo-1,1-difluoroethene (**96**) as an alternative source of electrophilic difluoroethene. The optimal conditions were applied to a variety of aryl and heteroaryl alcohols, and in general, gave good to excellent yields of the corresponding bromodifluoroethylated products **97**. Bromodifluoro ethers **97** can be further manipulated by hydrogenolysis of bromine to give ready access to the α,α-difluoroethyl ethers **98** (Scheme 1.14).

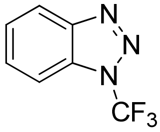
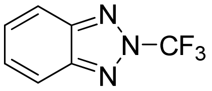
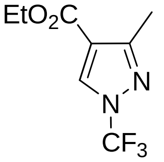
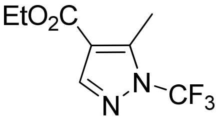
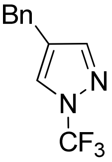
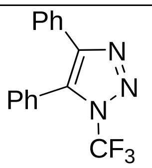
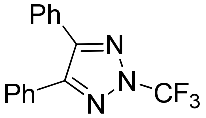
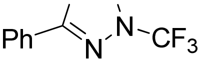
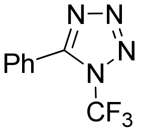


Scheme 1.14

In 2012, Togni and co-workers[25] reported direct electrophilic *N*-trifluoromethylation of azoles by a hypervalent iodine reagent **101**. The *in situ* silylation of the substrate by 1,1,1,3,3,3,-hexamethyldisilazane (HMDS) in the presence of a catalytic silica-supported sulfuric acid (SSA), followed by trifluoromethylation with a hypervalent iodine reagent **101** in CH_2Cl_2 at 35 °C in the presence of a catalytic amount of $HNTf_2$ and $LiNTf_2$ was selected as optimized reaction conditions. The results shown that a variety of azoles **99** were nicely converted to heteroaryltrifluoromethylated products **100** in moderate to good yields (Table 1.2).

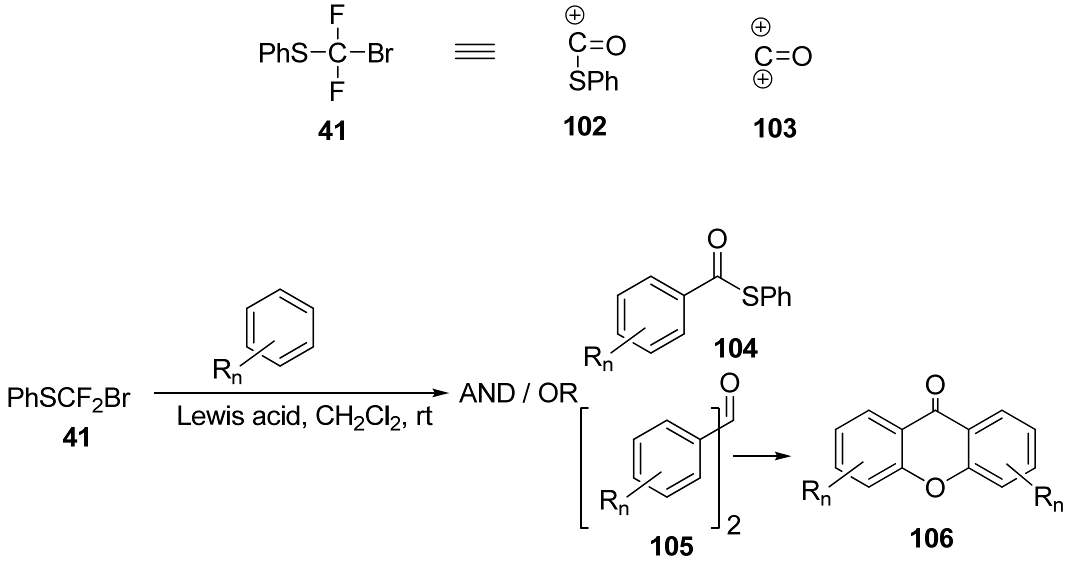
Table 1.2 Product scope for the direct *N*-trifluoromethylation of azoles



Entry	Major product	Minor Product	Yield (%)[a] Major / minor product
1			88:2 (64:–)
2			35:7 (33:–)
3		-	69 (66)
4			42:11 (21:11)
5			42:18 (18:10)

[a] Yields were calculated based on the ^{19}F NMR signals using $C_6H_5CF_3$ as an internal standard. Yields of isolated products are given in brackets (significant differences are mainly due to losses during isolation because of volatility).

By using carbocationic electrophilic strategy, our group have reported Friedel-Crafts-type alkylation with bromodifluoromethyl phenyl sulfide (**41**) through α-fluorocarbocations for syntheses of thioester **104**, benzophenones **105** and xanthones **106** (Scheme 1.15).[13]

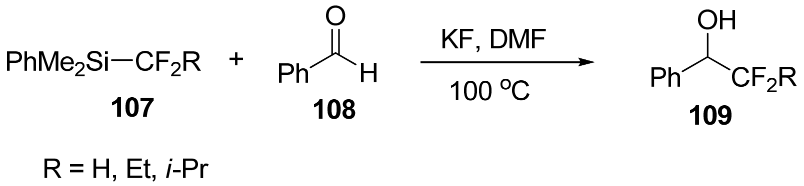


Scheme 1.15

1.1.3.2 Nucleophilic fluoroalkylation pathway

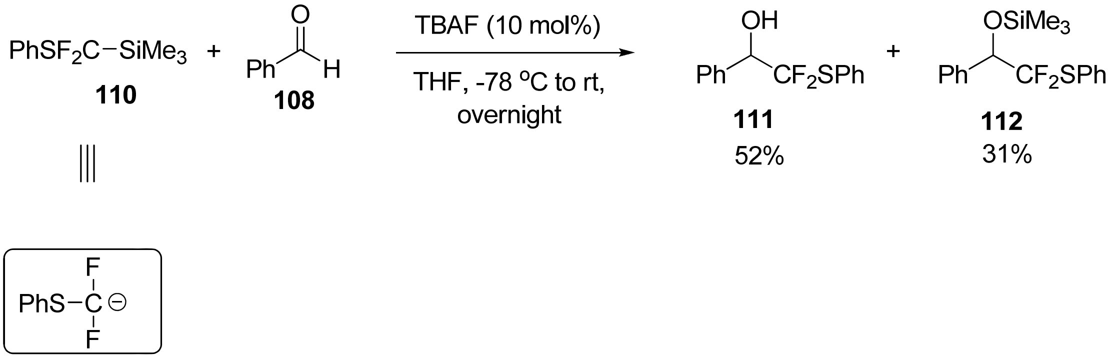
The first efficient nucleophilic trifluoromethylation was reported by Prakash, Olah, and co-workers in 1989 using (trifluoromethyl)trimethylsilane ($TMSCF_3$),[26] and the chemistry has been extended to other nucleophilic perfluoroalkylations with various substrates including carbonyl compounds, sulfur-based electrophiles, azirines, imines, organohalides, organotin compounds, and other.[27,9b] Compared to the well-known nucleophilic trifluoromethylation reactions, much less has been studied on nucleophilic di- and monofluoromethylations, although the latter two functionalities can play critical roles in the bioactive of fluoroorganics.

To obtain *gem*-difluoroalkylation compounds, Fuchikami and co-workers have attempted the fluoride-induced difluoromethylation of carbonyl compounds with difluoromethylsilane derivatives **107** in DMF and found that the reaction required high temperature (100 °C) giving good yields with aldehyde but poor yields with ketone (Scheme 1.16).[28,9b]



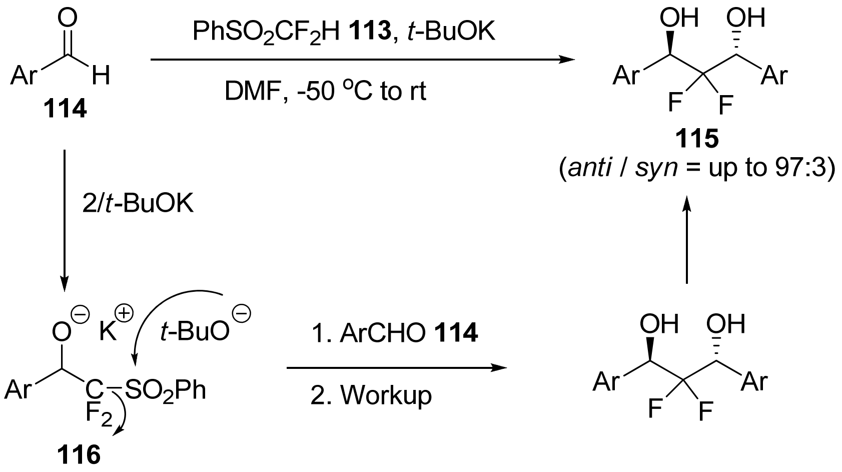
Scheme 1.16

Our group[12o] and Prakash[12m] reported the same difluoromethylating reagent, α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane (**110,** $PhSCF_2SiMe_3$), as α,α-difluoro-α-phenylsulfanylmethyl carbanion equivalent. Under the established reaction conditions, reaction of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane (**110**) (1.1 equiv) with benzaldehyde (1 equiv) took place between -78 °C to room temperature for 15 h in the presence of 10 mol% of anhydrous tetra-*n*-butylammonium fluoride (TBAF) in THF affording the desired products **111** and **112** in 52 and 31% yields, respectively (Scheme 1.17).[12o]



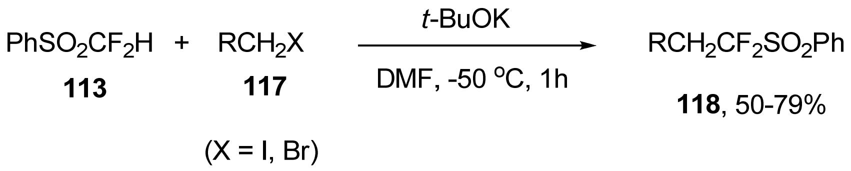
Scheme 1.17

In 2003, Prakash an co-workers[12j,9b] reported difluoromethylation of aldehydes using difluoromethyl phenyl sulfone $PhSO_2CF_2H$ (**113**) in the presence of *t*-BuOK which acted both as a base and a nucleophile. Sulfone **113** reacted stepwise with two equivalents of aldehydes to give new difluoromethylene-containing products **115** in good yields and excellent diasterioselectivity (Scheme 1.18).



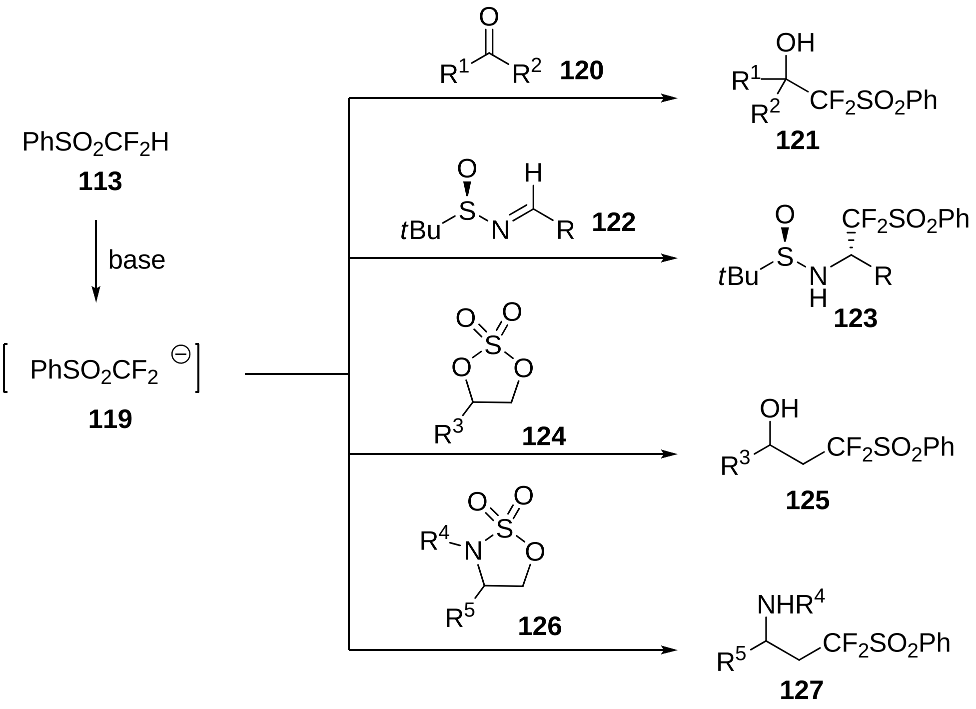
Scheme 1.18

In 2004, Prakash and co-workers[29] also reported nucleophilic difluoromethylation of primary alkyl halides using difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) (**113**) as difluoromethyl anion equivalent to give difluorinated products **118** in moderate to good yields (Scheme 1.19).



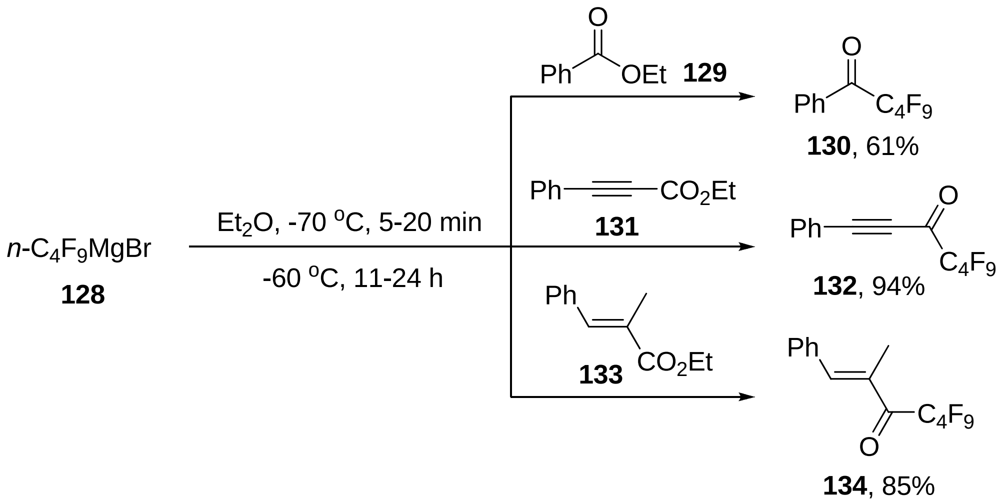
Scheme 1.19

The (phenylsulfonyl)difluoromethyl anion species **119** (generated from **113** and *t*-BuOK or LiHMDS) can efficiently undergo nucleophilic (phenylsulfonyl)difluoromethylation with a variety of electrophiles[9b] such as ketones **120**,[30a] imines **122**,[30b] cyclic sulfates **124**[30c] and cyclic sulfamides **126**[30c] to give the corresponding substitution or addition products in good to excellent yields (Scheme 1.20).



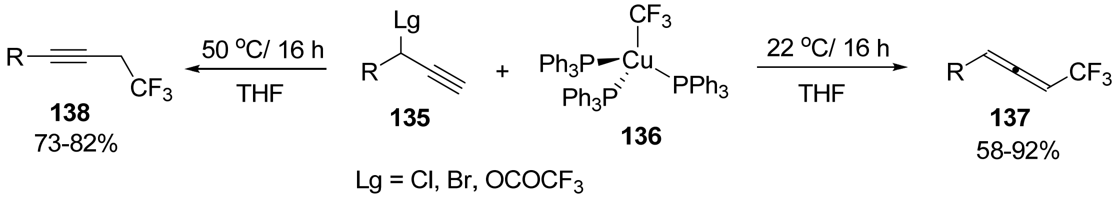
Scheme 1.20

Ma and co-workers[31] have reported an efficient method for the preparation of perfluoroalkyl ketones through the reaction of alkenoates, alkynoate, or regular carboxylic esters with perfluoroalkyl Grignard reagents. The reaction performed at -70 to 60 °C in Et_2O gave moderate to good yields of the corresponding perfluoroalkyl ketones in moderate to good yields (Scheme 1.21).



Scheme 1.21

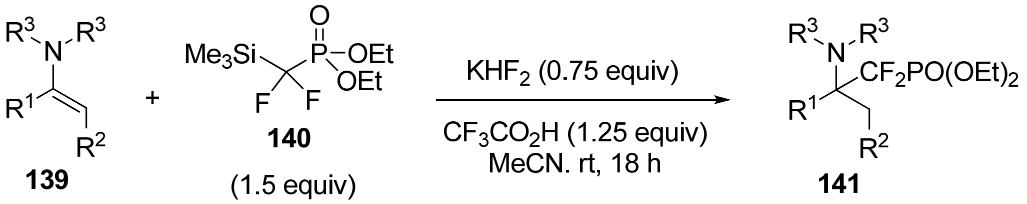
In 2012, Szabó and co-workers[32] have shown that a well-defined Cu–CF_3 complex **136** is an excellent reagent for trifluoromethylation of propargylic halides and trifluoroacetates **135** to give either alkynyl or linear allenylic trifluoromethylated products in moderate to good yields depending on the reaction temperature employed. The reaction was proven to proceed via an ionic mechanism involving nucleophilic transfer of CF_3 group from the Cu complex to the propargylic substrates (Scheme 1.22).

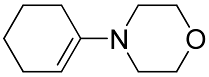
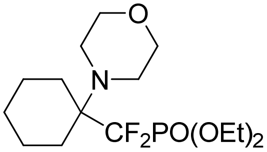
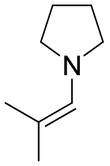
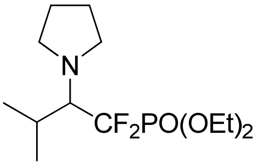
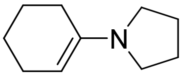
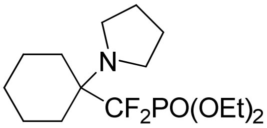


Scheme 1.22

Dilman and co-workers[33] have reported a successful nucleophilic fluoroalkylation reaction of enamines **139** with diethyl difluoro(trimethylsilyl)methylphosphonate (**140**) as difluoromethylating reagent. The reactions are promoted by hydrofluoric acid generated *in situ* from a homogeneous solution of potassium hydrodifluoride and trifluoroacetic acid in MeCN at room temperature for 18 h affording the corresponding products **141** in good yields (Table 1.3).

Table 1.3 Reactions of enamines with diethyl difluoro(trimethylsilyl)methylphosphonate

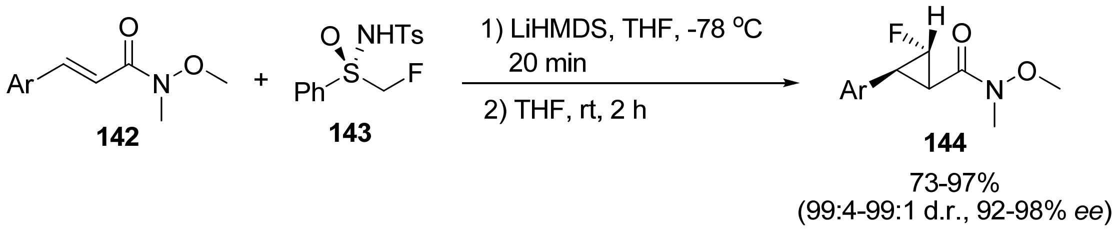


Entry	Substrate	Product	Yield (%)[a]
1			71
2			78
3			84

[a]Isolated yield.

A chiral α-fluoro carbanion strategy for the preparation of cyclopropanes that contain fluorinated tertiary stereogenic centers have been developed by Hu and co-workers[34] in 2012 (Scheme 1.23). The reaction of aryl-substituted α,β-unsaturated Weinreb amides **142** as the Michael acceptor with (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**143**) as a chiral fluoroalkylating reagent using LiHMDS as a base in THF, the corresponding enantiomerically enriched monofluorinated cyclopropanes **144** were obtained in good to excellent yields (73–

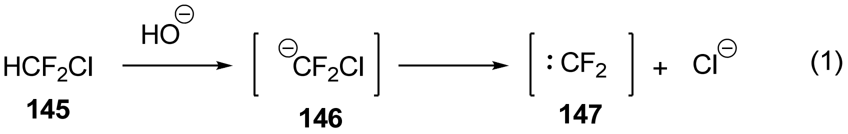
97%), excellent diastereoselectivity (94:4–99:1 d.r.), and high enantioselectivity (92–98% *ee*).



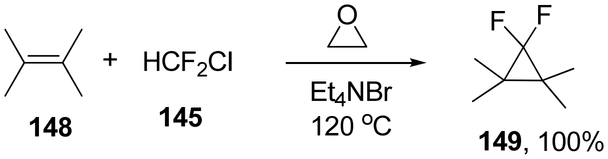
Scheme 1.23

1.1.3.3 Carbenic fluoroalkylation pathway[11a]

There are several methods developed for the generation of difluorocarbene (**147**) which is more stabilized and less reactive than other halo, and dihalocarbenes.

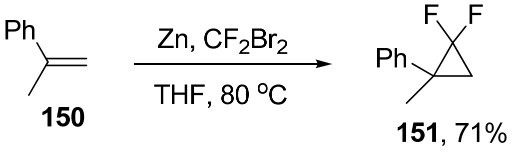


Dehydrohalogenation of chlorodifluoromethane using alkoxide or alkyllithium in the presence of alkenes gave poor yields of difluorocyclopropanes.[35] The low yields of cyclopropanes obtained in this reaction is due to the facile addition of strong base to difluorocarbene. To solve this problem, Weyerstahl and co-workers[36] reported an elegant approach for the preparation of difluorocyclopropanes **149** in almost quantitative yield (Scheme 1.24). The key factors are to employ a combination of oxirane and Et_4NBr at 120 °C in order to generate difluorocarbene **147** in a low concentration of base.



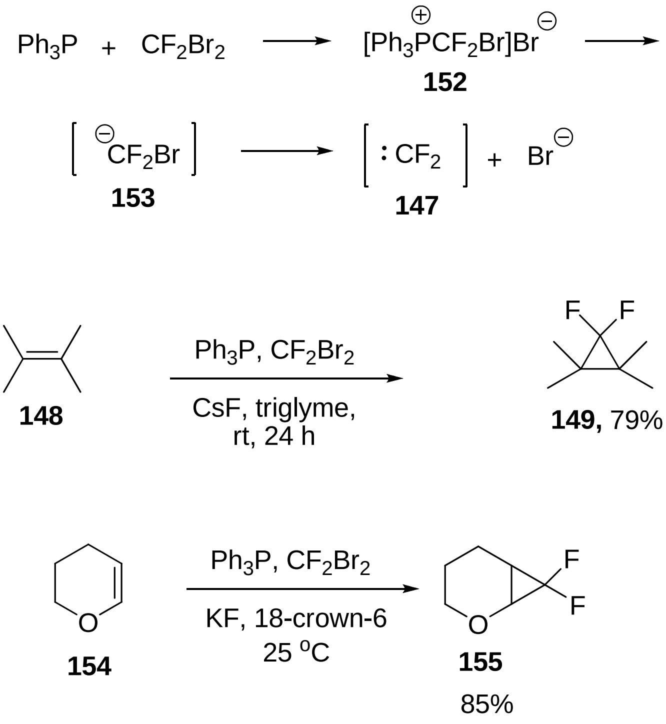
Scheme 1.24

Dolbier and co-workers[37] reported a room temperature reaction, similar to the Simmons–Smith reaction, between dibromodifluoromethane and zinc in THF as a method of forming difluorocyclopropanes from alkenes (Scheme 1.25). Yields of difluorocyclopropanes can be excellent with electron-rich alkenes but tend to be poor with less reactive substrates.



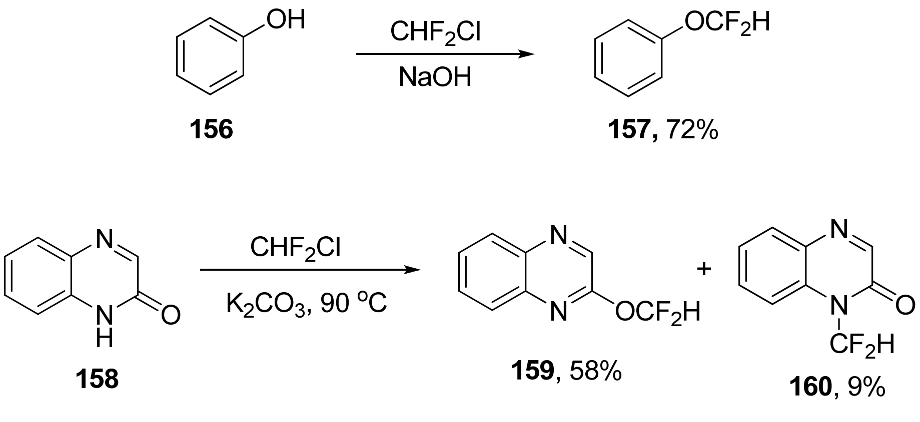
Scheme 1.25

Another method that utilized dibromodifluoromethane to generate difluorocarbene (**147**) was developed by Burton and Naae.[38a] They found that phosphonium salt **152** formed from dibromodifluoromethane and triphenylphosphine, could transfer difluorocarbene (**147**) to alkenes **148** when treated with cesium fluoride in a dry ether solvent at room temperature. In this manner, electron-rich alkenes were converted to *gem*-difluorocyclopropanes **149** in good yields. The use of potassium fluoride and a catalytic amount of 18-crown-6 has been reported to increase the yields of products (Scheme 1.26).[38b]



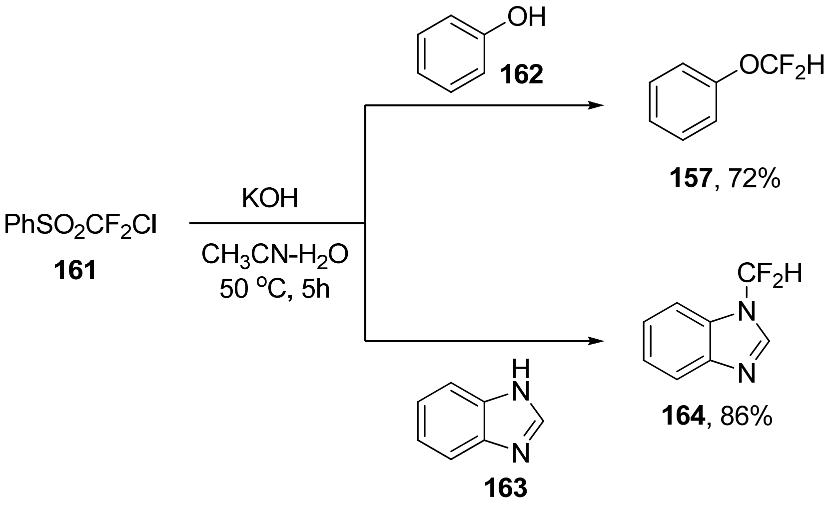
Scheme 1.26

Difluorocarbene (**147**), generated from the action of base on chlorodifluoromethane, can be effectively trapped by alkoxides and related species to form difluoromethyl derivatives. This reaction is very useful for the preparation of difluoromethyl ethers and related compounds (Scheme 1.27).[39] The reaction is believed to proceed via an anionic chain reaction involving the addition of difluorocarbene to the anion.



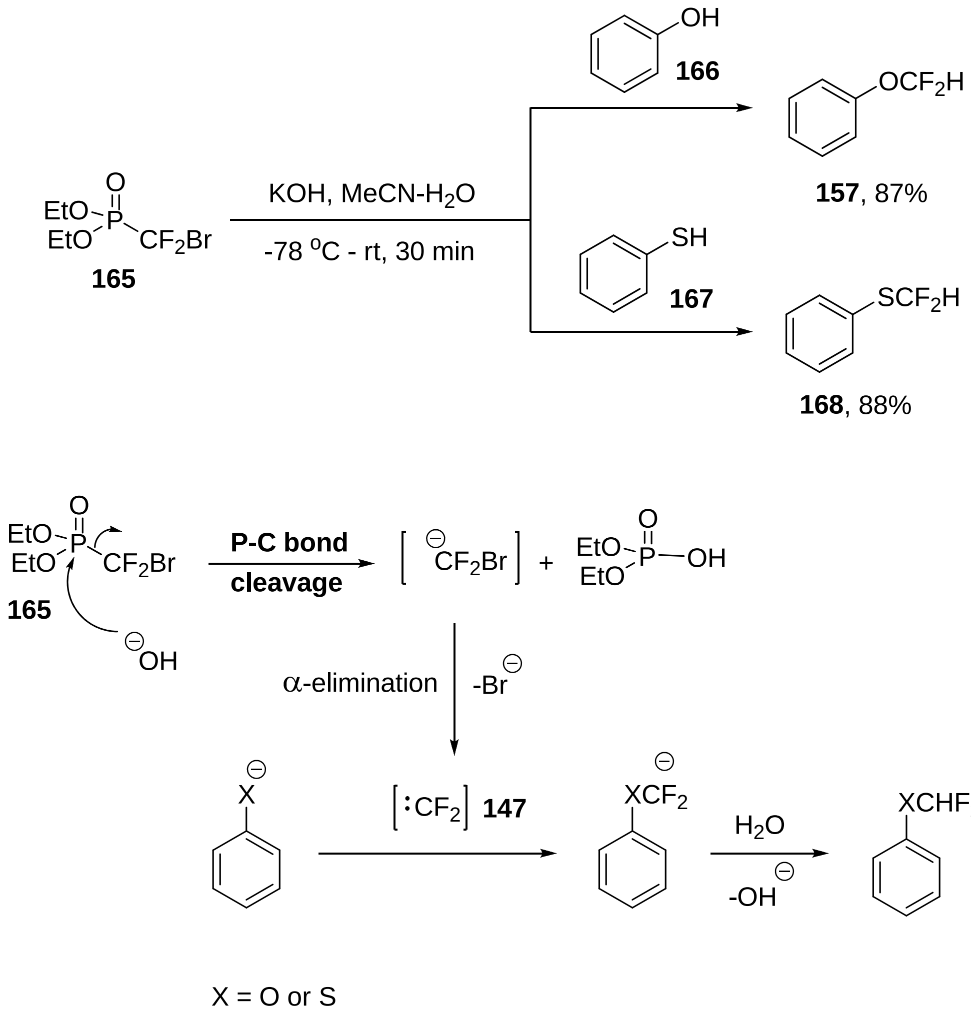
Scheme 1.27

In 2007, Hu and co-workers[40] reported that chlorodifluoromethyl phenyl sulfone (**161**) can be used as a difluorocarbene reagent for *O*- and *N*-difluoromethylations. This synthetic methodology was found synthetically useful for many other applications (Scheme 1.28).



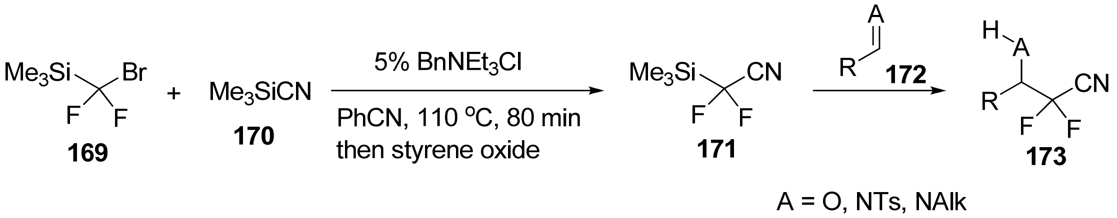
Scheme 1.28

A convenient method for the difluoromethylation of phenols (**166**) and thiophenols (**167**) was also reported by Zafrani and co-worker[41] in 2009 using diethylbromodifluoromethylphosphonate (**165**) as a difluorocabene precursor to give difluoromethyl ethers **157** and thioethers **168** in good to excellent yields. The mechanism of this reaction is believed to proceed via difluorocarbene intermediate. A key step of the reaction involves the hydrolysis-inducing P–C bond cleavage leading to bromodifluoromethyl anion which instantaneously eliminates bromide to give difluorocarbene (**147**). Subsequent trapping by a phenolate or a thiophenolate anion followed by protonation by water gave the corresponding difluoromethyl ether **157** or sulfide **168**, respectively (Scheme 1.29).



Scheme 1.29

A new fluorinated silicon reagent **171** was firstly synthesized by insertion of difluorocarbene into silyl cyanide **170**. The reaction was conducted by heating of (bromodifluoromethyl)trimethylsilane (**169**) with trimethylsilyl cyanide (**170**) in the presence of 5 mol% of benzyltriethylammonium chloride affording 2,2-difluoro-2-(trimethylsilyl)acetonitrile (**171**) (80% yield). The product bromosilane can be trapped using styrene oxide. Dilman and co-workers also demonstrated that the obtained 2,2-difluoro-2-(trimethylsilyl)acetonitrile (**171**) can be further used as cyanodifluoromethylating reagent toward aldehydes, *N*-alkylimines, *N*-tosylimines, and enamines under basic or acidic conditions (Scheme 1.30).[42]

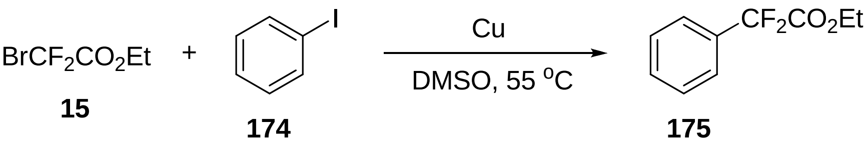


Scheme 1.30

1.1.3.4 Transition metal-mediated fluoroalkylation

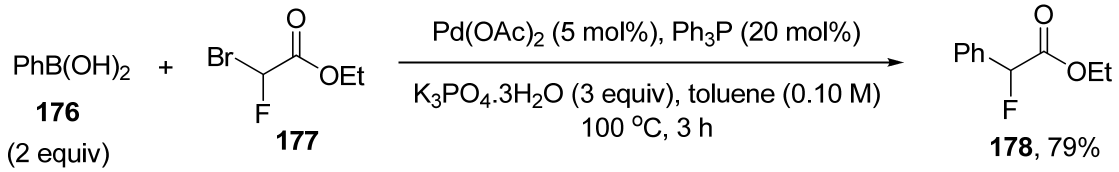
A versatile transition-metal-catalyzed or organocatalytic approach has also been developed for fluoroalkylation. Recently, transition-metal-catalyzed arylation has become a useful and general synthetic method for the preparation of α-arylacetic acid derivatives.[43]

Kumadaki and co-workers demonstrated that in the presence of copper powder, ethyl α-bromo-α,α-difluoroacetate (**15**) reacted with iodobenzene (**174**) to give cross-coupling products **175** and this was fairly process (Scheme 1.31).[15c]



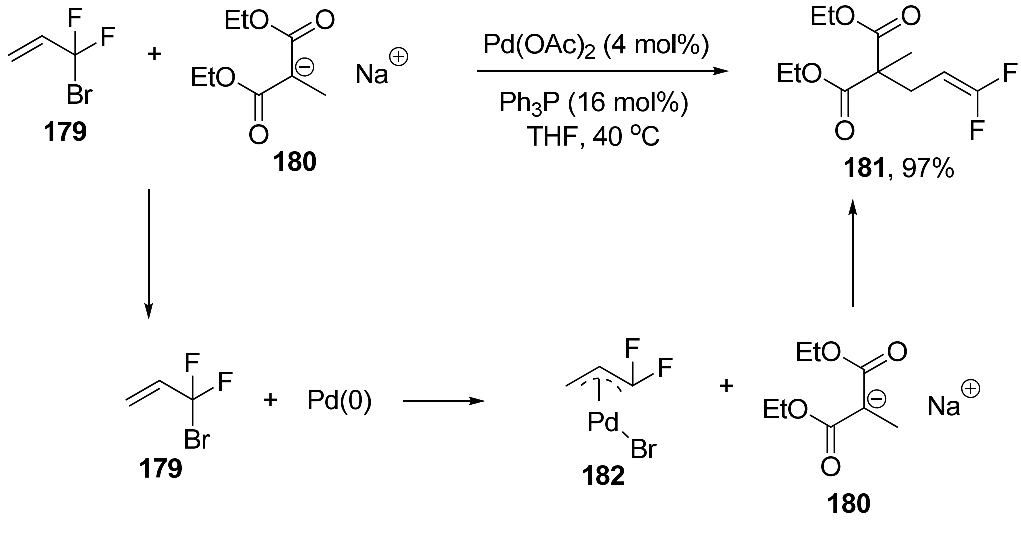
Scheme 1.31

Inspired by these results, Qing and co-workers[14h] developed the Suzuki–Miyaura cross-couplings of ethyl α-bromo-α-fluoroacetate (**177**) with phenylboronic acid (**176**) under palladium catalysis. The cross-coupling product **178** was obtained in 79% yield in the presence of $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), and $K_3PO_4.3H_2O$ (3 equiv) in toluene at 100 °C (Scheme 1.32).



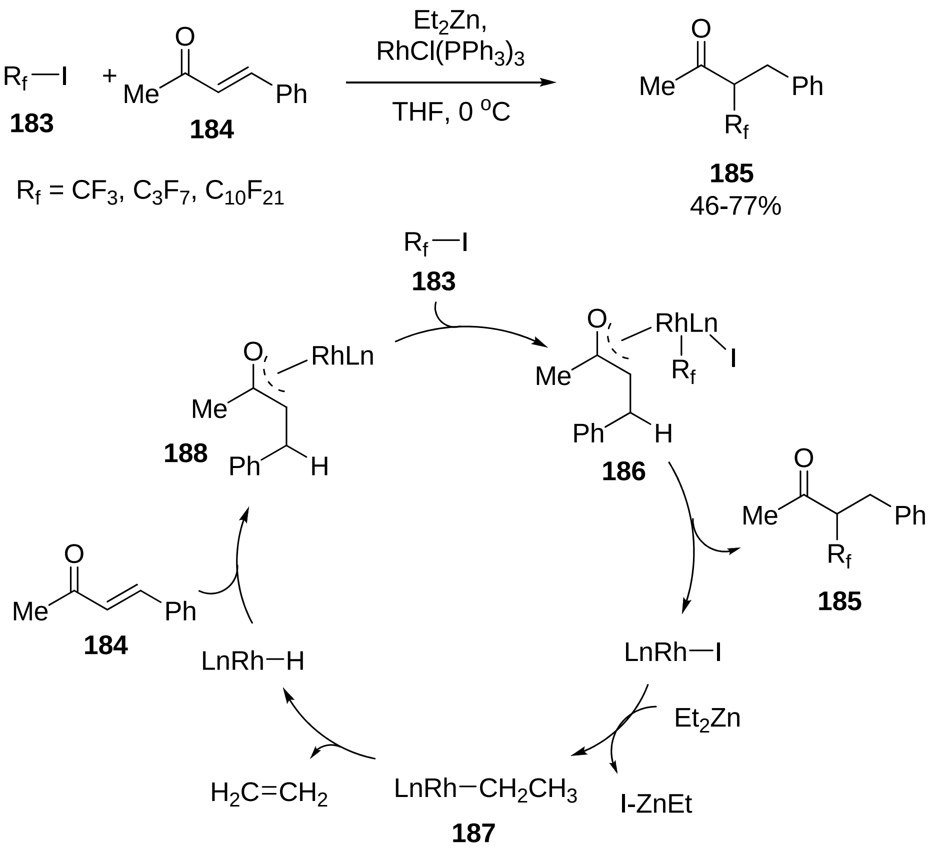
Scheme 1.32

The palladium catalyzed nucleophilic substitution of 3-bromo-3,3-difluoropropene (**179**) with sodium 1,3-diethoxy-2-methyl-1,3-dioxopropan-2-ide (**180**) in the presence of Pd(OAc)$_2$ (4 mol%), and Ph$_3$P (16 mol%) in THF at 40 °C to gave product **181** in 97% yield. The reaction might proceed through the (difluoroallyl)palladium complex **182**, which is formed by the oxidative addition of **179** to Pd(0) (generated from palladium acetate and triphenylphosphine) (Scheme 1.33).[14a]



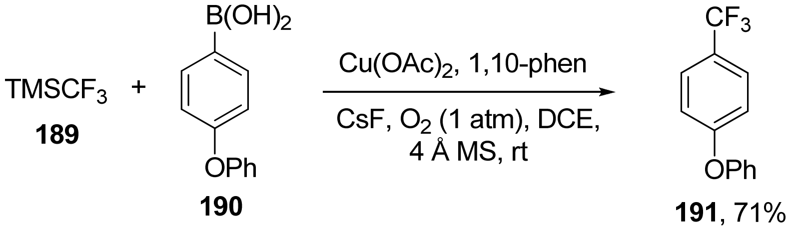
Scheme 1.33

In 2007, Ando and co-workers[44] reported Rh-catalyzed α-fluoroalkylation of α,β-unsaturated ketones **184** in the presence of Et$_2$Zn in THF at 0 °C to give reductive fluoroalkylation products **185** at the α-position of α,β-unsaturated ketones in moderate to good yields. The rhodium hydride complex generated from Rh catalyst was believed to play an important role in this reaction (Scheme 1.34).



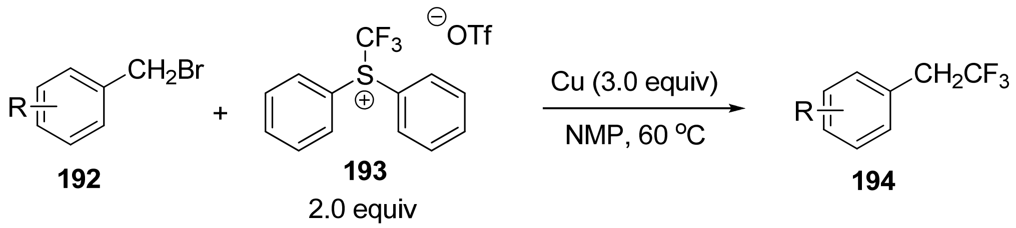
Scheme 1.34

Recently, Buchwald and co-workers[14i] have reported the room temperature copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids. By using $Cu(OAc)_2$ (1 equiv), phenanthroline (1.1 equiv), CsF (2 equiv), heteroaryl boronic acids **190** and $TMSCF_3$ (**189**) (2 equiv) as the trifluoromethylating reagent in an atmosphere of dry oxygen, 1-phenoxy-4-(trifluoromethyl)benzene (**191**) was obtained in 71% yield (Scheme 1.35).



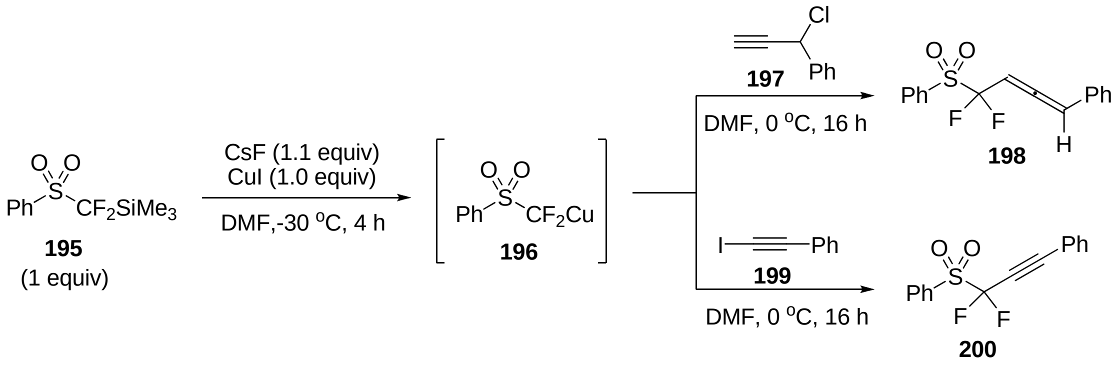
Scheme 1.35

In 2011, Shibata and co-workers[14j] developed copper-mediated chemoselective trifluoromethylation at the benzylic position through the use of shelf-stable electrophilic trifluoromethylating reagent **193** to give the corresponding product **194** in good to high yields under mild conditions (Scheme 1.36).



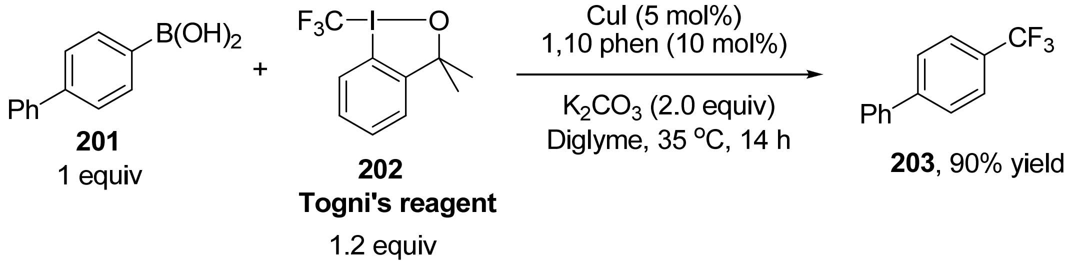
Scheme 1.36

Copper-mediated (phenylsulfonyl)difluoromethylation of propagyl chlorides **197** and alkynyl iodides **199** have been reported by Hu and co-workers[45] in 2011. They found that treatment of $PhSO_2CF_2TMS$ **195** (1 equiv) with CuI (1 equiv) in the presence of CsF (1.1 equiv) in DMF at -30 °C for 4 h could generate a new (difluoro(phenylsulfonyl)methyl)copper (**196**, $PhSO_2CF_2Cu$,)**.** This intermediate was found being an efficient difluoromethylating reagent for cross-coupling reactions with propagyl chlorides and alkynyl iodides to give $PhSO_2CF_2$-containing allenes **198** and alkynes **200** in moderate to good yields (Scheme 1.37).



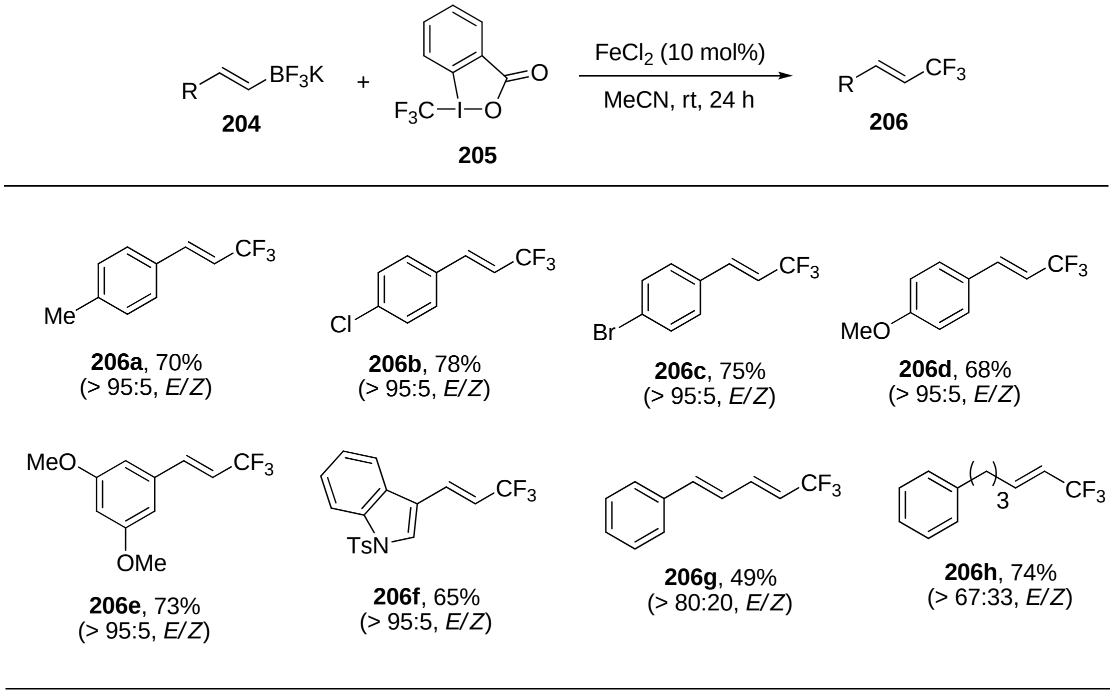
Scheme 1.37

CuI/1,10-Phenanthroline-catalyzed trifluoromethylation of 4-biphenylboronic acid (**201**) in the presence of Togni's reagent **202**[46] was reported by Shen and co-workers in 2011.[14k] The reaction worked well with a range of different substrates including heteroarylboronic acids and substrates with a variety of functional groups under mild reaction conditions (Scheme 1.38).



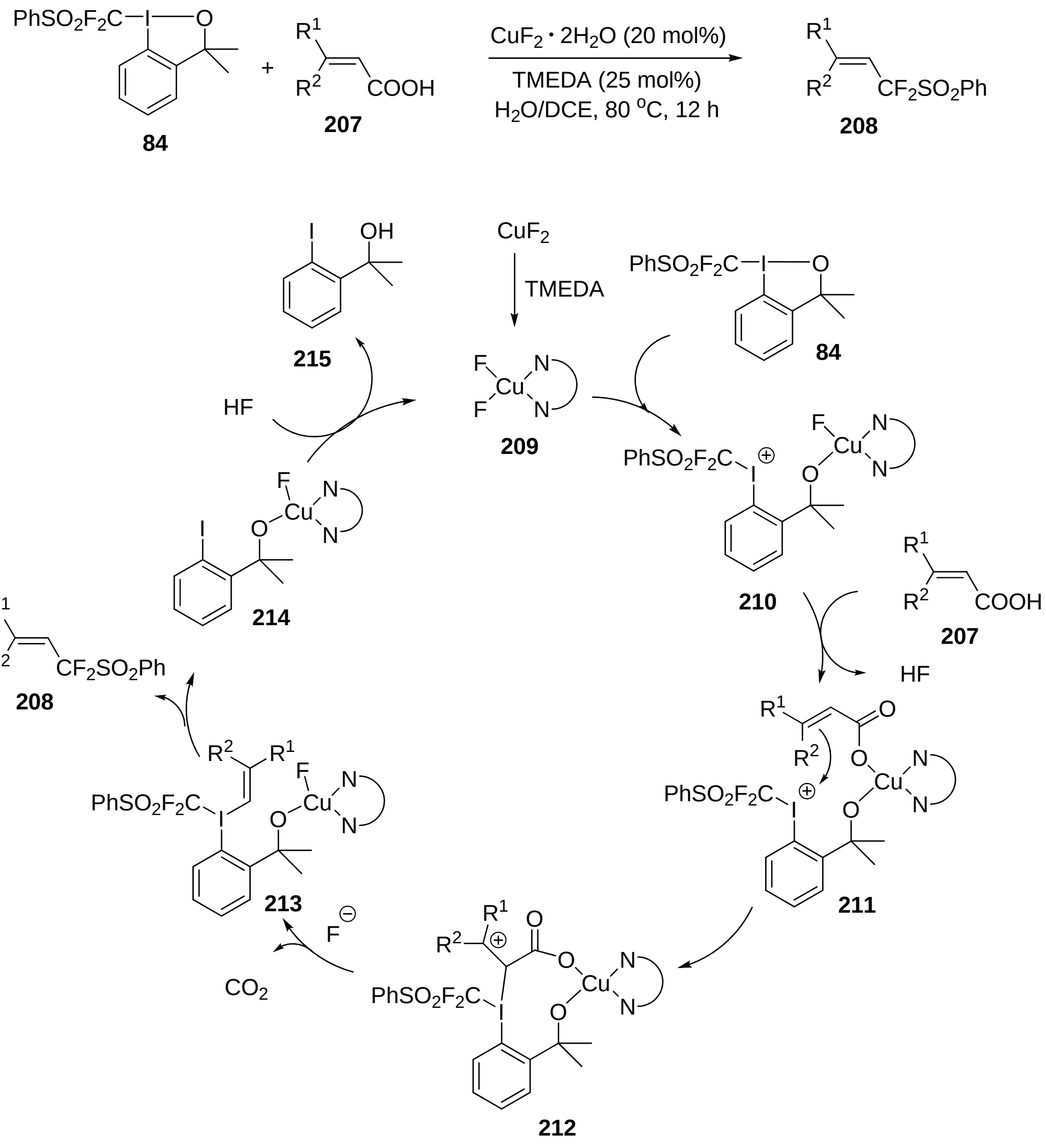
Scheme 1.38

By using Togni's reagent **205**, Buchwald and co-workers[47] have developed an iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates **204**. The reaction took place at room temperature in the presence of 10 mol% of $FeCl_2$ affording vinyl–CF_3 containing products **206** in good yields. The results are shown in Scheme 1.39.



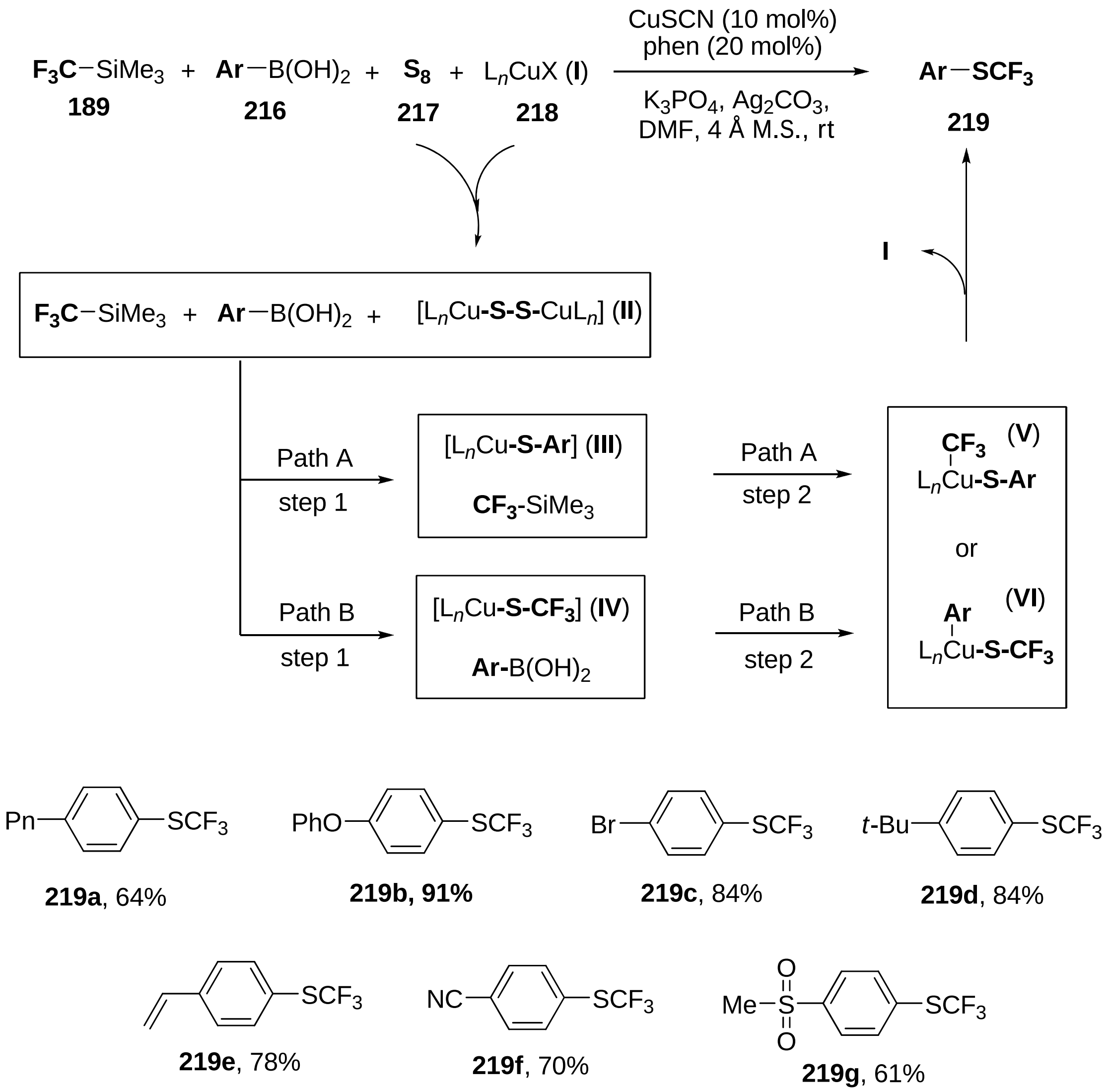
Scheme 1.39

Hu an co-workers[48] have recently disclosed their success in developing a new protocol for vinylic difluoromethylation through copper-catatlyzed decarboxylative fluoroalkylation of α,β-unsaturated carboxylic acids with a hypervalent iodine(III)-CF_2SO_2Ph reagent **84**. A variety of α,β-unsaturated carboxylic acids **207** were subjected to the optimized reaction conditions and furnished the corresponding difluoromethylated **208** in good yields. After thoroughly investigating the reaction, they found that Lewis acid ($CuF_2 \cdot 2H_2O$) played an important role in the reaction by both enhancing the electrophilicity of the hypervalent iodine(III)-CF_2SO_2Ph reagent **84** and promoting the decarboxylation of α,β-unsaturated carboxylic acids **207** (Scheme 1.40).



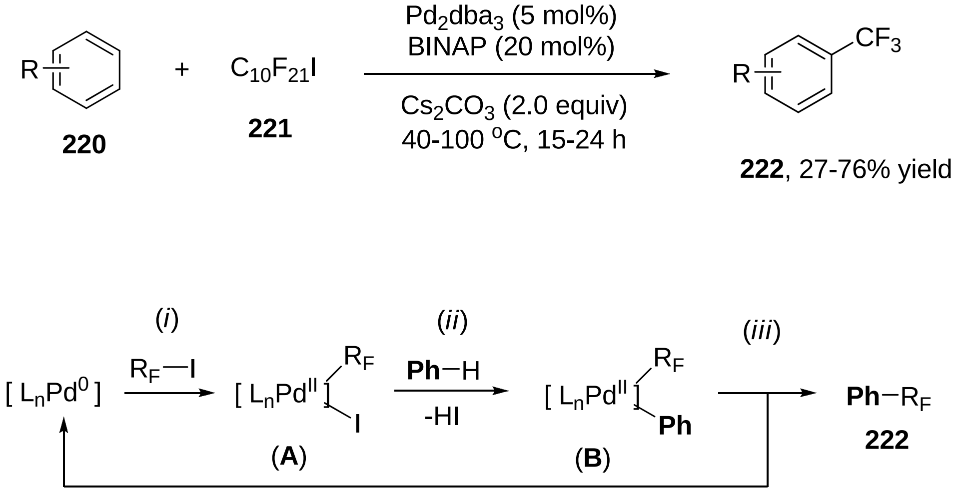
Scheme 1.40

The first example of copper-catalyzed oxidative trifluoromethylthiolation of arylboronic acids **216** with TMSCF$_3$ **189** (the Ruppert–Prakash reagent) and elemental sulfur (**217**) at room temperature has been reported by Qing and co-workers.[49] Under hypothesis, Cu^{I} disulfide complex (**II**), generated *in situ* in the reaction, would react with aryl boronic acid **216** to give intermediate **III** (Path A) followed by reacting with TMSCF$_3$ **189**, providing the key intermediate **V**. Eventually, oxidation of complex **V** to complex L$_n$Cu^{III}(CF$_3$)(ArS), followed by reductive elimination would lead to the expected aryltrifluoromethyl thioether **219**. Alternatively, the reaction could undergo via intermediate **IV** (Path B) which was reacted with arylboronic acids **216** to give copper complex **VI**. Finally, reductive elimination of **VI** provided the same expected product **219** (Scheme 1.41). After examining substrate scope of the reaction, they found that the reaction conditions allowed for the trifluoromethylthiolation of aryl broronic acids containing a wide range of functional groups, including ester, ketones, nitrile, and sulfonyl groups.



Scheme 1.41

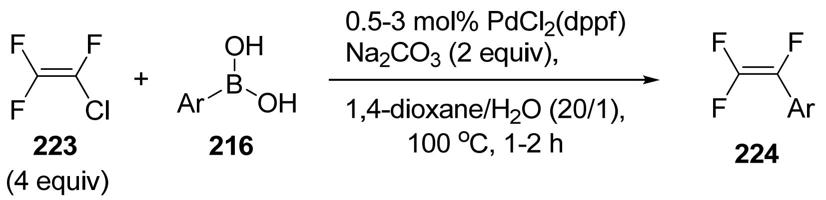
Sanford and co-workers[141] reported a new Pd-catalyzed reaction for the coupling between perfluoroakyl iodides **221** and simple aromatic substrates **220**. The perfluoroalkylated arene products **222** were obtained in good to excellent yields in the presence of a phosphine-ligated Pd catalyst and Cs_2CO_3 as a base. There are several potential mechanisms for these reactions. One possibility is similar to that proposed by Fagnou[50] for Pd-catalyzed C–H arylation with aryl halide. This mechanism would involve: (i) oxidative addition of R_FI (perfluoroakyl iodides) **221** to Pd^0 to generate Pd^{II} intermediate **A**, (ii) arene activation at **A** to form the diorgano Pd^{II} species **B**, and (iii) C–C bond-forming reductive elimination to release the product **222** and regenerate the Pd^0 catalyst (Scheme 1.42).

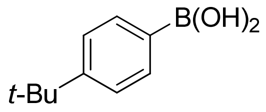
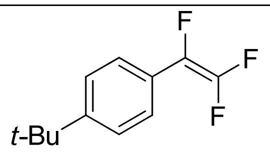
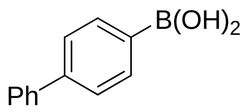
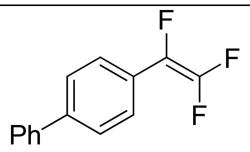
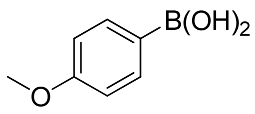
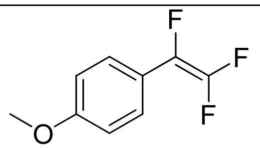
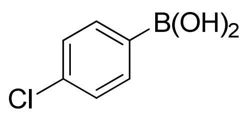
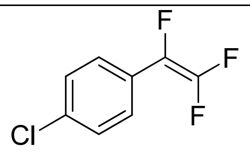
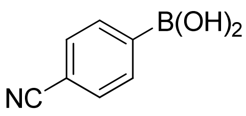
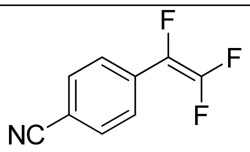
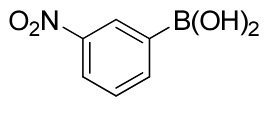
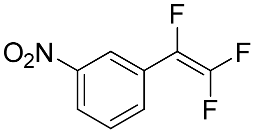


Scheme 1.42

Since α,β,β-trifluorostyrene derivatives **224** are important intermediates for functional materials such as proton exchange membranes and liquid crystal, Yamakawa and co-workers[51] have achieved the Pd-catalyzed arylation of chlorotrifluoroethylene **(223)** (CTFE) and arylboronic acids **216** via the Suzuki–Miyaura coupling to obtain α,β,β-trifluorostyrene derivatives **224** in good yields. The results of this reaction are shown in Table 1.4.

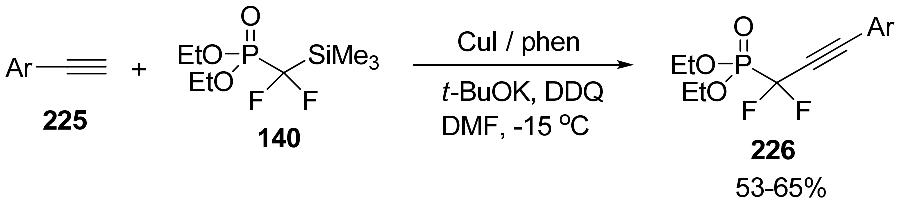
Table 1.4 Pd-Catalyzed arylation of CTFE usig aryboronic acids[a]



Entry	**Substrate 216**	**Catalyst (mol%) / reaction time (h)**	**Product 224**	**Yield (%)[b]**
1		1 / 2		87
2		1 / 2		79
3		0.5 / 2		71
4		1 / 2		70
5		2 / 2		65
6		1 / 2		80

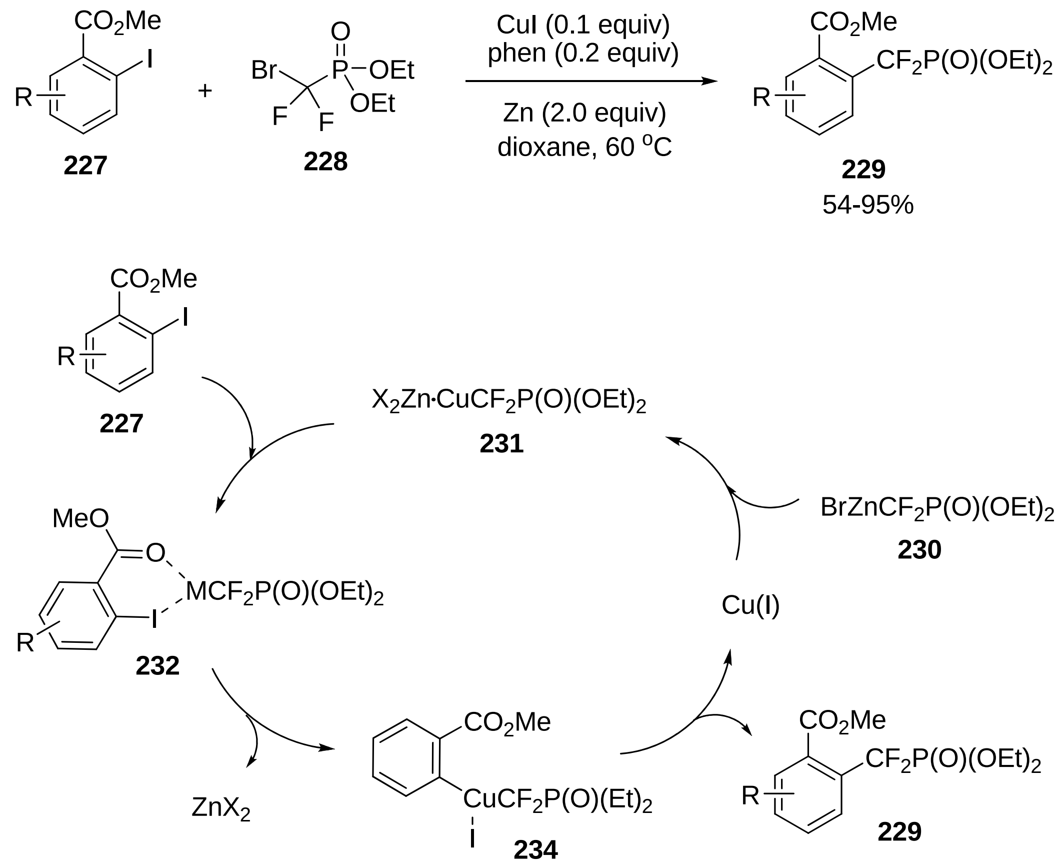
[a]The reaction was conducted with $PdCl_2$(dppf) (0.005–0.03 mmol), arylboronic acids (1.0 mmol), CTFE (4 mmol), and Na_2CO_3 (2.0 mmol) in 1,4-dioxane (2.0 mL) and H_2O (0.1 mL) at 100 °C. [b]Isolated yield.

Recently, Qing and co-workers[52] have reported the developed method for generating the $(EtO)_2P(O)CF_2Cu$ species from $(EtO)_2P(O)CF_2SiMe_3$ **140** in the presence of 1,10-phenanthroline, and *t*-BuOK in DMF at -15 °C. With a suitable coupling partner, a variety of terminal arylalkynes **225** and diethyl difluoro(trimethylsilyl)methylphosphonate (**140**) smoothly underwent copper-mediated cross-coupling reaction affording a series of α,α-difluoropropargylphosphonates **226** in moderate yields (Scheme 1.43).



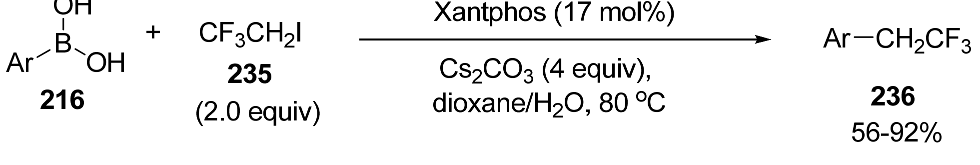
Scheme 1.43

Zhang and co-workers[53] have reported a copper-catalyzed cross-coupling reactions of iodobenzoates **227** with bromozinc-difluorophosphate **230**, generated from diethyl bromodifluoromethylphosphate **228** and zinc in dioxane. This reaction provides a convenient protocol for the preparation of aryldifluorophosphates **229** with high efficiency and excellent functional group compatibility (Scheme 1.44).



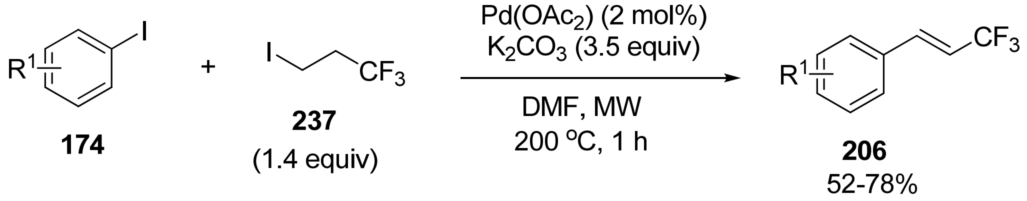
Scheme 1.44

In 2012, Hu and co-workers[54] reported palladium catalyzed cross-coupling reaction between phenylboronic acids (**216**) and trifluoroethyl iodide (**235**) providing an alternative method for the preparation of (2,2,2-trifluoroethyl)arenes **236** in moderate to good yields (Scheme 1.45).



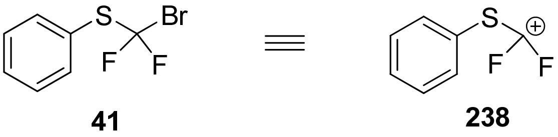
Scheme 1.45

In 2012, Prakash and co-workers[55] reported a palladium catalyzed Heck reaction between aryl iodides (**174**) and commercially accessible 1-iodo-3,3,3-trifluoropropane (**237**) under basic conditions. Under such conditions, 1-iodo-3,3,3-trifluoropropane (**237**) undergoes dehydrohalogenation to produce 3,3,3-trifluoropropene (vinyl-CF_3) *in situ*, which would react with aryl iodides (**174**) with palladium(II) acetate as a catalyst to yield the desired β-trifluoromethylstyrenes **206** in moderate to good yields (Scheme 1.46).

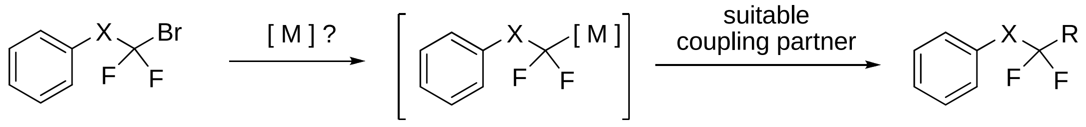


Scheme 1.46

In continuing our on-going research on the introduction of the *gem*-difluoromethylene moiety into an organic molecule, we envisaged that bromodifluoromethyl phenyl sulfide (**41**) would be a good reagent for the generation of α,α-difluorocarbocation species **238** by its reaction with Lewis acids; trapping this intermediate with a nucleophile would provide a facile route for the formation of difluoromethylated compound (Scheme 1.47). We were also interested in transition metal-mediated fluoroalkylation (Scheme 1.48) for synthesis of difluoromethylated compound employing bromodifluoromethyl phenyl sulfide (**41**) and its derivates as difluoromethylating reagents. It is anticipated that the results will lead to new preparative method of organofluorine compounds which may be medicinally and industrially useful.



Scheme 1.47



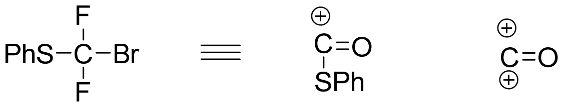
X = S, SO, or SO_2
M = transition metal

Scheme 1.48

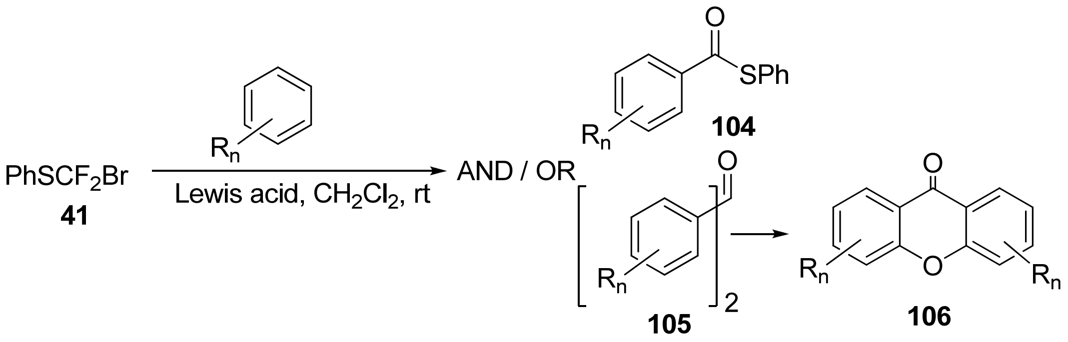
CHAPTER II

RESULTS AND DISCUSSION

Our research group has a long-attending interest in the introduction of the *gem*-difluoromethylene moiety into organic molecules by a carbocationic electrophilic strategy. Our research group previously demonstrated the reactivity of bromodifluoromethyl phenyl sulfide (**41**) towards Lewis acids such as $SnCl_4$, $AlCl_3$ $TiCl_4$ through the Friedel-Crafts alkylation of activated aromatic compounds giving substantial yields of thioesters **104** and benzophenones **105**. This is the first example of the application of **41** as the synthetic equivalent of thioester cation **102** and geminal carbonyl dication **103** through the Friedel-Crafts alkylation (Scheme 2.1).[13] The method provides a quick and convenient entry into thioesters **104**, benzophenones **105**, and naturally occurring xanthone derivatives **106**.



41 **102** **103**



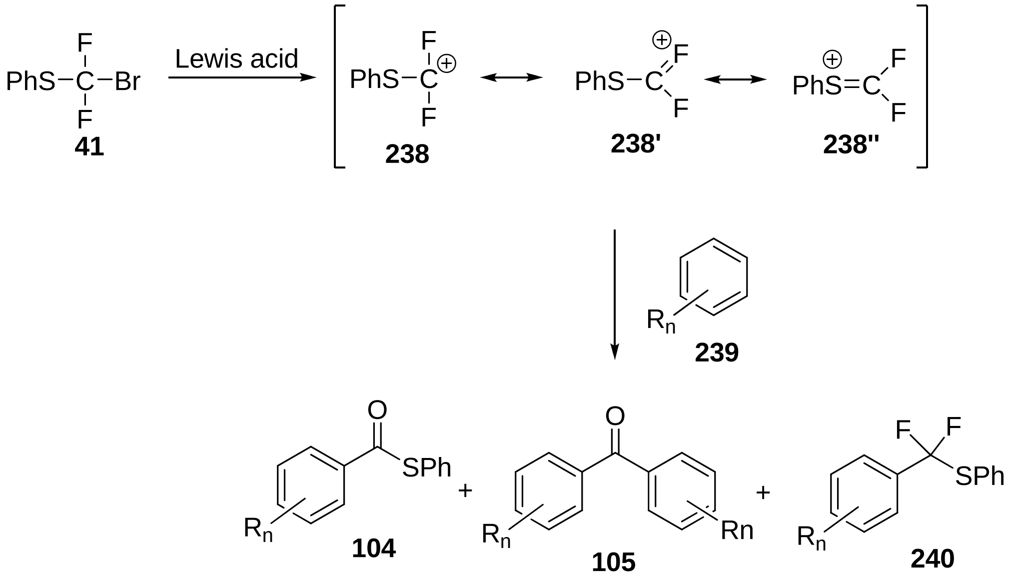
Scheme 2.1

In order to further study on the reactivity of bromodifluoromethyl phenyl sulfide (**41**) towards Lewis acids in detail, and gaining more insight into the role of

Lewis acids, solvents, temperature, and reaction mechanism, the additional experiments were established and thoroughly investigated.

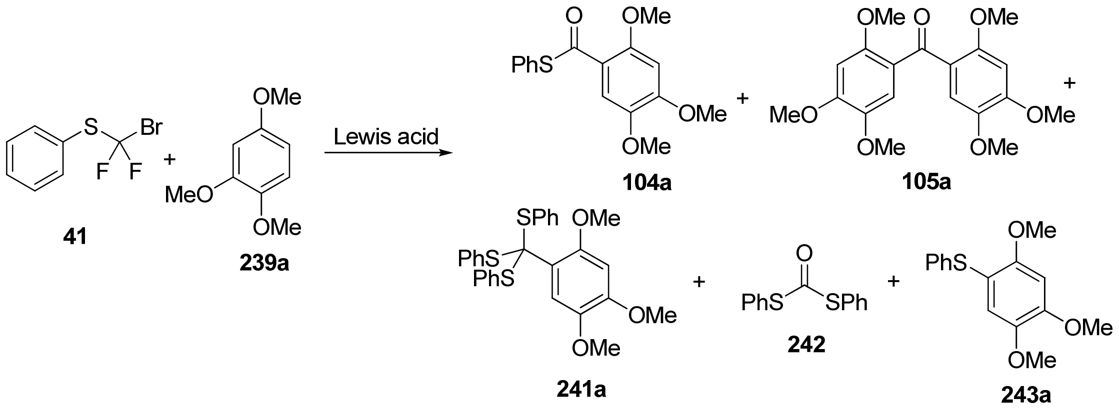
2.1 Investigation of the reaction of bromodifluoromethyl phenyl sulfide (41) and 1,2,4-trimethoxybenzene (239a) mediated by Lewis acids

Under the hypothesis that bromodifluoromethyl phenyl sulfide (**41**) would be a good reagent for the generation of α,α-difluorocarbocation species (**238**) by its reaction with Lewis acid, Friedel-Crafts alkylation reaction of bromodifluoromethyl phenyl sulfide (**41**) with activated aromatic compounds was examined. The mesomeric interaction of unshared electron pairs of fluorine atoms (**238′**) together with those of the phenylsulfanyl moiety (**238a″**) would have added stability to the carbocation intermediate,[56] Subsequent trapping of the cationic intermediate with a carbon nucleophile would provide a facile route for the formation of a new C-C bond (Scheme 2.2). In order to study this reaction in detail with the aim of achieving reaction optimization, obtaining the desired fluorinated product **240** and altering the selectivity for **104** and **105**, an array of Lewis acids was examined. The results are summarized in Table 2.1.



Scheme 2.2

Table 2.1 Results of the effect of Lewis acids[a]



Entry	**41** (equiv)	**239a** (equiv)	Conditions	Yield (%)[b]				
				104a	**105a**	**241a**	**242**	**243a**
1	1	1	$AlCl_3$ (2 equiv), rt, 1 h, CH_2Cl_2	79	4	0	0	0
2	2	1	$EtAlCl_2$ (1.1 equiv), rt, 18 h, toluene	16	12	7	0	0
3	1	1	$Al(Me)_3$ (1.1 equiv), rt, 48 h, hexanes	0	0	0	0	0
4	1	1	$Al(Me)_3$ (1.1 equiv), rt, 24 h, CH_2Cl_2	0	2	0	0	0
5	2	1	$Al(Me)_3$ (4 equiv), rt, 15 h, CH_2Cl_2	9	0	0	0	0
6	2	1	DABAL-Me_3 (1 equiv), rt, 24 h, MeCN	0	0	0	0	0
7	2	1	DABAL-Me_3 (1 equiv), reflux, 12 h, MeCN	0	0	0	0	0
8	2	1	DABAL-Me_3 (2 equiv), rt, 48 h, CH_2Cl_2	0	0	0	0	0
9	2	1	$BF_3·OEt$ (40 equiv), 70 °C, 16 h	0	21	0	10	0

Table 2.1 Results of the effect of Lewis acids[a] (Continued)

Entry	**41** (equiv)	**239a** (equiv)	Conditions	Yield (%)[b]				
				104a	**105a**	**241a**	**242**	**243a**
10	1	1	$Ag(O_2CCF_3)$ (1 equiv), rt, 18 h, $CHCl_3$	0	0	0	9	0
11	2	1	$Zn(BF_4)_2 \cdot xH_2O$ (1.7 equiv), rt, 72 h, $[BMIM]BF_4$	0	0	0	13	0
12	1	2	$ZnBr_2$ (1 equiv), rt, 16 h, CH_2Cl_2	0	0	0	0	0
13	1.2	1	$Et_3Si[B(C_6F_5)_4]$ (1.1 equiv), rt, 48 h, hexanes	60	0	0	0	0
14	1	1	$[BMIM]Al_2Cl_7$(16 equiv), 0 ^oC, 0.5 h	36	0	0	0	0
15	1	1	$Sm(OTf)_3$, (1 equiv), rt, 2 h, THF/CH_2Cl_2	0	0	0	0	0
16	1	1	$SmCl_3$ (1 equiv), rt, 1 h, THF/CH_2Cl_2	0	0	0	0	0
17	1	1	$InCl_3$ (1 equiv), rt, 16 h, THF/CH_2Cl_2	0	0	0	0	0
18	1	1	$Bi(OTf)_3$ (0.2 equiv), rt, 24 h, CH_2Cl_2	4	12	0	0	0
19	1	1	$Bi(OTf)_3$ (0.2 equiv), rt, 24 h, $[BMIM]BF_4$	3	26	0	0	0
20	1	1	$Bi(OTf)_3$ (0.2 equiv), 90 ^oC, 2 h, $[BMIM]BF_4$	0	12	0	0	0
21	5	1	$Bi(OTf)_3$ (0.2 equiv), 90 ^oC, 24 h, $[BMIM]BF_4$	0	0	0	6	0
22	1	1	$Bi(OTf)_3$ (0.2 equiv), rt, 24 h, $[BMIM]PF_6$	6	30	0	0	0

Table 2.1 Results of the effect of Lewis acids[a] (Continued)

Entry	**41** (equiv)	**239a** (equiv)	Conditions	Yield (%)[b]				
				104a	**105a**	**241a**	**242**	**243a**
23	1	1	In(OTf)$_3$ (0.2 equiv), rt, 24 h, [BMIM]BF$_4$	0	0	0	0	0
24	1	1	Hf(OTf)$_4$ (0.2 equiv), rt, 24 h, [BMIM]BF$_4$	0	0	0	0	0
25	1	1	Sm(OTf)$_3$ (0.2 equiv), rt, 24 h, [BMIM]BF$_4$	0	0	0	0	0
26	1	1	Yb(OTf)$_3$ (0.2 equiv), rt, 24 h, [BMIM]BF$_4$	0	0	0	0	0
27	1	1	Yb(OTf)$_3$ (0.2 equiv), 100 °C, 24 h, CH_3NO_2	0	0	0	0	0
28	1	1	Sc(OTf)$_3$ (0.2 equiv), rt, 24 h, [BMIM]BF$_4$	0	4	0	0	0
29	2	1	HFIP, rt, 72 h	11	10	tr[c]	tr[c]	0
30	2	1	Bi(OTf)$_3$ (0.4 equiv), rt, 72 h, HFIP	18	6	0	0	0
31	2	1	Yb(OTf)$_3$ (0.4 equiv), rt, 72 h, HFIP	23	8	tr[c]	0	0
32	2	1	Hf(OTf)$_4$ (0.4 equiv), rt, 72 h, HFIP	33	14	0	0	0
33	1	1	$FeCl_3$ (0.2 equiv), rt, 15 h, CH_2Cl_2	0	0	0	0	0
34	1	1	$FeCl_3$ (0.2 equiv), reflux, 12 h, EtOAc	0	0	0	0	30

[a]In all cases, a solution of Lewis acid was added to a solution of **41** and **239a**. [b]Yields were calculated based on limiting agent. [c]tr = trace amount of product was detected by TLC analysis.

In a preliminary study, a mixture of bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a**) was treated with a commercially available $AlCl_3$ in CH_2Cl_2 at room temperature. With 2 equiv of $AlCl_3$ at room temperature for 1 h, a mixture of thioester **104a** and benzophenone **105a** were obtained in 79% and 4% yields, respectively (Table 2.1, Entry 1). Reducing the Lewis acidity of $AlCl_3$ by replacing one chlorine atom of $AlCl_3$ with an ethyl group ($EtAlCl_2$) in the presence of 2 equiv of bromodifluoromethyl phenyl sulfide (**41**) in toluene resulted in significantly lower yield of thioester **104a** (16% yield) (Table 2.1, Entry 2). Additionally, benzophenone **105a** and orthothioester **241a** were isolated in 12 and 7% yields, respectively. It should be emphasized that the orthothioester **241a** was fairly unstable and was isolated when the crude reaction mixture was quickly separated by column chromatography. Replacing all the chlorine atoms of $AlCl_3$ with methyl group ($Al(Me)_3$) completely diminished the Lewis acidity of the Al(III). No reaction took place when the reaction was performed in hexanes as the solvent (Table 2.1, Entry 3). Trace amount of benzophenone **105a** (2% yield) was isolated when the reaction was carried out using $Al(Me)_3$ in CH_2Cl_2 and reaction was allowed to being stirred at room temperature for 24 h (Table 2.1, Entry 4). Increasing the equiv of both $Al(Me)_3$ (4 equiv) and bromodifluoromethyl phenyl sulfide (**41**) (2 equiv) allowed thioester **104a** to be isolated in 9% yield as a sole product (Table 2.1, Entry 5). The use of a stable bis(trimethylaluminun)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3)[57] in various solvents such as CH_2Cl_2, and MeCN at room temperature or under refluxing conditions failed to provide any products while all the starting materials were leaved intact according to the TLC analysis (Table 2.1, Entries 6-8). Treatment of bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a**) with boron trifluoride etherate (40 equiv) at 70 ^{o}C for 16 h produced benzophenone **105a** and *S,S*-diphenyl carbonodithioate (**242**) in 21% and 10% yields, respectively (Table 2.1, Entry 9). In the presence of $Ag(O_2CCF_3)$ (1 equiv) in $CHCl_3$ at room temperature for 18 h, *S,S*-diphenyl carbonodithioate (**242**) was isolated in 9% yield as a sole product (Table 2.1, Entry 10). *S,S*-Diphenyl carbonodithioate (**242**) (13% yield) was also observed when $Zn(BF_4)_2{\cdot}xH_2O$ (1.7 equiv) was used as a Lewis acid in the presence of [BMIM][BF_4] at room temperature for 72 h (Table 2.1, Entry 11). In the case of $ZnBr_2$ used as a Lewis acid in CH_2Cl_2 as the solvent, Friedel-Crafts alkylation reaction of bromodifluoromethyl phenyl sulfide (**41**) with 1,2,4-trimethoxybenzene (**239a**) was not observed at all in which all of the starting materials were recovered in quantitative yields (Table 2.1, Entry 12). A powerful fluorine abstraction reagent

($[Et_3Si]^+[B(C_6F_5)_4]^-$)[58] was next chosen as a Lewis acid. The reaction performed in hexanes at room temperature for 48 h gave thioester **104a** as a sole product (60% yield) (Table 2.1, Entry 13). A highly Lewis acidic ionic liquids $[BMIM]Al_2Cl_7$[59] was prepared and used as both catalyst and solvent for Friedel-Crafts reaction of bromodifluoromethyl phenyl sulfide (**41**) providing 36% yield of thioester **104a** (Table 2.1, Entry 14). The reaction employing mild Lewis acids $Sm(OTf)_3$, $SmCl_3$, and $InCl_3$ in (1:1) THF/CH_2Cl_2 at room temperature did not provide any products (Table 2.1, Entries 15-17). The reactions mediated by lanthanide salts as catalysts in ionic liquids [including $Bi(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Sm(OTf)_3$, $Hf(OTf)_4$ and $Yd(OTf)_3$] were after examined. The benzophenone **105a** (30% yield) and thioester **104a** (6% yield) were obtained when bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a)** were treated with $Bi(OTf)_3$ (0.2 equiv) in $[BMIM][PF_6]$ at room temperature for 24 h (Table 2.1, Entry 22). Lower yields of **104a** (3% yield) and **105a** (26% yield) were observed when $[BMIM][BF_4]$ was employed as solvent in place of $[BMIM][PF_6]$ (Table 2.1, Entries 19 vs 22). The reaction using $Bi(OTf)_3$ (0.2 equiv) in $[BMIM][BF_4]$ at 90 °C for 24 h led to neither of the product **104a** nor **105a** while *S,S*-diphenyl carbonodithioate (**242**) was isolated in 6% yield (Table 2.1, Entry 21). In the case of $In(OTf)_3$, $Sm(OTf)_3$, $Hf(OTf)_4$ and $Yb(OTf)_3$ in $[BMIM][BF_4]$, no reaction was observed (Table 2.1, Entries 23-26). Only 4% yield of **105a** was isolated when $Sc(OTf)_3$ was employed as Lewis acid in $[BMIM][BF_4]$ at room temperature for 24 h (Table 2.1, Entry 28). A combination of Lewis acid and a weak Bronsted acid 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), known as effective solvent for promoting the Friedel–Crafts reactions,[60] was also examined. In a preliminary study, bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a**) were treated with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at room temperature for 72 h affording products **104a** and **105a** in 11% and 10% yields, respectively (Table 2.1, Entry 29). With an aim to enhance the reactivity of the reaction, a combination of $Bi(OTf)_3$ and HFIP was employed. Products **104a** and **105a** were obtained in only 18% and 6% yields, respectively (Table 2.1, Entry 30). A combination of $Yb(OTf)_3$ and HFIP gave comparable results to those of $Bi(OTf)_3$ and HFIP (Table 2.1, Entry 31). When bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a**) were treated with $Hf(OTf)_4$ in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at room temperature for 72 h, the products **104a** and **105a** were obtained in 33% and 14% yields, respectively (Table 2.1, Entry 32). The Friedel–Crafts reaction of bromodifluoromethyl phenyl sulfide (**41**) with 1,2,4-trimethoxybenzene (**239a**) in the presence of $FeCl_3$ in CH_2Cl_2 resulted no reaction at all (Table 2.1, Entry 33). Surprisingly, the corresponding sulfide product **243a** (30% yield) was obtained in this reaction mediated by $FeCl_3$ in EtOAc under refluxing temperature (Table 2.1, Entry 34).

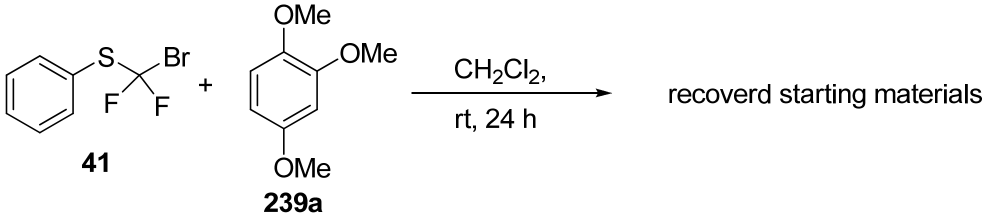
2.2 Investigation of the reaction mechanism of the reaction of bromodifluoromethyl phenyl sulfide (41) and 1,2,4-trimethoxybenzene (239a) mediated by Lewis acids

In order to gain more insight into the reaction mechanism, additional experiments were designed on the framework of the possibility of the electron transfer process (SET) and extensive NMR experiments.

2.2.1 Investigation of the electron transfer process (SET)

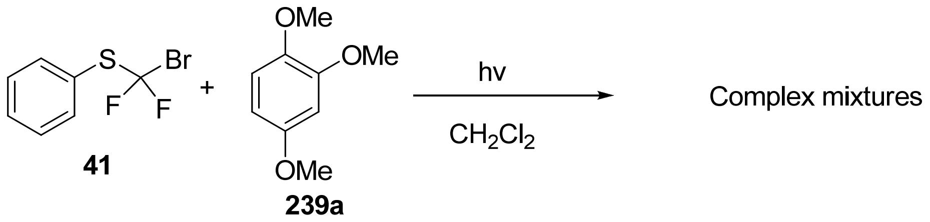
In the case of the electron transfer process (SET), two control reactions were carried out.

In the first experiment, bromodifluoromethyl phenyl sulfide (**41**) was mixed with 1,2,4-trimethoxybenzene (**239a**) in the absence of a Lewis acid and the mixture was stirred at room temperature for 24 h (Scheme 2.3). According to TLC analysis, no formation of any product could be detected; only starting materials **41** and **239a** were recovered in quantitative yields.



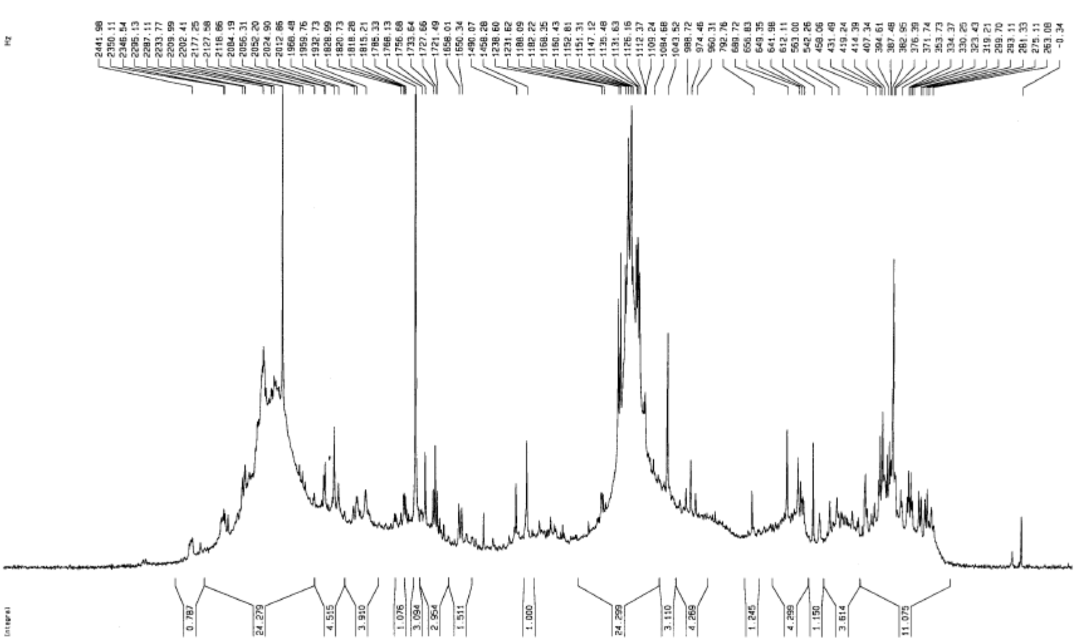
Scheme 2.3

In the second experiment, the reaction of bromodifluoromethyl phenyl sulfide (**41**) and 1,2,4-trimethoxybenzene (**239a**) under photochemical reaction conditions employing a 1 L Hanovia photochemical reactor equipped with a 450 W medium-pressure Hg lamp was conducted, again without the addition of a Lewis acid. The reaction mixture was worked up after 1 h of irradiation. The TLC pattern of the crude product showed no definite spot, and only heavy tailing was detected. The ^{1}H NMR spectrum revealed a complex mixture, and no identifiable products were observed (Scheme 2.4).



^{1}H NMR Spectrum of crude product of UV irradiation

(300 MHz, $CDCl_3$)

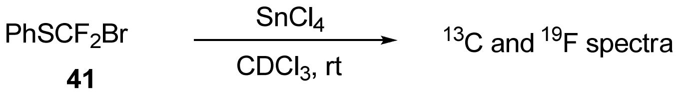


Scheme 2.4

2.2.2 NMR experiments

In a preliminary study, the reactions performed in both $TiCl_4$ and $SnCl_4$ were selected for NMR studies. In the absence of an aromatic nucleophile, when a solution of compound **41** in $CDCl_3$ was treated with $TiCl_4$, a brown viscous material was formed instantaneously on the wall of the NMR tube, hampering the recording of the NMR signals. In contrast, the reaction mediated by $SnCl_4$ gave a clear yellowish solution. Therefore, $SnCl_4$ was chosen as a Lewis acid for NMR studies in order to further investigate possible intermediates formed during the reaction.

2.2.2.1 Reaction of bromodifluoromethyl phenyl sulfide (41) (1 equiv) with $SnCl_4$ (2 equiv) in $CDCl_3$



$$\underset{\textbf{41}}{PhSCF_2Br} \xrightarrow[CDCl_3,\ rt]{SnCl_4} {}^{13}C \text{ and } {}^{19}F \text{ spectra}$$

A solution of bromodifluoromethyl phenyl sulfide (**41**) (1 equiv) in $CDCl_3$ was treated with 1 M solution of $SnCl_4$ (2 equiv) in $CDCl_3$ under argon atmosphere. The reaction mixture was sampled to NMR tube and was monitored by ^{13}C and ^{19}F NMR spectroscopy. Without an added aromatic compound, low-temperature ^{19}F NMR experiment revealed that no evidence of fluorinated intermediate was formed at -78 °C, -40 °C and -20 °C, respectively. When the reaction was warmed up to room temperature, a new highfield shift of the fluorine signal from δ_F = -21.95 ppm (corresponding to the fluorine signal of compound **41**) to δ_F = -27.60 ppm was observed after 1 h of mixing. After 24 h of mixing, the signal at δ_F = -27.60 ppm became the major peak in comparison with the signal at δ_F = -21.95 ppm. The observed highfield shift at δ_F = -27.60 ppm is consistent with fluorine signal of chlorodifluoromethyl phenyl sulfide (**244**).[40,61] It is possible that a liberated chlorine atom of $SnCl_4$ attacks electrophilic *α,α*-difluorocarbocation intermediate **238** which is stabilized by unshared electron pairs of fluorine atoms **238'** together with those of the phenylsulfanyl moiety **238''** (Scheme 2.5).

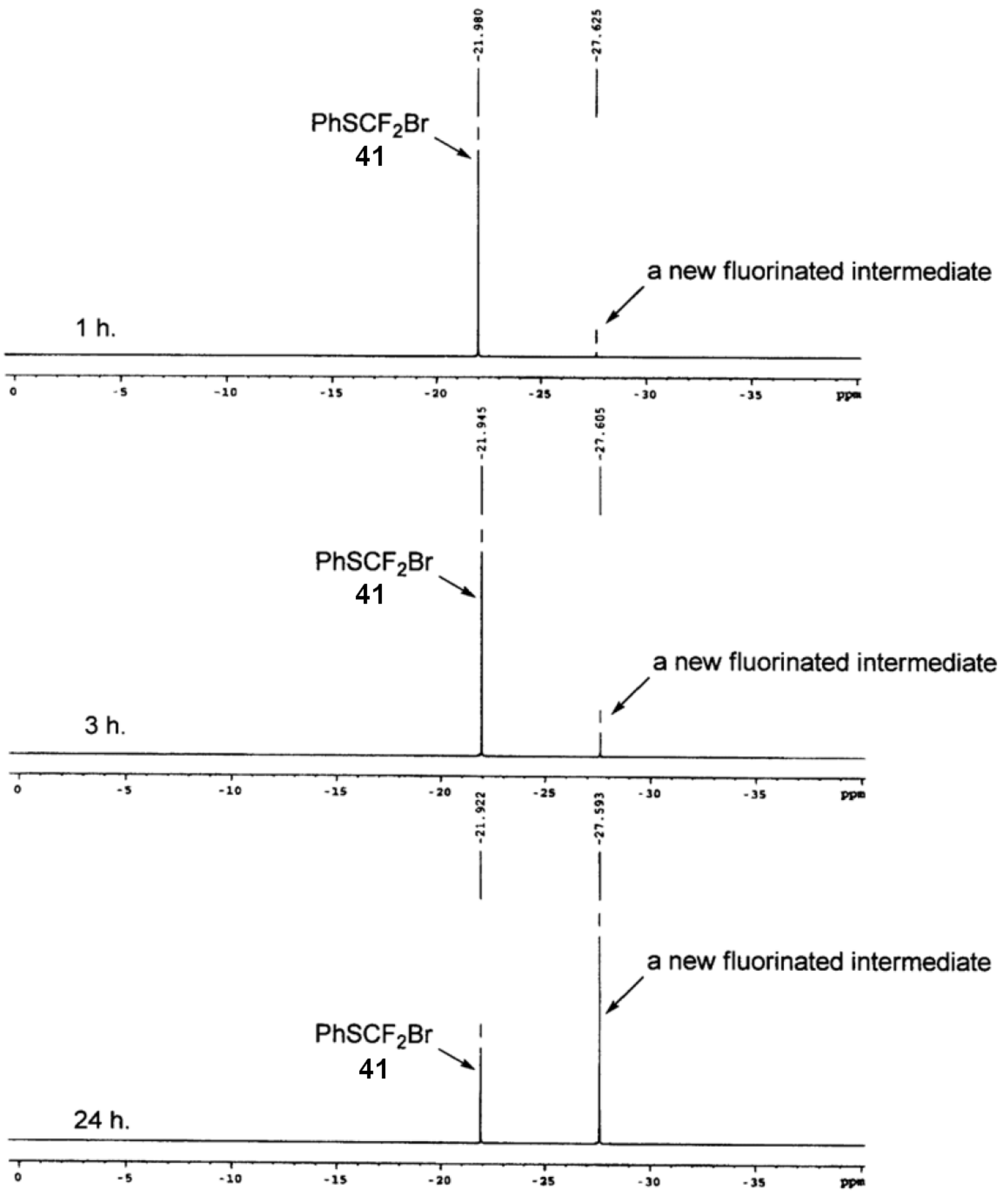
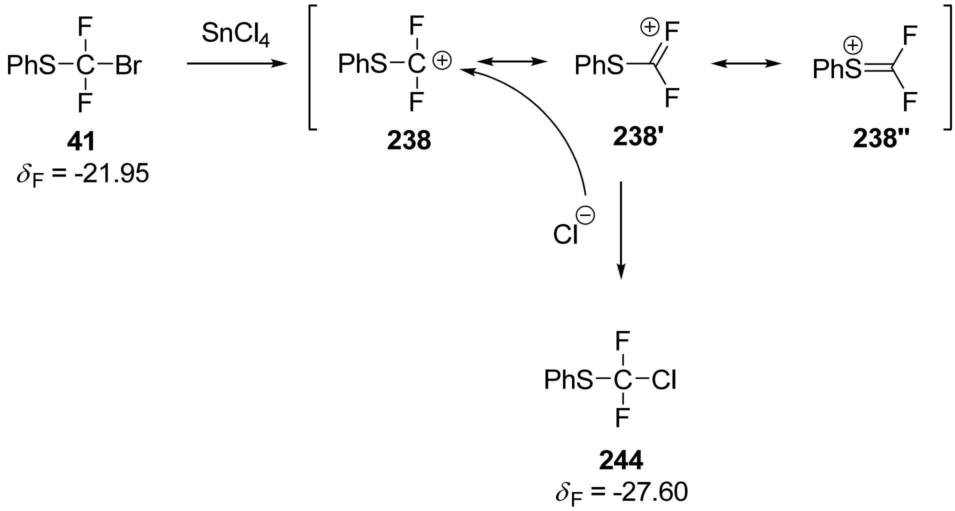


Figure 2.1 **^{19}F NMR spectra (470 MHz, CDCl$_3$) of the reaction of bromodifluoromethyl phenyl sulfide (41) in the presence of SnCl$_4$ (after 1 h, 3 h and 24 h of mixing)**



Scheme 2.5

In the ^{13}C NMR spectra, complex patterns downfield from the triplet signal (δ_C = 119.26 ppm, J = 336.37 Hz) corresponding to the *gem*-difluoro-substituted carbon atom of compound **41** were observed. After 24 h of mixing compound **41** with $SnCl_4$, we found a new downfield triplet signal at δ_C = 130.48 ppm (J = 322.37 Hz) corresponding to the *gem*-difluoro-substituted carbon of chlorodifluoromethyl phenyl sulfide (**244**). At this point, it can be concluded that compound **41** reacted with $SnCl_4$, most likely, to give a carbocationic intermediate even though the signal of carbocationic intermediate was not observed by NMR in this case.

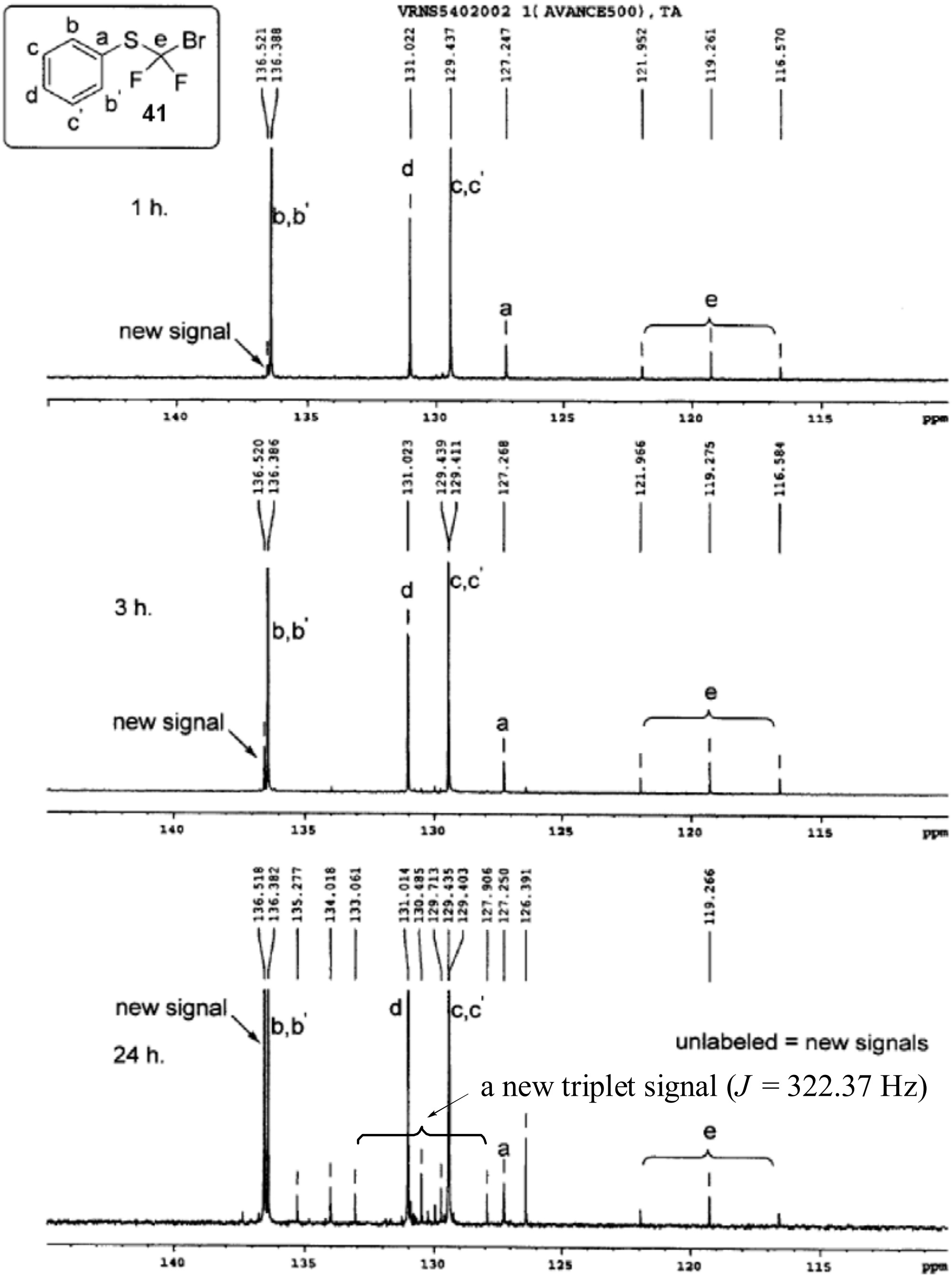
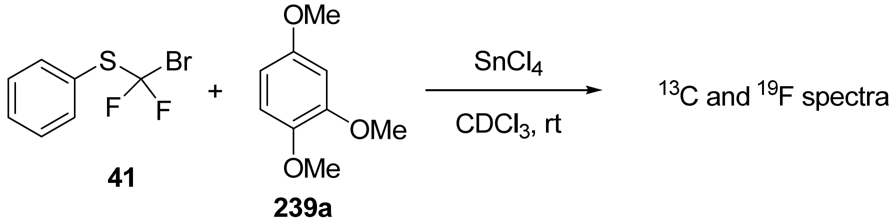


Figure 2.2 ^{13}C **NMR spectra (125 MHz, $CDCl_3$) of the reaction of bromodifluoromethyl phenyl sulfide (41) in the presence of $SnCl_4$ (after 1 h, 3 h and 24 h of mixing)**

2.2.2.2 Reaction of bromodifluoromethyl phenyl sulfide (41) (2 equiv) and 1,2,4-trimethoxybenzene (239a) (1 equiv) in the presence of $SnCl_4$ (4 equiv) in $CDCl_3$



In the presence of aromatic compound **239a**, after 1 h of mixing, a highfield shift of the fluorine signal from δ_F = -21.95 ppm to δ_F = -27.60 ppm was observed. These results are similar to those observed when **239a** was not employed in the reaction. However, after 24 h of mixing, the signal at δ_F = -21.95 ppm almost disappeared, and the ^{19}F NMR spectrum showed a marked enhancement in the intensity of the signal peak at δ_F = -27.60 ppm.

In the ^{13}C NMR spectra, at the beginning of the experiment, the signals that could be observed were attributed to those of compounds **41** and **239a**. New signals were observed as the reaction time increased. After 24 h, the triplet signals at δ_C = 119.26 ppm (J = 336.37 Hz) corresponding to *gem*-difluoro-substituted carbon atom of compound **41** almost disappeared (in a good agreement with the ^{19}F NMR spectroscopic data), and the spectrum became much more complex, particularly in the region between δ = 140 and 125 ppm. As a result, it is difficult to precisely assign the signals of any intermediates formed in the reaction by using ^{13}C NMR spectroscopy. It is worth mentioning that the very weak carbonyl signals corresponding to thioester (δ_C = 184.88 ppm) and benzophenone (δ_C = 196.06 ppm) derivatives could also be detected by ^{13}C NMR spectroscopy. However, both signals appeared to be of low intensity relative to those of the pure compounds. We believe that this might be explained by partial hydrolysis of compounds such as **245**, **246** and **247** (Scheme 2.6). In addition, when the reaction mixture was monitored by TLC analysis, the spots corresponding to thioester and benzophenone derivatives could not be observed, probably due to a very low concentration of the products in the crude reaction mixture. In contrast, both spots can be clearly observed by TLC after the reaction mixture was exposed to aqueous quenching.

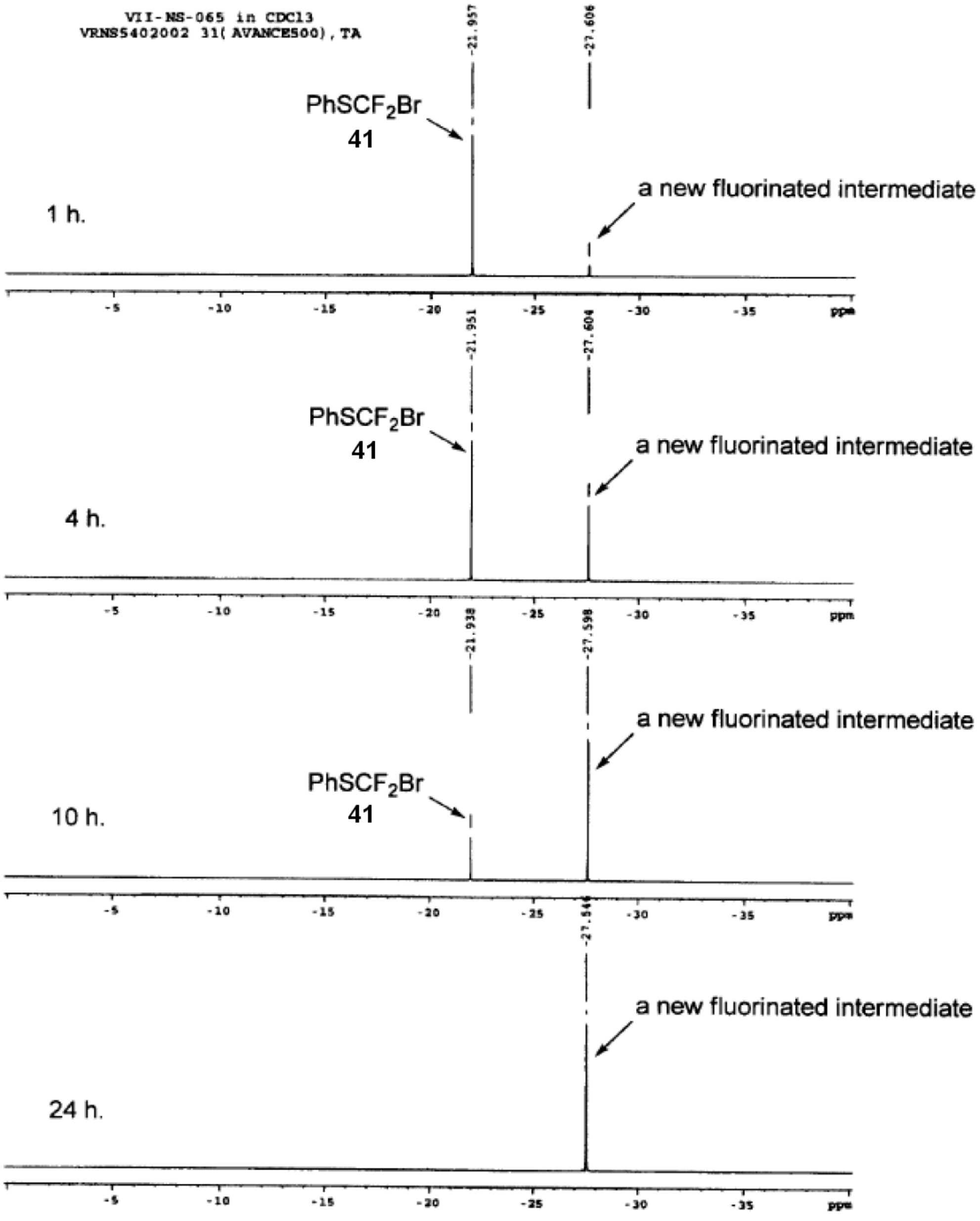


Figure 2.3 ^{19}F NMR spectra (470 MHz, $CDCl_3$) of the reaction of bromodifluoromethyl phenyl sulfide (41) and 1,2,4-trimethoxybenzene (239a) in the presence of $SnCl_4$ (after 1 h, 4 h, 10h and 24 h of mixing)

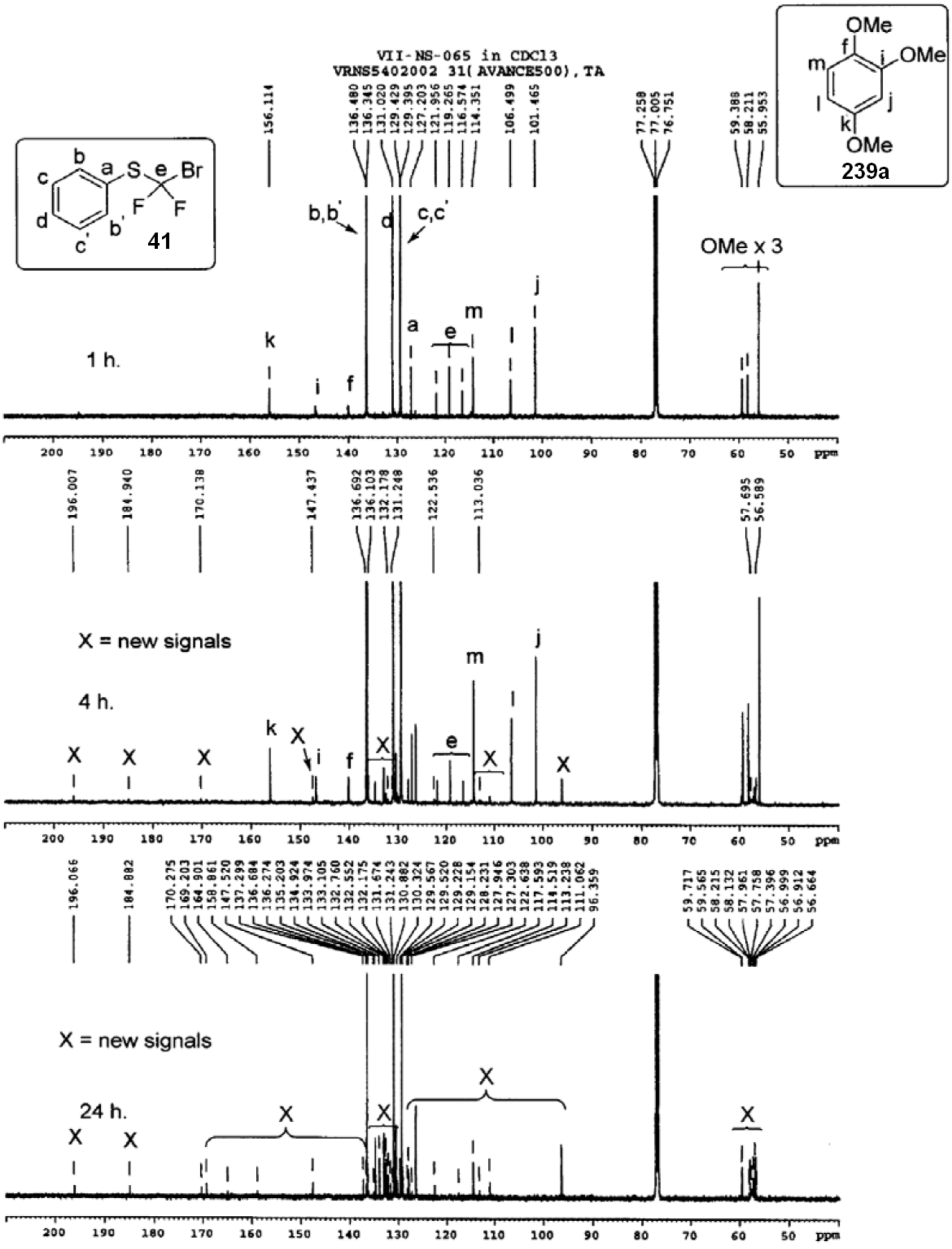
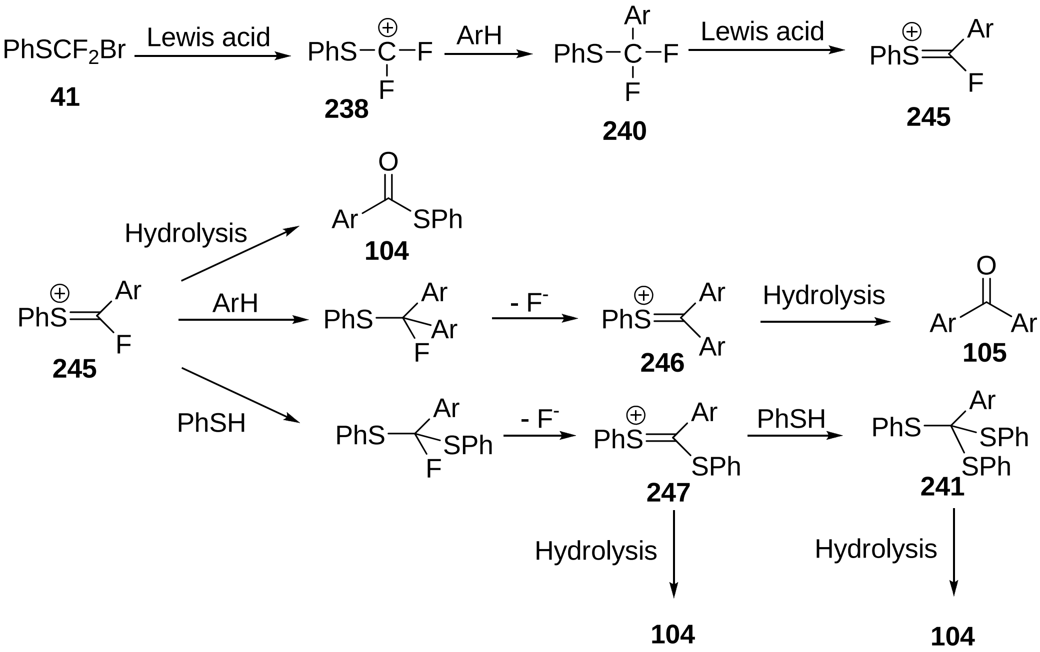


Figure 2.4 **^{13}C NMR spectra (125 MHz, $CDCl_3$) of the reaction of bromodifluorophenylsulfanylmethane (41) and 1,2,4-trimethoxybenzene (239a) in the presence of $SnCl_4$ (after 1h, 4h and 24 h of mixing)**

2.3 The proposed mechanism for the formation of thioester 104, benzophenone 105 and orthothioester 241

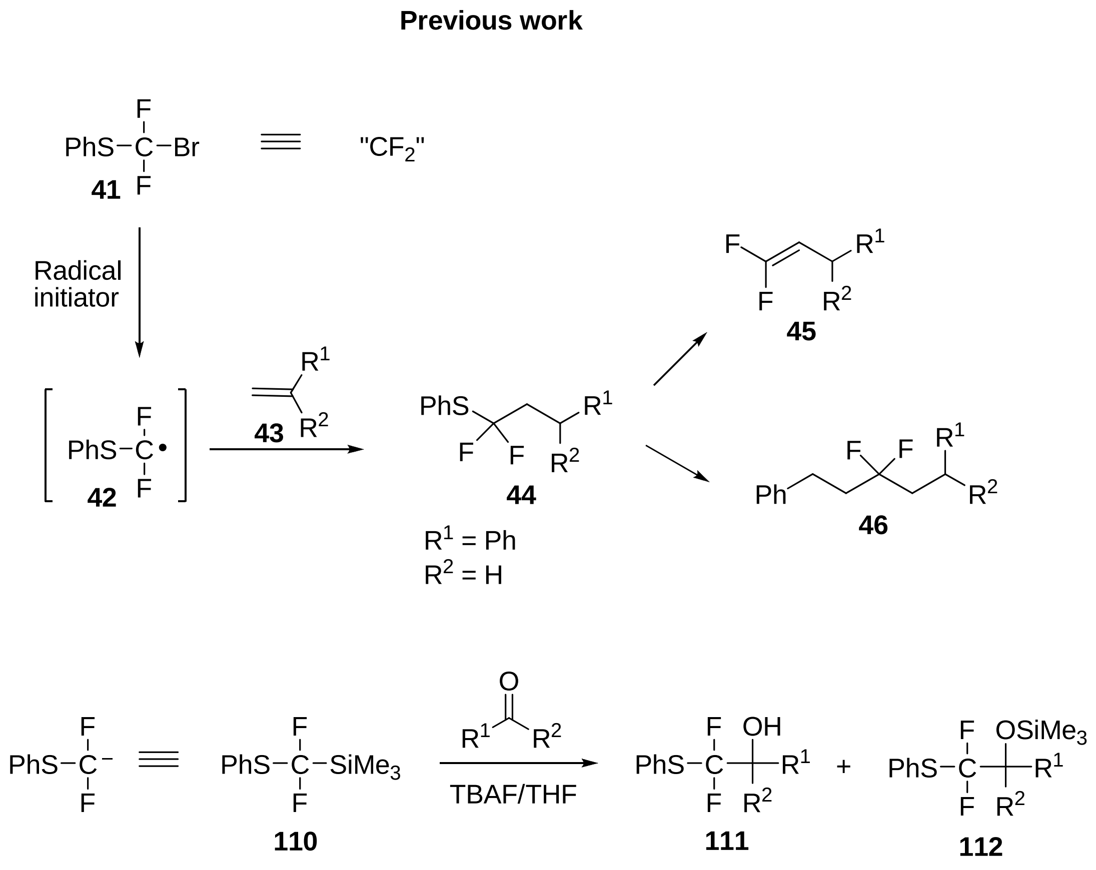
The proposed mechanism for the formation of thioester **104**, benzophenone **105**, and orthothioester **241** could be rationalized as shown in Scheme 2.6. It is worth noting that the proposed mechanistic pathway was based, in part, on NMR experiments (^{19}F and ^{13}C NMR) previously discussed. The first step entails reaction of compound **41** with a Lewis acid to give carbocation intermediate **238**. The reaction of carbocation **238** with added aromatic compound gave adduct **240**, which can further react with the Lewis acid to generate cationic intermediate **245**. Hydrolysis of **245** will yield thioester **104**. Subsequent trapping with a second molecule of aromatic compound followed by hydrolysis of intermediate **246** will lead to benzophenone product **105**. In the case where orthothioester **241** was isolated, we believe that partial hydrolysis of cationic intermediates **245**, **246** and **247** took place during the reaction, liberating benzenethiol, which can act as nucleophile. This was supported by our ^{13}C NMR study, indicating that partial hydrolysis to thioester **104** and benzophenone **105** took place during the reaction.



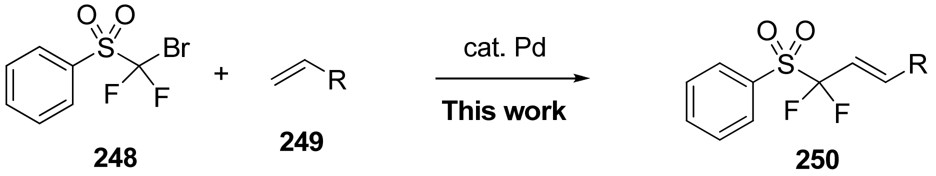
Scheme 2.6

2.4 Palladium-mediated Heck-type reaction of [(bromodifluoromethyl)sulfonyl]benzene (248)

In continuing our on-going research on the introduction of the *gem*-difluoromethylene moiety into an organic molecule by radical[101] and carbanion[12o] methodologies (Scheme 2.7), we now aimed to develop a new Pd-catalyzed Heck-type reaction for fluoroalkylation reaction of alkenes with [(bromodifluoromethyl)sulfonyl]benzene (**248**) (Scheme 2.8) in order to develop a new method for preparation of organofluorine compounds which may be medicinally and industrially useful.



Scheme 2.7

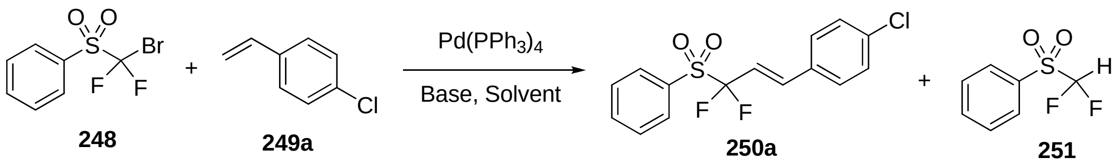


Scheme 2.8

2.4.1 Optimization of Pd-catalyzed reaction of [(bromodifluoromethyl)sulfonyl]benzene (248) with 4-chlorostyrene (249a)

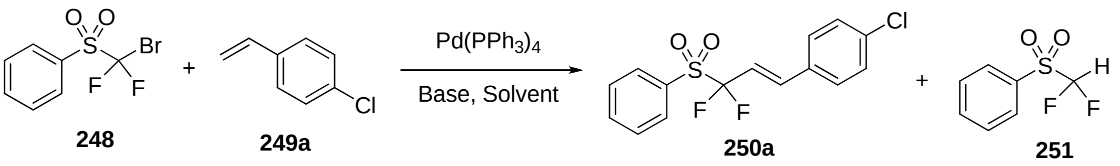
We started our investigation on 10 mol% of $Pd(PPh_3)_4$ catalyzed reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with *p*-chlorostyrene (**249a**) (Table 2.2). We were pleased to observe that the reaction of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (1 equiv) and *p*-chlorostyrene (**249a**) (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (10 mol%) in toluene (100 ^oC, 24 h) providing the desired coupling product **250a** (6% yield) (Table 2.2, Entry 1). Inspired by this result, Et_3N was employed as base in order to enhance the reactivity of the reaction. Unfortunately, instead of getting higher yield of the desired coupling product **250a**, (difluoromethylsulfonyl)benzene (**251**) was obtained in 5% yield (Table 2.2, Entry 2). The same trend was observed when benzene was used as the solvent in the presence of Et_3N as a base (Table 2.2, Entry 3). Cs_2CO_3 also failed to promote the reaction (Table 2.2, Entry 4). In contrast, when a solid-liquid phase transfer, tetrabutylammonium bromide (Bu_4NBr),[62] was used as an additive in the presence of $Pd(PPh_3)_4$ (10 mol%) and Cs_2CO_3 (1.5 equiv) in toluene, the reduced product **251** was isolated in 30% yield as a sole product (Table 2.2, Entries 5 vs 4). The reaction in polar aprotic solvents, such as DMF and MeCN and using Et_3N as a base, gave (difluoromethylsulfonyl)benzene **(251)** as a sole product in 38% and 52% yields, respectively, and no detectable desired product **250a** was observed (Table 2.2, Entries 7 and 9). Efforts to improve the yield of product **250a** were then focused on an increasing the amount of $Pd(PPh_3)_4$. When the amount of $Pd(PPh_3)_4$ was increased to 30 mol% in the presence of various bases, including Et_3N, Cs_2CO_3 and K_2CO_3, in toluene at 100 ^oC, compound **250a** was obtained in 2%, 22% and 40% yields, respectively (Table 1, Entries 16-18). We were pleased to find that the yield of **250a** was further improved to 60% yield when increasing the catalyst loading to 35 mol% and the equivalent of **249a** from 1.5 equiv to 3.0 equiv by using K_2CO_3 as a base (Table 2.2, Entry 20). Lowering or increasing the stoichiometry of *p*-chlorostyrene (**249a**) employed in the presence of $Pd(PPh_3)_4$ (35 mol%) and K_2CO_3 (1.5 equiv) led to slightly lower yields of **250a** (Table 2.2, Entries 19 and 22). No improvement was observed when the reaction was carried out using 40 mol% of $Pd(PPh_3)_4$ or under refluxing conditions (Table 2.2, Entries 21 and 24). In order to identify the optimal conditions, we used 35 mol% of $Pd(PPh_3)_4$, 1 equiv of [(bromodifluoromethyl)sulfonyl]benzene (**248**) and 3 equiv of *p*-chlorostyrene (**249a**) to further examine other essential reaction parameters with respect to types of bases, solvents and reaction temperature. In contrast to the result shown in Table 2.2, Entry 20, significant lower yield of **250a** (35% yield) was obtained when the reaction was carried out in the absence of potassium carbonate (Table 2.2, Entry 20 vs Entry 23). When a series of bases such as Ag_2CO_3, KOAc, KF, K_3PO_4, $KHCO_3$, Na_2CO_3, $CaCO_3$, Cs_2CO_3, Et_3N and *t*-BuOK were screened, K_2CO_3 proved to be an optimal base (Table 2.2, Entry 20 vs Entries 26-35). Based on the reaction conditions shown in Table 2.2, Entry 20, if 18-crown-6 was employed as an additive, only the reduced product **251** was obtained in 23% yield without the formation of the desired product **250a** (Table 2.2, Entries 36 vs 20). The reaction in strong, polar, aprotic solvents such as DMF and MeCN gave the reduced product **251** in 40% and 50%, respectively (Table 2.2, Entries 37-38). When benzene was employed as solvent, the yield of **250a** (60% yield) was comparable to the reaction performed in toluene (Table 2.2, Entries 41 vs 20). When the reaction was carried out employing commercially available 15% PTS/H_2O[63] (α-tocopherol-based diester of sebacic acid) as solvent in the presence of $Pd(PPh_3)_4$ (35 mol%) and Et_3N (2 equiv) at 100 °C, extensive decomposition of starting materials was observed (Table 2.2, Entry 44). In view of the recent report on the success of the Heck reaction in ionic liquids,[64] in the present work both [BMIM][BF_4] and [BMIM][PF_6] were employed, but the desired product **250a** was not observed (Table 2.2, Entries 42 and 43). Ether-type solvent such as 1,4-dioxane was also attempted in this reaction. Unfortunately, the desired product **250a** was obtained in low yield (35% yield) (Table 2.2, Entry 39).

Table 2.2 Optimization of $Pd(PPh_3)_4$ catalyzed fluoroalkylation of 4-chlorostyrene (**249a**) with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a]



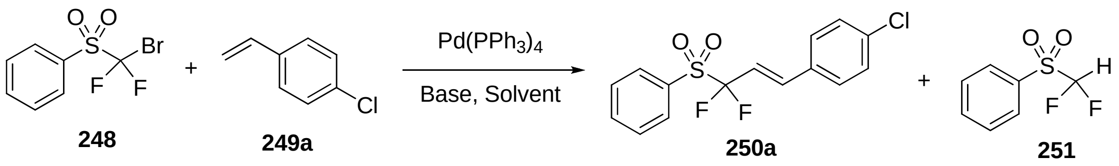
Entry	249a (equiv)	$Pd(PPh_3)_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b]	
						250a	251
1	1.5	10	-	toluene	100, 24	6	0
2	1.5	10	Et_3N, 2.0	toluene	100, 24	tr[e]	5
3	1.5	10	Et_3N, 2.0	benzene	Reflux, 41	tr[e]	8
4	1.5	10	Cs_2CO_3, 1.5	toluene	100, 70	4	tr[e]
5	1.5	10	Cs_2CO_3, 1.5	toluene	100, 24	0	30[c]
6	1.5	10	-	DMF	100, 24	0	tr[e]
7	1.5	10	Et_3N, 2.0	DMF	100, 24	0	38
8	1.5	10	Cs_2CO_3, 1.5	DMF	100, 24	0	tr[e]
9	1.5	10	Et_3N, 2.0	MeCN	Reflux, 24	0	52
10	1.5	10	Et_3N, 2.0	1,4-dioxane	Reflux, 24	tr[e]	tr[e]
12	3.0	10	K_2CO_3, 1.5	toluene	100, 24	8	0
13	3.0	10	KF, 2.0	toluene	100, 24	5	0

Table 2.2 Optimization of Pd(PPh_3)$_4$ catalyzed fluoroalkylation of 4-chlorostyrene (**249a**) with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a] (Continued)



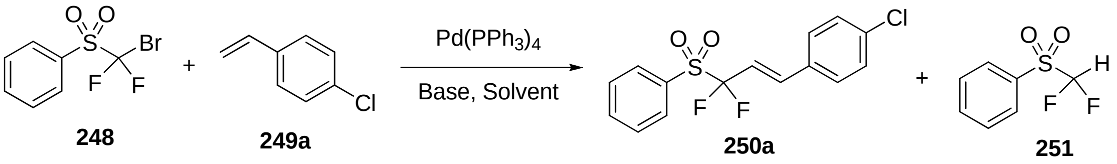
Entry	249a (equiv)	Pd(PPh_3)$_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b]	
						250a	251
14	3.0	10	K_2CO_3, 1.5	Tol:H_2O (2.5:1)	100, 24	5	0
15	1.5	30	-	toluene	100, 24	14	0
16	1.5	30	Et_3N, 2.0	toluene	100, 24	2	21
17	1.5	30	Cs_2CO_3, 1.5	toluene	100, 2	22	24
18	1.5	30	K_2CO_3, 1.5	toluene	100, 4	40	tr[e]
19	1.5	35	K_2CO_3, 1.5	toluene	100, 4	49	0
20	**3.0**	**35**	**K_2CO_3, 1.5**	**toluene**	**100, 4**	**60**	**0**
21	3.0	40	K_2CO_3, 1.5	toluene	100, 4	56	0
22	5.0	35	K_2CO_3, 1.5	toluene	100, 4	52	0
23	3.0	35	-	toluene	100, 18	35	0
24	3.0	35	K_2CO_3, 1.5	toluene	reflux, 4	44	0
25	3.0	35	K_2CO_3, 1.5	toluene	80, 4	53	0

Table 2.2 Optimization of $Pd(PPh_3)_4$ catalyzed fluoroalkylation of 4-chlorostyrene (**249a**) with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a] (Continued)



Entry	249a (equiv)	$Pd(PPh_3)_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b]	
						250a	251
26	3.0	35	Ag_2CO_3, 1.5	toluene	100, 18	9	0
27	3.0	35	KOAc, 3.0	toluene	100, 4	45	0
28	3.0	35	KF, 3.0	toluene	100, 4	44	0
29	3.0	35	K_3PO_4, 1.5	toluene	100, 4	59	0
30	3.0	35	$KHCO_3$, 3.0	toluene	100, 4	55	0
31	3.0	35	Na_2CO_3, 1.5	toluene	100, 4	42	0
32	3.0	35	$CaCO_3$, 1.5	toluene	100, 4	31	0
33	3.0	35	Cs_2CO_3, 1.5	toluene	100, 4	39	30
34	3.0	35	Et_3N, 2.0	toluene	100, 4	23	25
35	3.0	35	*t*-BuOK, 2.0	toluene	100, 4	0	0
36	3.0	35	K_2CO_3, 1.5	toluene	100, 4	0	23[d]
37	3.0	35	K_2CO_3, 1.5	DMF	100, 19	0	40

Table 2.2 Optimization of $Pd(PPh_3)_4$ catalyzed fluoroalkylation of 4-chlorostyrene (**249a**) with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a] (Continued)



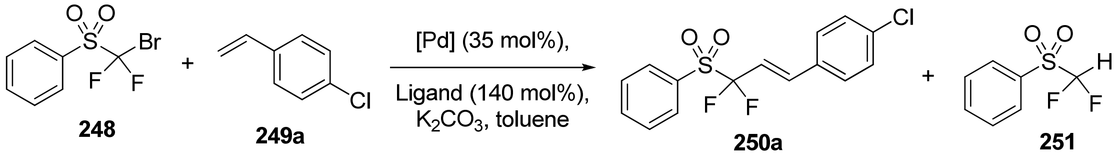
Entry	249a (equiv)	Pd(PPh$_3$)$_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b]	
						250a	251
38	3.0	35	K_2CO_3, 1.5	MeCN	reflux, 19	0	50
39	3.0	35	K_2CO_3, 1.5	1,4-dioxane	100, 4	35	19
40	3.0	35	K_2CO_3, 1.5	Tol:H_2O (2.5:1)	100, 4	57	0
41	3.0	35	K_2CO_3, 1.5	benzene	reflux, 5	60	0
42	3.0	3.5	K_2CO_3, 1.5	[BMIM] [BF_4]	100, 4	0	tr[e]
43	3.0	3.5	K_2CO_3, 1.5	[BMIM] [PF_6]	100, 4	0	10
44	3.0	35	Et_3N, 2.0	15% PTS/H_2O	100, 4	0	0

[a]Reaction conditions: a mixture of **249a**, **248** (1 equiv), $Ph(PPh_3)_4$, base and solvent was heated as temperature indicated. [b]Isolated yields based on **248**. [c]1.5 equivalent of Bu_4NBr was added as additive. [d]1.5 equivalent of 18-crown-6 was added as additive. [e]tr = trace amount of product was detected by TLC analysis.

2.4.2 Optimization of Pd-catalyzed reaction of [(bromodifluoromethyl)sulfonyl]benzene (248) with 4-chlorostyrene (249a) in the presence of different Pd precursors

After performing extensive experiments as shown in Table 2.2, the reaction conditions shown in Entry 20, Table 2.2 were chosen as standard reaction conditions. The effects of the Pd metal precursors and the phosphine ligands, which are known to have significant impact on the Heck reaction, were next evaluated. Pd(II) reagents including $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, $PdCl_2$ in the presence of PPh_3 led to inferior results, yielding the desired product **250a** in the range of 35-40% yields (Table 2.3, Entries 1-3). The use of electron-poor phosphine ligands including $P(C_6H_4CF_3)_3$ and $P(C_6H_4F)_3$ in the presence of $PdCl_2$ gave very low yields of **250a** (Table 2.3, Entries 8 and 9). Greater than 70% yield of the reduced product **251** was obtained, when $P(Cy)_3$ (Table 2.3, Entry 6) and $P(Bu)_3$ (Table 2.3, Entry 7) were used as electron-rich phosphine ligands. When monodentate phosphine ligand $P(2\text{-furyl})_3$ and bidentate phosphine ligand dppp were employed, the reduced product **251** was obtained in 16% and 37% yields, respectively (Table 2.3, Entries 5 and 10). In the case where the highly-active air- and moisture-stable palladacycles (XPhos)Pd^{II}phenethylamine chloride[65] was employed, the desired product **250a** was not observed in the reaction conditions (Table 2.3, Entry 11). From the results shown in Table 2.2 and Table 2.3, the reaction between [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (1 equiv) and *p*-chlorostyrene (**249a**) (3.0 equiv) in the presence of $Pd(PPh_3)_4$ (35 mol%) and K_2CO_3 (1.5 equiv) in toluene (100 ^{o}C, 4 h) was established as an optimized reaction conditions (Table 2.2, Entry 20) for promotion of the Heck-type coupling of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with other styrene derivatives.

Table 2.3 Pd-catalyzed fluoroalkylation of 4-chlorostyrene (**249a**) with [(bromodifluoromethyl)sulfonyl]benzene (**248**) in the presence of different Pd precursors and phosphine ligands[a]



Entry	[Pd] catalyst	Ligand	Temp (°C), time (h)	Yield (%)[b]	
				250a	**251**
1	$Pd(OAc)_2$	PPh_3	100, 4	40	0
2	$PdCl_2(PhCN)_2$	PPh_3	100, 10	35	0
3	$PdCl_2$	PPh_3	100, 24	37	0
4	$PdCl_2$	P(*o*-tol)$_3$	reflux, 24	0	0
5	$PdCl_2$	P(2-furyl)$_3$	100, 24	0	16
6	$PdCl_2$	$P(Cy)_3$	100, 5	0	72
7	$PdCl_2$	$P(Bu)_3$	100, 5	0	74
8	$PdCl_2$	$P(C_6H_4CF_3)_3$	reflux, 6	12	0
9	$PdCl_2$	$P(C_6H_4F)_3$	100, 24	tr[d]	0
10	$PdCl_2$	dppp	reflux, 6	0	37[c]
11	(XPhos)Pd^{II}Phenethyl-amine chloride	-	100, 5	0	0

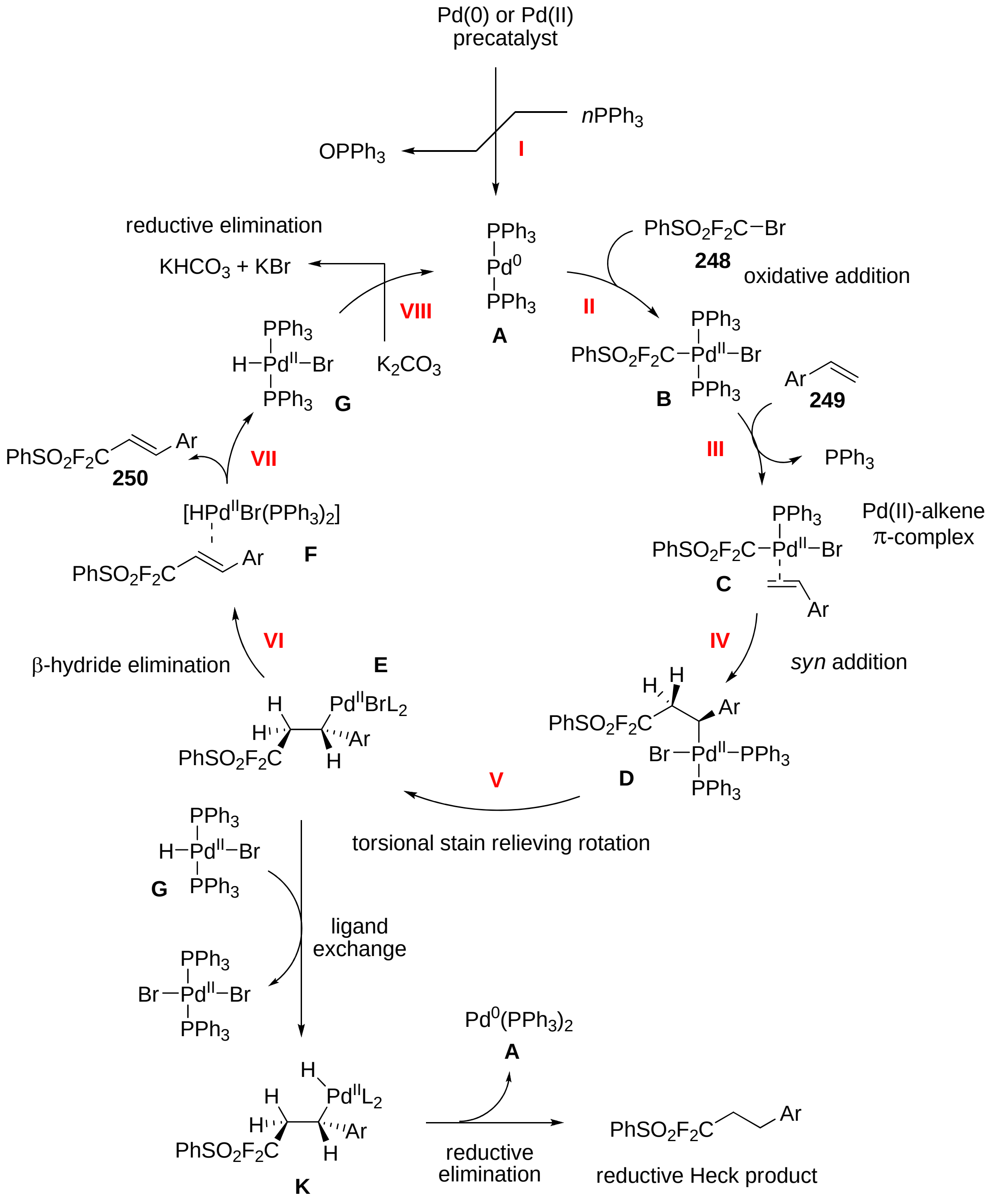
[a] Reaction conditions: 3 equiv of **249a**, 1 equiv of **248**, 35 mol% of [Pd] catalyst, 140 mol% of phosphine ligand, base, and solvent, heating at 100 °C. [b] Isolated yield of all products are based on **248**. [c] 70 mol% of dppp was used. [d] tr = trace amount of product was detected by TLC analysis.

2.4.3 Proposed mechanism for Pd-mediated fluoroalkylation of styrenes with [(bromodifluoromethyl)sulfonyl]benzene (248)

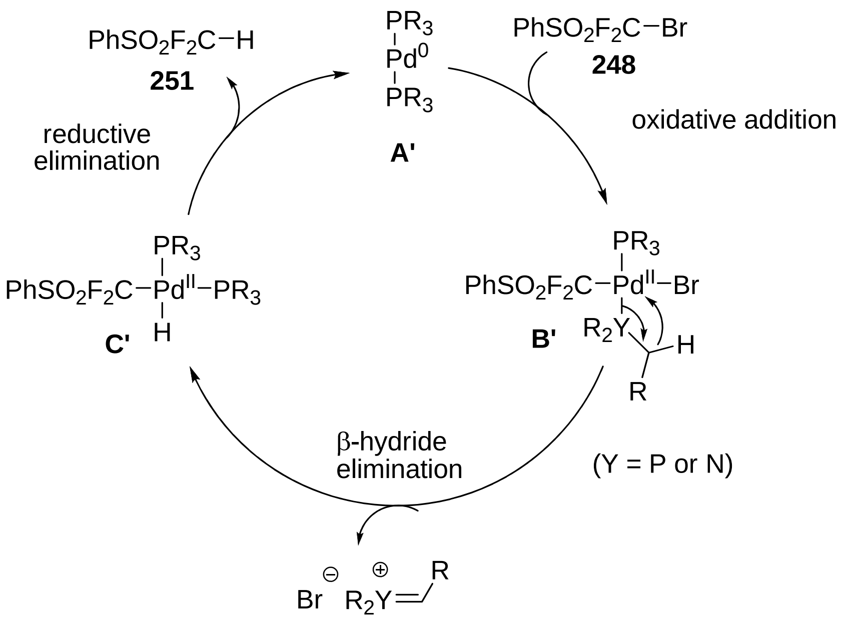
The mechanism for Pd-mediated fluoroalkylation of styrenes with [(bromodifluoromethyl)sulfonyl]benzene (**248**) is proposed according to the well-known Heck reaction.[66] In the first step of the catalytic cycle, di(triphenylphosphine)palladium(0) (**A**) is generated *in situ* from the palladium(II) precatalyst and triphenylphosphine or derived from $Pd(PPh_3)_4$ by releasing two molecules of the phosphine ligands. $(PPh_3)_2Pd(0)$ **A** is the catalytically active species (14 electron-complex)[67] for oxidative addition in Heck reaction in which palladium inserts itself in the difluoromethyl–bromide bond affording intermediate **B**. The following palladium–alkene π-complex **C** is formed when alkene **249** is coordinated to a free-coordination site generated by losing one of the ligands. A new C–C bond intermediate **D** is formed in the migratory insertion step in a *syn* addition manner. A torsional strain is relieved by rotation to form intermediate **E** to facilitate β-hydride elimination. After β-hydride elimination, a new palladium-alkene π-complex **F** is formed and then is destroyed by releasing the alkene **250** from palladium(II)-hydride complex **G**. Deprotonation of palladium(II)-hydride complex **G** in reductive elimination step by base abstraction regenerates the active palladium(0) catalyst (**A**) to complete a catalytic cycle (Scheme 2.9).

In the case where reductive Heck product was observed, we believe that ligands exchange between the palladium(II)-hydride complex **G** and intermediate **E** providing a new palladium(II)-hydride complex **K**. Subsequent reductive elimination gives reductive Heck product and regenerates the palladium(0) catalyst **A** (Scheme 2.9).

The pathway for the formation of (difluoromethylsulfonyl)benzene (**251**) was also proposed. It is believed that a palladium(II)-hydride complex **C'** is formed by β-hydride elimination of the palladium complex **B'**. Subsequent reductive elimination gives reduced product **251** and regenerates the palladium(0) catalyst **A** to complete a catalytic cycle (Scheme 2.10).[66f,68c]


Pd(0) or Pd(II) precatalyst
nPPh3
OPPh3
I
reductive elimination
KHCO3 + KBr
K2CO3
VIII
PPh3
Pd0
PPh3
A
PhSO2F2C−Br
248
oxidative addition
II
PhSO2F2C−PdII−Br
B
Ar
249
III
PPh3
Pd(II)-alkene π-complex
C
IV
syn addition
D
Br−PdII−PPh3
V
torsional stain relieving rotation
E
PdIIBrL2
VI
β-hydride elimination
[HPdIIBr(PPh3)2]
F
VII
250
H−PdII−Br
G
ligand exchange
Br−PdII−Br
Pd0(PPh3)2
PdIIL2
K
reductive elimination
reductive Heck product

Scheme 2.9



Scheme 2.10

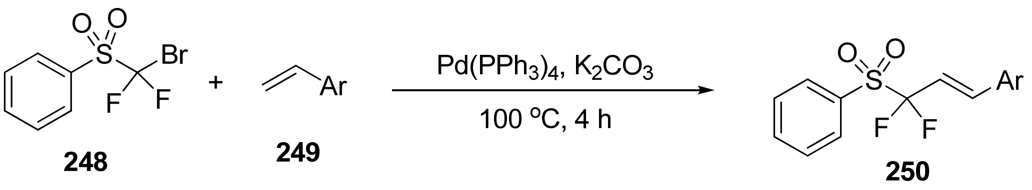
2.4.4 Pd-mediated fluoroalkylation of styrene derivatives with [(bromodifluoromethyl)sulfonyl]benzene (248)

After established the optimized reaction conditions [styrene (3.0 equiv), [(bromodifluoromethyl)sulfonyl]benzene (**248**) (1.0 equiv), $Pd(PPh_3)_4$ (35 mol%), and K_2CO_3 (1.5 equiv) in toluene at 100 °C for 4 h], the scope and generality of Pd-mediated reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with a variety of structurally different styrene derivatives **249** were examined.

For styrene derivatives, the reaction efficiency is dependent on the nature and the position of the substituent on the aromatic ring. Styrene derivatives bearing an electron-withdrawing atom on the *para* position of the vinyl moiety gave the corresponding products in good yields. For instance, *p*-chlorostyrene (**249a**) and *p*-fluorostyrene (**249b**) were nicely converted to the corresponding products **250a** and **250b** in 60% and 54% yields, respectively (Table 2.4, Entries 1 and 2). Nevertheless, the reaction was found sensitive to the position on the phenyl ring to which the substituents attached. *m*-Chlorostyrene (**249c**), *m*-fluorostyrene (**249d**) and *m*-nitrostyrene (**249e**) yielded the corresponding adducts **250c**, **250d** and **250e** in much lower yields; 40%, 25% and 8% yields, respectively (Table 2.4, Entries 3-5), while *o*-

chlorostyrene (**249f**) led to only trace amount of the desired product **250f** (Table 2.4, Entry 6). In the case of methyl 4-vinylbenzoate (**249i)**, the desired coupling product **250i** was obtained in 17% yield (Table 2.4, Entry 9). Simple styrene (**249g**) and *p*-methylstyrene (**249h**) gave the desired product **250g** (41% yield) and **250h** (52% yield) in moderate yields (Table 2.4, Entries 7 and 8). Lower yields were obtained with the electron-releasing substituted styrenes. For instance, *p*-acetoxystyrene (**249j**) and *p*-methoxystyrene (**249k**) gave the corresponding adducts in 17% and 16% yields, respectively (Table 2.4, Entries 10-11). In addition, β-vinylnapthalene (**249l**) yielded product **250l** in low yields (17% yield) (Table 2.4, Entry 12). When sterically substituted α-vinylnapthalene (**249m**) and 9-vinylanthracene (**249n**) were employed as substrate, the desired products **250m** and **250n** were not detected in this reaction conditions (Table 2.4, Entries 13 and 14). In the case of 1,1-diphenylethylene (**249o**) employed as substrate, an approximately 1 : 1 inseparable mixture of adduct **250o** and reductive Heck product **252** was obtained in 82% combined yields (Table 2.4, Entry 15). From this results, we envisaged the yield of reductive Heck product **252** could be improved by using reductive Heck conditions[68] [1,1-diphenylethylene (**249o**) (3.0 equiv), [(bromodifluoromethyl)sulfonyl]benzene (**248**) (1.0 equiv), $Pd(PPh_3)_4$ (35 mol%), formic acid (4.5 equiv) and Et_3N (6.0 equiv) in toluene at 100 ^oC for 4 h]. Unfortunately, the ratio of the products **250o** and **252** were not affected but the yield of the products were decreased (Table 2.4, Entry 16). Surprisingly, corresponding product **250p** was not detected when 1-(chloromethyl)-4-vinylbenzene (**249p**) was employed as substrate. It is possible that palladium catalyst was destroyed by interacting with chloromethyl moiety of 1-(chloromethyl)-4-vinylbenzene (**249p**) instead of oxidative addition to [(bromodifluoromethyl)sulfonyl]benzene (**248**) (Table 2.4, Entry 17). A trace amount of bubble bond rearrangement product (**253**) was observed when α-methyl styrene (**249q**) was employed (Table 2.4, Entry 18). When vinyl-substituted heteroaromatics **249r** and **249s** were used as substrates, neither of the products **250r** nor **250s** was detected (Table 2.4, Entries 19 and 20).

Table 2.4 Pd-mediated Heck-type reactions of styrene derivatives with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a]



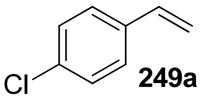
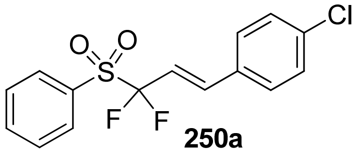
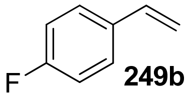
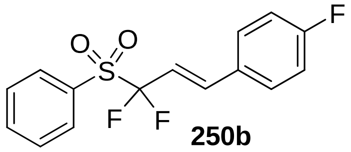
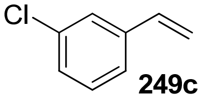
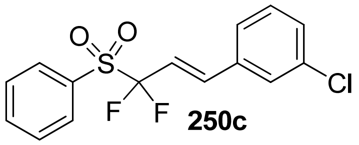
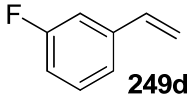
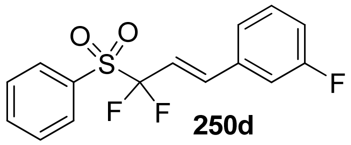
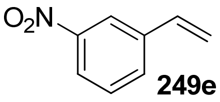
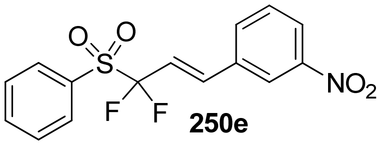
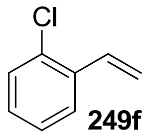
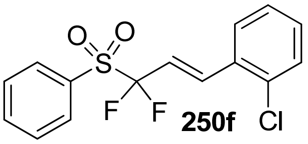
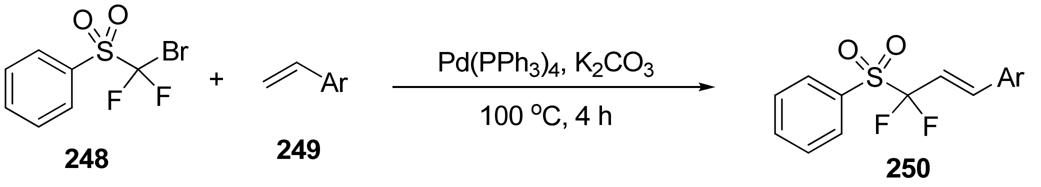
Entry	Substrate	Product	Yield (%)[b]
1	 **249a**	 **250a**	60
2	 **249b**	 **250b**	54
3	 **249c**	 **250c**	40
4	 **249d**	 **250d**	25
5	 **249e**	 **250e**	8
6	 **249f**	 **250f**	tr[c]

Table 2.4 Pd-mediated Heck-type reactions of styrene derivatives with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a] (Continued)



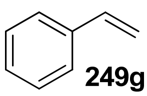
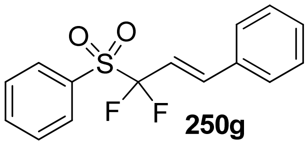
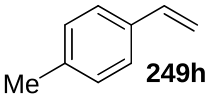
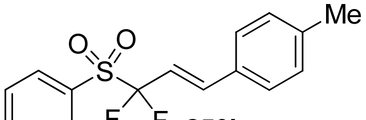
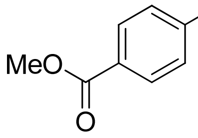
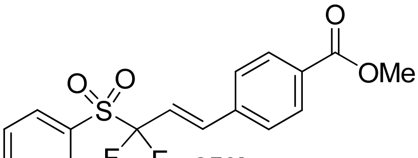
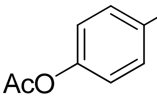
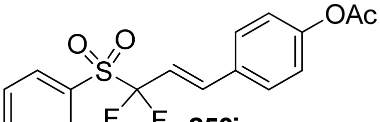
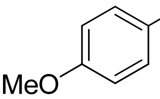
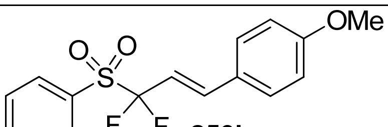
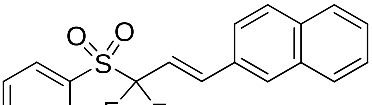
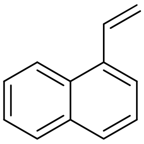
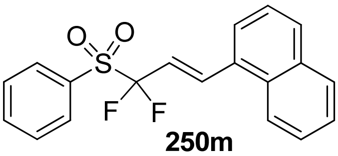
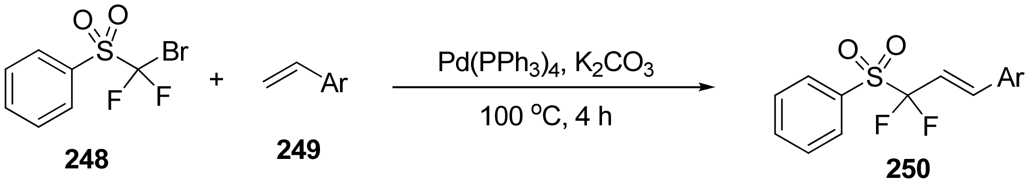
Entry	Substrate	Product	Yield (%)[b]
7	 **249g**	 **250g**	41
8	 **249h**	 **250h**	52
9	 **249i**	 **250i**	17
10	 **249j**	 **250j**	17
11	 **249k**	 **250k**	16
12	 **249l**	 **250l**	17
13	 **249m**	 **250m**	0

Table 2.4 Pd-mediated Heck-type reactions of styrene derivatives with [(bromodifluoromethyl)sulfonyl]benzene (**248**)^a (Continued)



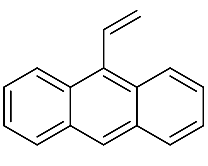
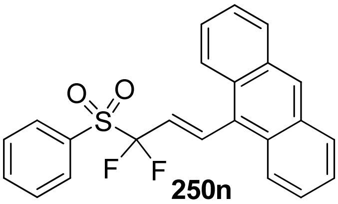
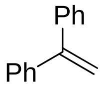
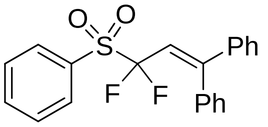
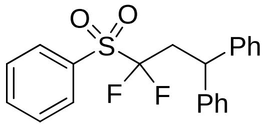
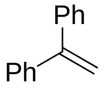
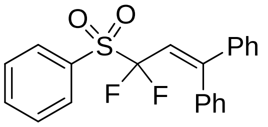
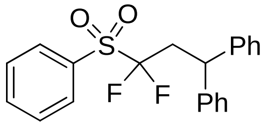
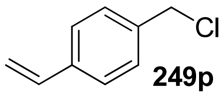
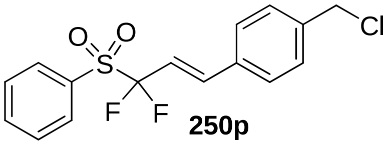
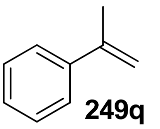
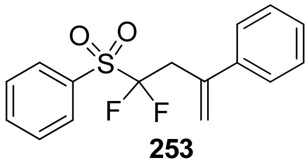
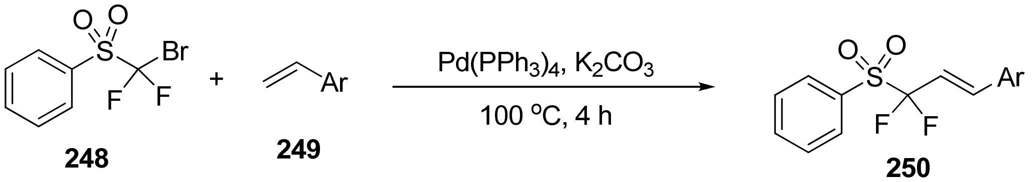
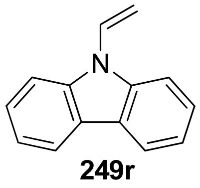
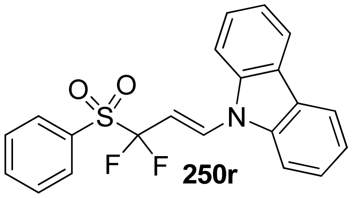
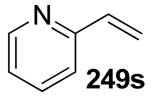
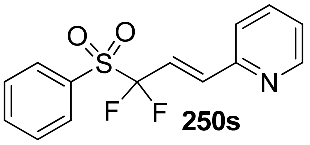
Entry	Substrate	Product	Yield[b] (%)
14	 **249n**	 **250n**	0
15	 **249o**	 **250o** +  **252**	(**250o**, 45/**252**, 37)
16	 **249o**	 **250o** +  **252**	(**250o**, 20/**252**, 16)^c
17	 **249p**	 **250p**	0
18	 **249q**	 **253**	tr^c

Table 2.4 Pd-mediated Heck-type reactions of styrene derivatives with [(bromodifluoromethyl)sulfonyl]benzene (**248**)^a (Continued)



Entry	Substrate	Product	Yield (%)^b
19	 **249r**	 **250r**	0
20	 **249s**	 **250s**	0

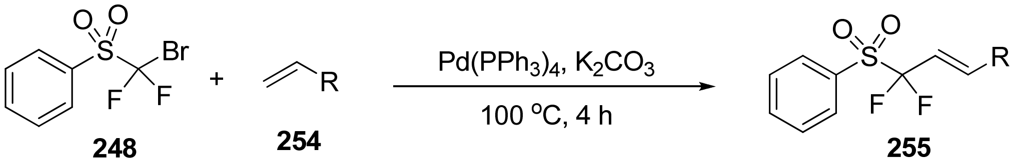
^{a}Reaction conditions: **249** (3 equiv), **248** (1 equiv), Pd(PPh$_3$)$_4$ (35 mol%), K$_2$CO$_3$ (1.5 equiv), toluene, 100 °C, 4h. ^{b}Isolated yields based on **248**. ^{c}1,1-diphenylethylene (**249o**) (3.0 equiv), [(bromodifluoromethyl)sulfonyl]benzene (**248**) (1.0 equiv), Pd(PPh$_3$)$_4$ (35 mol%), formic acid (4.5 equiv) and Et$_3$N (6.0 equiv) in toluene at 100 °C for 4 h. ^{c}tr = trace amount of product was detected by TLC analysis.

2.4.5 Pd-mediated Heck-type reaction of vinyl ethers, activated alkenes and simple alkenes with [(bromodifluoromethyl)sulfonyl]benzene (248)

When vinyl ethers being used as substrate, we found that *tert*-butyl vinyl ether (**254a**) and 3,4-dihydro-2*H*-pyran (**254c**) underwent C–C coupling smoothly under standard reaction conditions affording products **255a** and **255c** in 45% and 41% yield, respectively (Table 2.5, Entries 1 and 3). In the case of *n*-butyl vinyl ether (**254b**), an 2.3:1 inseparable mixture of compounds **255b** and **256** was detected in 56% combined yields (Table 2.5, Entry 2). No desired coupling product **255d** was observed when 5-methylfuran-2(3*H*)-one (**254d**) was employed (Table 2.5, Entry 4). The highly efficient Heck substrates such as butyl acrylates **254e** and **254f** were also examined. Unfortunately, the desired products **255e** and **255f** were not observed (Table 2.5, Entries 5 and 6). A separable mixture of ***trans***- and ***cis*-255g** was isolated in 43% and 26% yields, repectively, when phenyl(vinyl)sulfane (**254g**) was used as substrate

(Table 2.5, Entry 7). Substrates of vinylsulfonylbenzene (**254h**), allyl(phenyl)sulfane (**254i**) and aliphatic allylbenzene (**254j**), did not work and the desired coupling products were not detected (Table 2.5, Entries 8-10).

Table 2.5 Pd-mediated Heck-type reactions of vinyl ethers, activated alkenes and simple alkenes with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a]



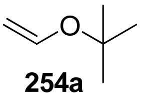
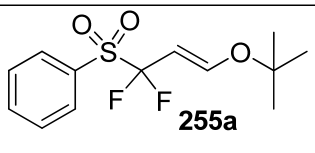
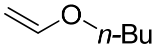
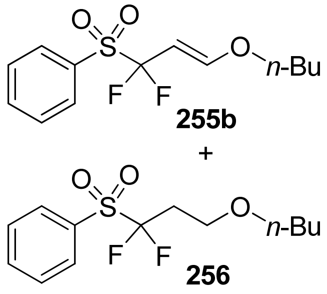
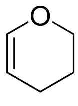
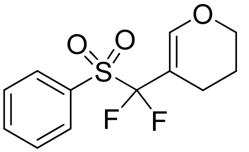
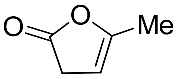
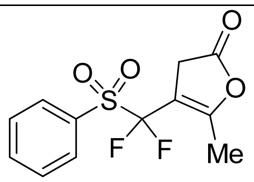
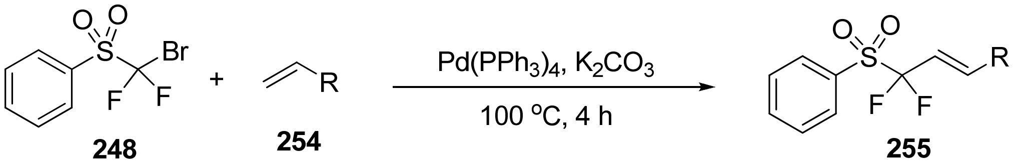
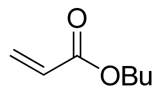
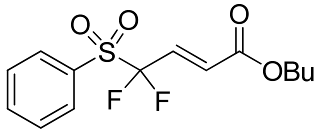
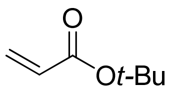
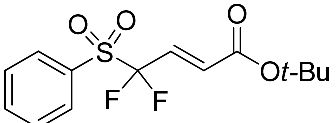
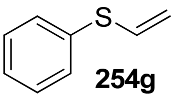
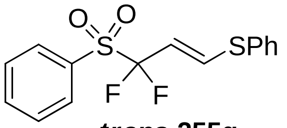
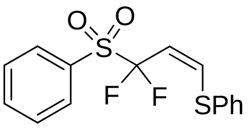
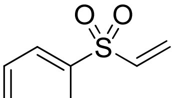
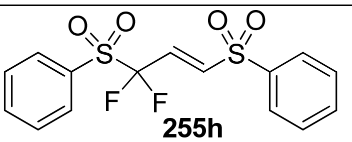
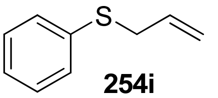
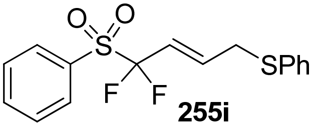
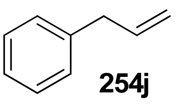
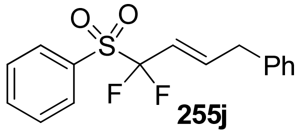
Entry	Substrate	Product	Yield (%)[b]
1	 **254a**	 **255a**	45
2	 **254b**	 **255b** + **256**	(**255b**, 39/**256**, 17)
3	 **254c**	 **255c**	41
4	 **254d**	 **255d**	0

Table 2.5 Pd-mediated Heck-type reactions of vinyl ethers, activated alkenes and simple alkenes with [(bromodifluoromethyl)sulfonyl]benzene (**248**)[a] (Continued)



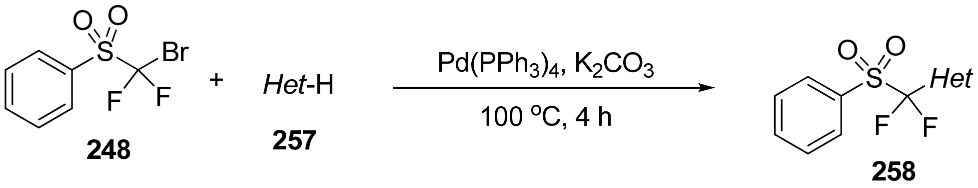
Entry	Substrate	Product	Yield (%)[b]
5	 **254e**	 **255e**	0
6	 **254f**	 **255f**	0
7	 **254g**	 ***trans*-255g** +  ***cis*-255g**	43 26
8	 **254h**	 **255h**	0
9	 **254i**	 **255i**	0
10	 **254j**	 **255j**	0

[a]Reaction conditions: **254** (3 equiv), **248** (1 equiv), $Pd(PPh_3)_4$ (35 mol%), K_2CO_3 (1.5 equiv), toluene, 100 °C, 4h. [b]Isolated yields based on **248**.

2.4.6 Pd-mediated coupling reaction of [(bromodifluoromethyl)-sulfonyl]benzene (248) with heteroaromatic compounds

With the success on the reaction of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) with styrene derivatives **249**, the reaction of **248** with heteroaromatic compounds **257** was then further examined under standard reaction conditions. The reaction underwent C–C coupling smoothly, especially when using 1-methylpyrrole (**257a**) and 1-benzylpyrrole (**257b**) as substrates affording the desired coupling products **258a** (73% yield) and **258b** (69% yield) in high yields (Table 2.6, Entries 1 and 2). Moderate yields of corresponding product **258c** (38% yield) was obtained when 1-phenylpyrrole (**257c**) was used as substrate (Table 2.6, Entry 3). Significant lower yields were observed when 2-methylfuran (**257d**) and *N*-methylindole (**257f**) were employed as substrates (Table 2.6, Entries 4 and 6). In the case where thiophene (**257e)** was employed as substrate, an inseparable mixture of isomeric products **258e** and **258e'** was obtained in 31% combined yields (Table 2.6, Entry 5). No desired coupling products were detected when 1*H*-pyrrole (**257g**), oxazole (**257h**), thiazole (**257i**), isoxazole (**257j**), 1-methyl-1*H*-pyrazole (**257k**), benzofuran (**257l**), 1-methyl-1*H*-imidazole (**257m**) and pyridine (**257n**) were used as substrates (Table 2.6, Entries 7-14). The inefficiency of the reactions employing these substrates is probably as a result of an unshared electron pair of heteroatom in heteroaromatic coordinating tightly to the palladium complex, causing them inappropriate intermediate for electrophilic substitution pathway (S_EAr) before complex decomposition (Scheme 2.11).

Table 2.6 Pd-mediated coupling reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with heteroaromatic compounds **257**[a]



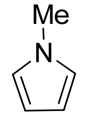
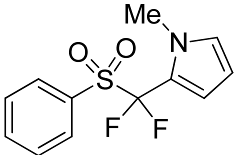
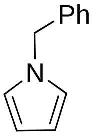
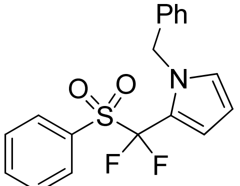
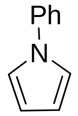
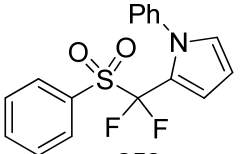
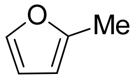
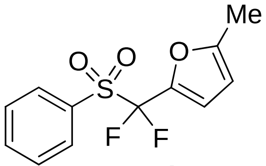
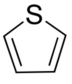
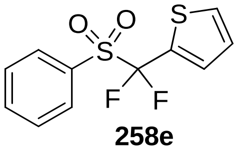
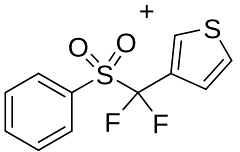
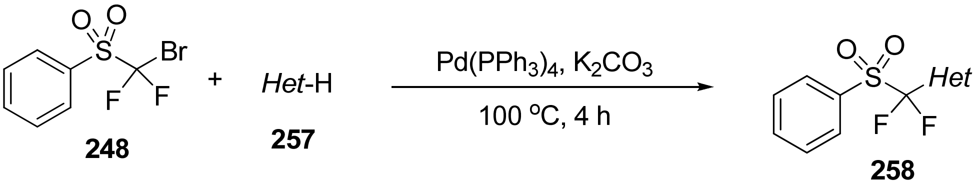
Entry	Substrate	Product	Yield (%)[b]
1	 **257a**	 **258a**	73
2	 **257b**	 **258b**	69
3	 **257c**	 **258c**	38
4	 **257d**	 **258d**	29
5	 **257e**	 **258e** +  **258e'**	(**258e**, 26/**258e'**, 5)

Table 2.6 Pd-mediated coupling reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with heteroaromatic compounds **257**[a] (Continued)



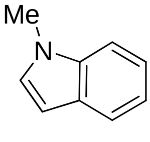
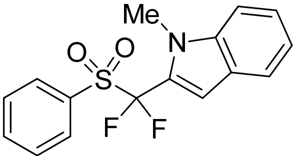
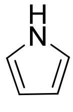
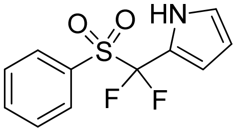
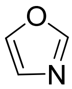
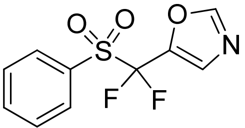
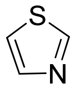
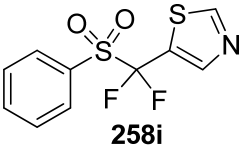
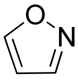
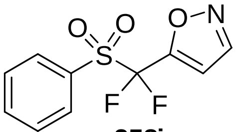
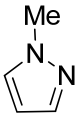
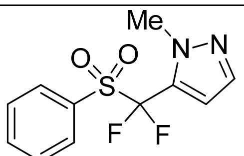
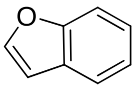
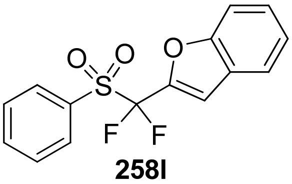
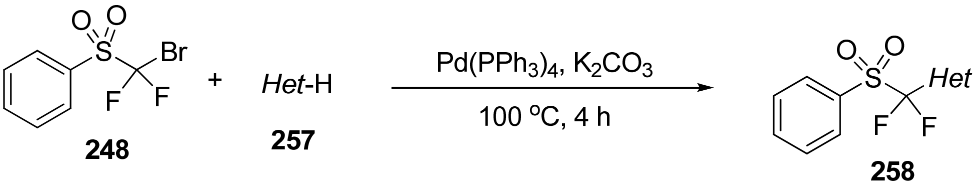
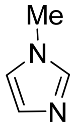
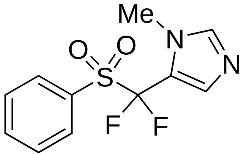
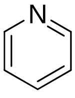
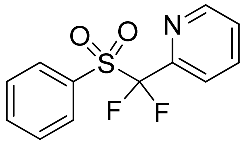
Entry	Substrate	Product	Yield (%)[b]
6	 **257f**	 **258f**	24
7	 **257g**	 **258g**	0
8	 **257h**	 **258h**	0
9	 **257i**	 **258i**	0
10	 **257j**	 **258j**	0
11	 **257k**	 **258k**	0
12	 **257l**	 **258l**	tr

Table 2.6 Pd-mediated coupling reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with heteroaromatic compounds **257**[a] (Continued)



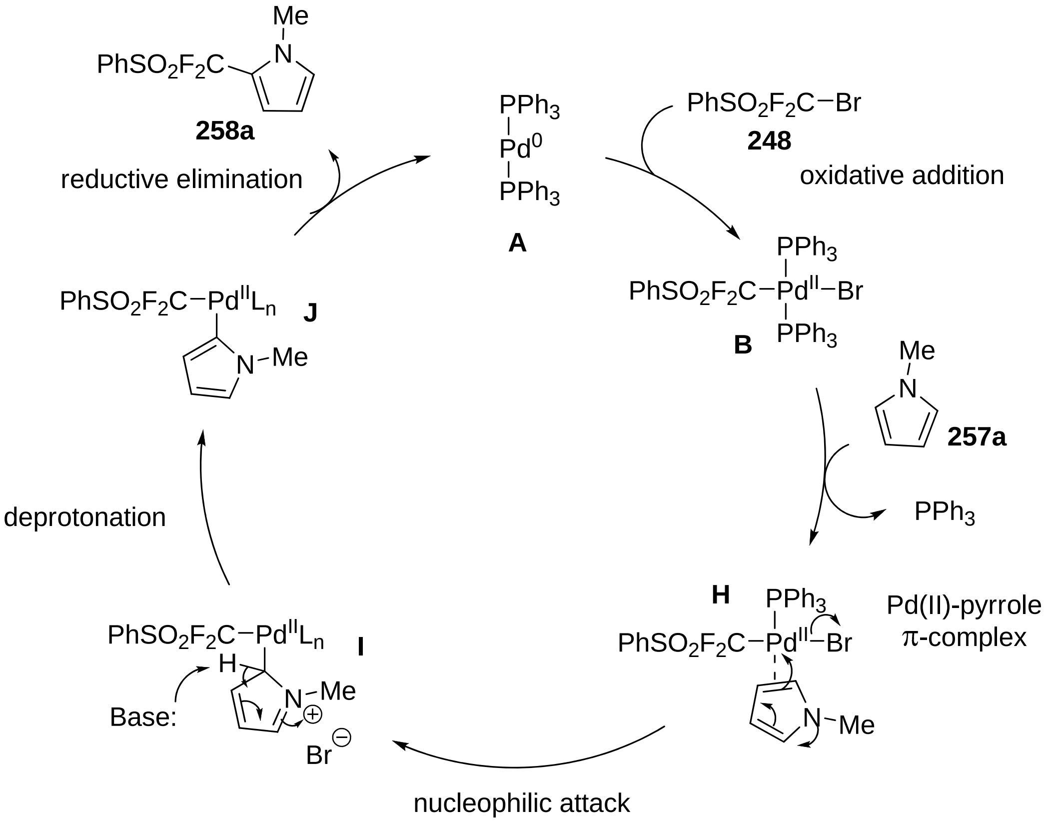
248 **257** **258**

Entry	Substrate	Product	Yield (%)[b]
13	 **257m**	 **258m**	0
14	 **257n**	 **258n**	0

[a]Reaction conditions: **257** (3 equiv), **248** (1 equiv), $Pd(PPh_3)_4$ (35 mol%), K_2CO_3 (1.5 equiv), toluene, 100 °C, 4h. [b] Isolated yields based on **248**.

2.4.7 The proposed reaction mechanism of Pd-mediated fluoroalkylation of heteroaromatics 257 with [(bromodifluoromethyl)sulfonyl]-benzene (248)

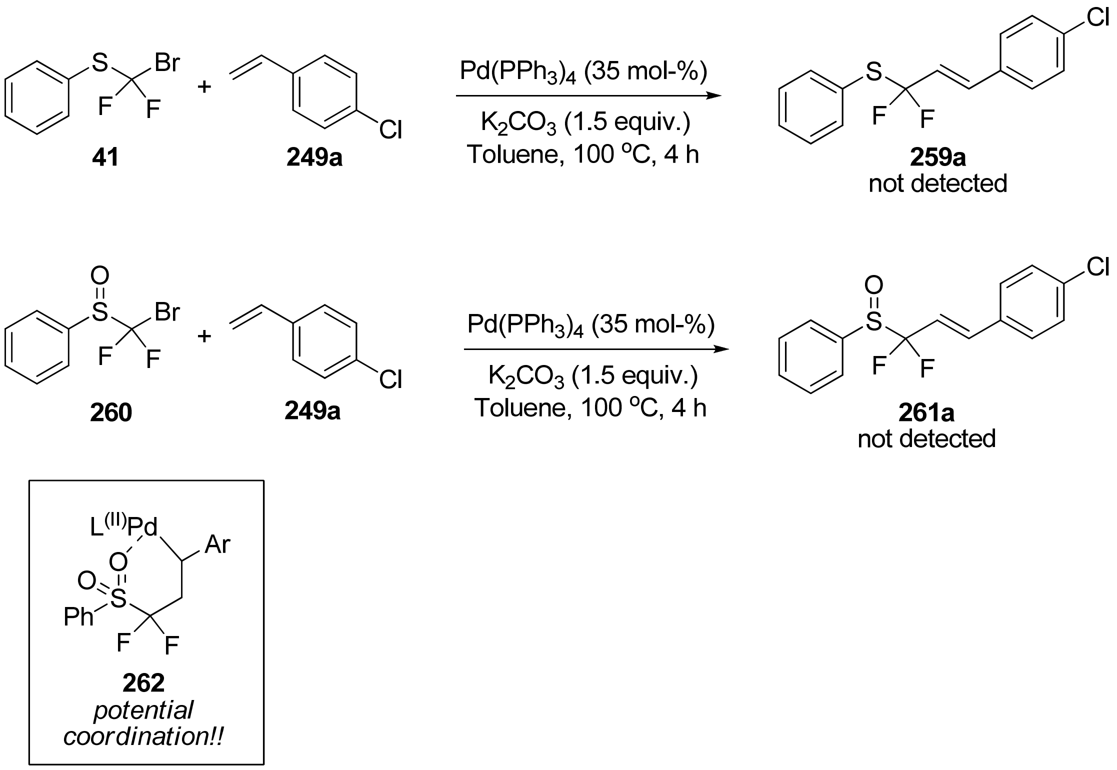
The proposed reaction mechanism of Pd-mediated fluoroalkylation of heteroaromatics **257** with [(bromodifluoromethyl)sulfonyl]benzene (**248**) based on previously reported electrophilic aromatic substitution mechanism (S_EAr)[69] involves 1) oxidative addition of [(bromodifluoromethyl)sulfonyl]benzene (**248**) to the Pd complex **A** affording intermediate **B**, 2) coordination of the pyrrole (**257a**) to Pd to give intermediate **H**, 3) an electrophilic attack by difluormethylsulfonylbenzene palladium bromide species **H** to α-position of 1-methyl-1*H*-pyrrole (**257a**) to form intermediate **I**, 4) proton abstraction to produce intermediate **J**. Subsequent reductive elimination gives product **258a** and regenerates the palladium(0) catalyst **A** to complete catalytic cycle (Scheme 2.11).



Scheme 2.11

2.4.8 The investigation of the role of the sulfonyl moiety of [(bromodifluoromethyl)sulfonyl]benzene (248) in Pd(0)-catalyzed Heck type reactions

According to the previously discussed reaction mechanism shown in Scheme 53 and in order to gain more insight into the role of the sulfonyl moiety to this transformation, the reactions of *p*-chlorostyrene (**249a**) with bromodifluoromethyl phenyl sulfide (**41**) and [(bromodifluoromethyl)sulfinyl]benzene (**260**) were carried out under standard conditions. To our surprise, the desired product (**259a**) and (**261a**) were not detected from the reactions (Scheme 2.12). This result implied that apart from the strong electron withdrawing effect of the sulfonyl moiety, the coordination of the lone pair oxygen of the sulfonyl group to the palladium metal center helps stabilizing the intermediate formed through a stabilized six-membered palladacycle complex **262** which may play an important role in facilitating the course of the coupling reaction. The inefficiency of the reaction of this conversion to some substrates tested in the present work could be explained by weaker $PhS(O)_2–CF_2^-$ bond, according to computational studies based on the density functional theory (DFT).[12q] therefore, it is more likely to decompose into difluorocarbene and the corresponding sulfinate under the reaction conditions, if a suitable counterpart is not reactive enough to undergo the C–C coupling at a reasonable rate.

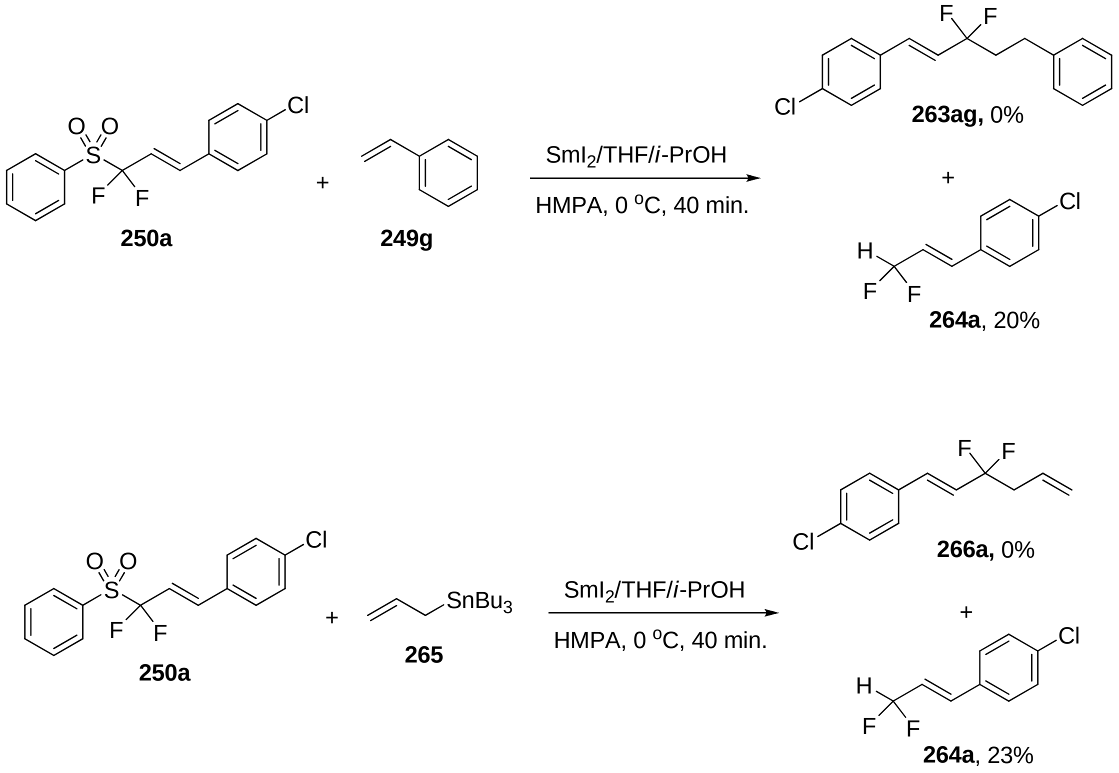


Scheme 2.12

2.5 The synthetic application of allyl sulfones containing $PhSO_2CF_2$-moiety

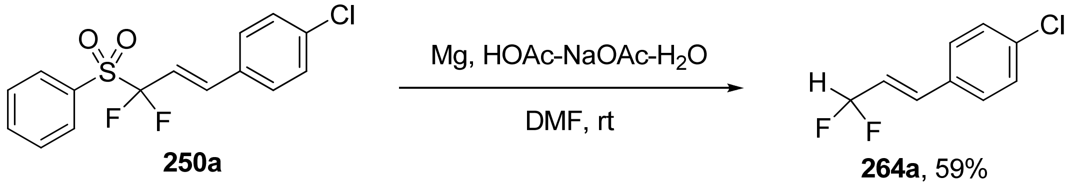
To further demonstrate the synthetic applications of allyl sulfones containing $PhSO_2CF_2$-moiety, the radical addition reaction between (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) and styrene (**249g**) was first examined by using SmI_2/THF/*i*-PrOH/HMPA conditions which has previously been reported by our grorp.[101] Thus treatment of (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) and styrene (**249g**) with 5.0 equiv of

SmI_2/THF/*i*-PrOH/HMPA at 0 °C gave the reductive desulfonylation product (**264a**) in 20% yield. Unfortunately, the radical addition product **263ag** was not detected (Scheme 2.13). When allyltributylstannane (**265**) was employed as redical trapping substrate, instead of the desired product (**266a**), (*E*)-1-chloro-4-(3,3-difluoroprop-1-enyl)benzene (**264a**) was obtained in 23% yield as a sole product.



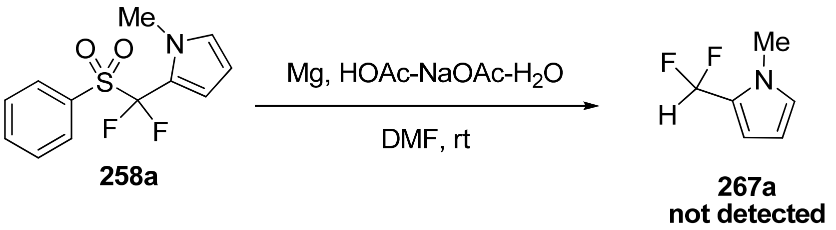
Scheme 2.13

Based on the results shown in Scheme 57, the reductive desulfonylation reaction of (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) was next examined. Upon using Mg/HOAc/NaOAc desulfonylation system that was previously reported by Ni and Hu,[12n] (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) can be transformed into (*E*)-1-chloro-4-(3,3-difluoroprop-1-enyl)benzene (**264a**) in 59% yield (Scheme 2.14).



Scheme 2.14

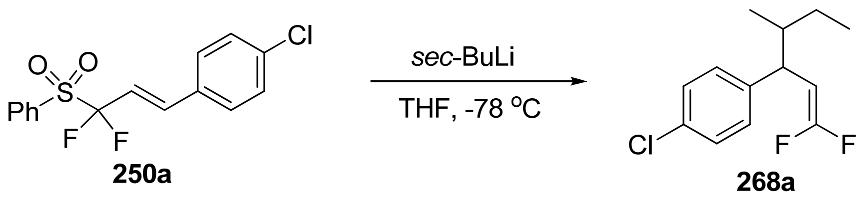
The synthetic utility of coupling product **258a** for synthesis of CF_2H-substituted compound was also investigated (Scheme 2.15). Unfortunately, an attempted reductive desulfonylation reaction of $PhSO_2CF_2$-bearing adduct **258a** using Mg/HOAc/NaOAc failed to produce the desired product **267a**; only the starting material **258a** was recovered in quantitative yield.



Scheme 2.15

After searching for the synthetic applications of allyl sulfones containing $PhSO_2CF_2$-moiety, we were pleased to find that when allyl sulfone **250a** was treated with 1.2 equiv of *sec*-BuLi in THF at -78 ^{o}C for 1h, the corresponding product **268a** was obtained in 28% yield along with recovered starting material **250a** (38%) (Table 2.7, Entry 1). The results of the optimized reaction conditions were shown in Table 2.7. Upon optimization of several reaction parameters, the highest yield of corresponding product **268a** (58% yield) was obtained, when the reaction was carried out employing 2.2 equiv of *sec*-BuLi in THF at -78 ^{o}C (Table 2.7, Entry 4)

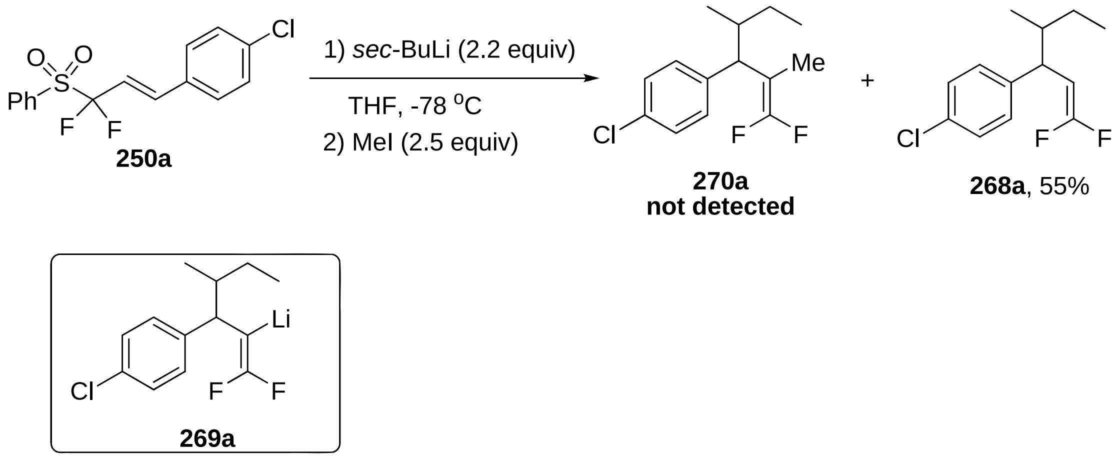
Table 2.7 Reaction of *sec*-butyllithium with (*E*)-1-chloro-4-(3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl)benzene (**250a**)



Entry	*sec*-BuLi (equiv.)	Solvent	Time [h]	Temp.[^{o}C]	Yield [%][a]	
					268a	**250a**
1	1.2	THF	1	-78	28	38
2	1.5	THF	1	-78	43	22
3	2.0	THF	1	-78	48	-
4	2.2	THF	1	-78	58	-
5	2.5	THF	1	-78	54	-

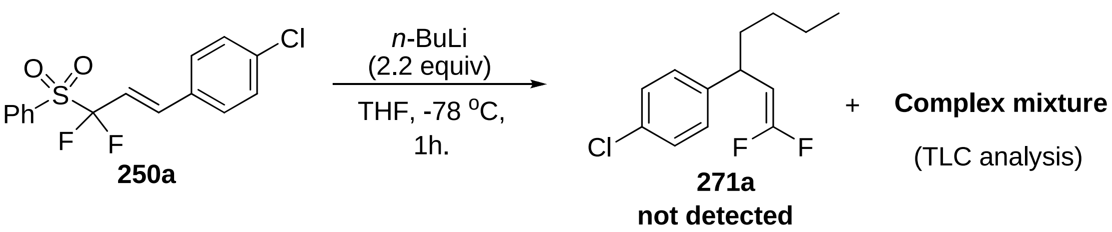
[a] Isolated yield

According to the excess amount of the base employed, the nucleophilic intermediate **269a** might be generated *in situ* in this reaction conditions which can further react with iodomethane via the S_N2 pathway to give methyl-substituted product **270a**. Unfortunately, the desired product **270a** was not detected, while product **268a** was isolated in 55% yield (Scheme 2.16).



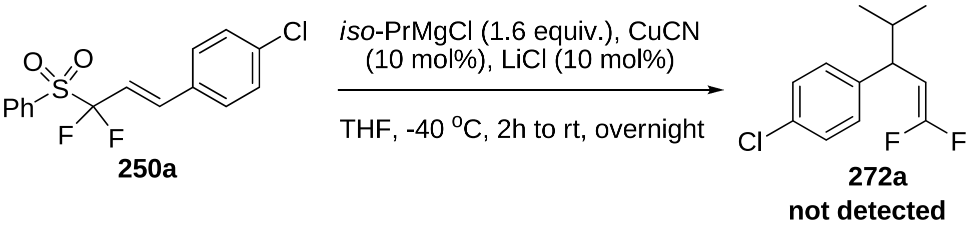
Scheme 2.16

In order to explore the scope and generality of this transformation, the reaction employing *n*-BuLi in place of *sec*-BuLi under the optimal conditions (Table 2.7, Entry 4) was attempted. Unfortunately, the expected product **271a** was not detected. According to TLC analysis, no definite spot was observed in the reaction (Scheme 2.17).



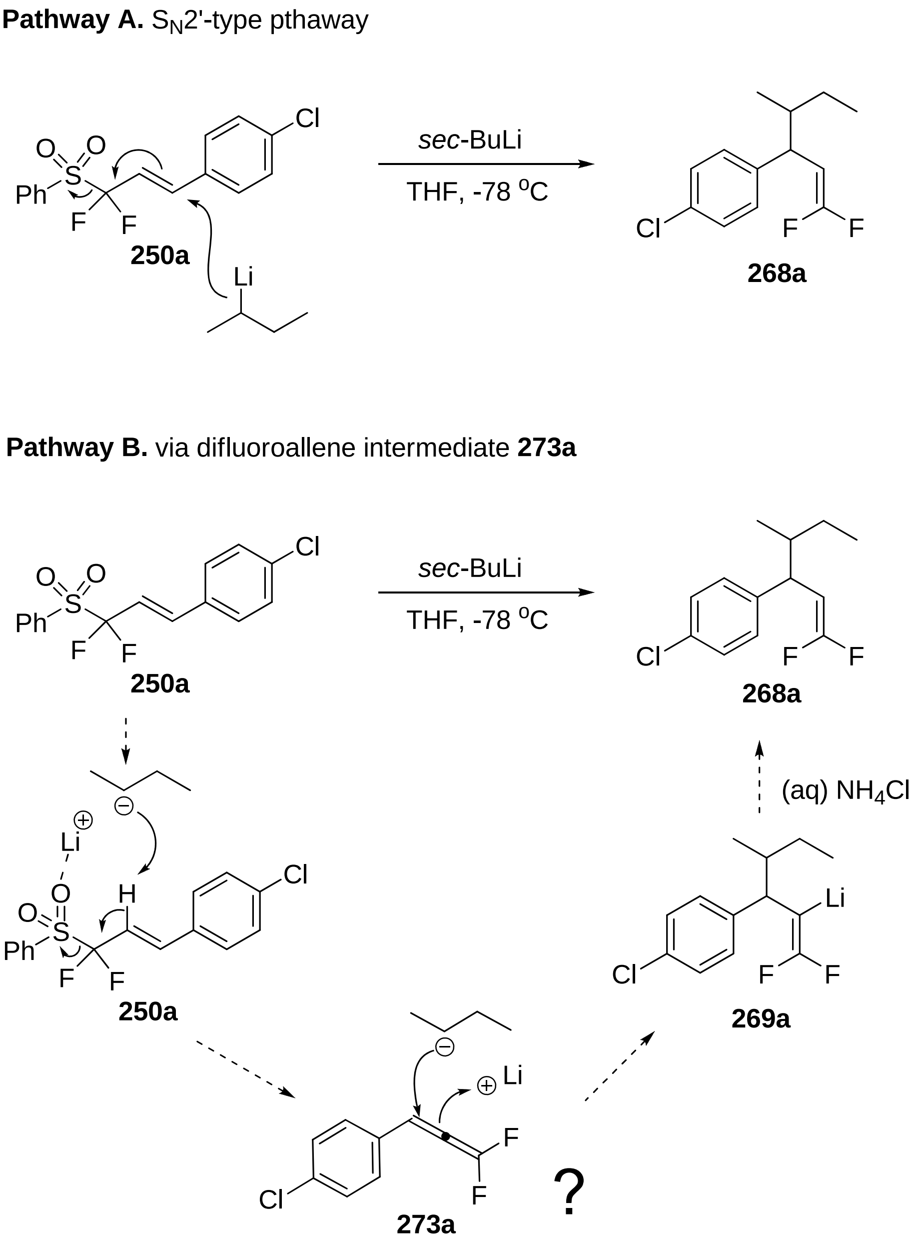
Scheme 2.17

In order to understand the reaction mechanism of this transformation, the S_N2'-type pathway was examined.[70] According to the procedure reported by Tellier and co-workers in 1998, the reaction of **250a** with 1.6 equiv of *i*-PrMgCl in the presence of CuCN (10 mol%), LiCl (10 mol%) in THF at -40 °C was carried out. Under the above-mentioned conditions, the S_N2'-type product **272a** was not observed; only compound **250a** recovered in 55% yield (Scheme 2.18).



Scheme 2.18

Even though the mechanism of this reaction is still unclear, the results obtained suggested that the substitution process might involves elimination, addition reaction through a *gem*-difluoroallene intermediate **273a** (Pathway B, Scheme 2.19) which is consistent with the amount of *sec*-BuLi used (at least 2.0 equiv) in this transformation, but S$_N$2'-type pathway could not be ruled out (Pathway A, Scheme 2.19).

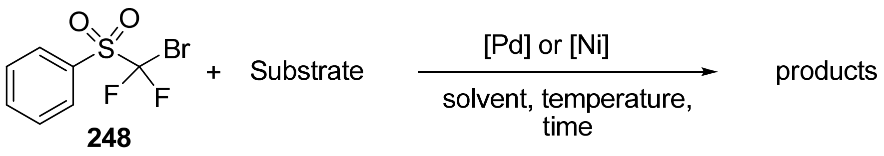


Scheme 2.19

2.6 The investigation of [(bromodifluoromethyl)sulfonyl]benzene 248 under various reaction conditions

Having accomplished the difluoromethylation of styrene derivatives and some heteroaromatic compounds, the studies of similar reaction broader scope of transition metals and substrates were briefly investigated. Thus the difluoromethylation, reactions of [(bromodifluoromethyl)sulfonyl]benzene **248** with a variety of substrates in the presence of transition metal-mediated reaction including palladium, and nickel were examined. The results are summarized in Table 2.8. The reaction of [(bromodifluoromethyl)sulfonyl]benzene **248** and tributyl(phenylethynyl)-stannane (**274**) in the presence of $Pd(PPh_3)_4$ (0.05 equiv) in THF at room temperature for 72 h gave homocoupling product 1,4-diphenylbuta-1,3-diyne (**276**) in 25% yield. Unfortunately, the desired product (3,3-difluoro-3-(phenylsulfonyl)prop-1-ynyl)benzene (**275**) was not observed (Table 2.8, Entry 1). When tributyl(vinyl)stannane (**277**) was used as substrate, the desired product (1,1-difluoroallylsulfonyl)benzene (**278**) was not detected (Table 2.8, Entries 2-3) indicating that both tributyl(phenylethynyl)stannane (**274**) and tributyl(vinyl)stannane (**277**) were not suitable coupling partners of this palladium mediated reaction. So we turned our attention to phenyl boronic acid **279** known as Suzuki–Miyaura substrate which was subjected in the reaction conditions ($PhSO_2CF_2Br$ (1 equiv), $Pd(PPh_3)_4$ (0.35 equiv), and K_2CO_3 (1.5 equiv) in toluene at 100 ^{o}C for 4 h) resulting complex mixture (Table 2.8, Entry 4). The reported Heck-reaction[66c,71a] by using a combination of $NiCl_2(PPh_3)_2$(0.1 equiv) and Zn^0(3.0 equiv) was also evaluated in the reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) and styrene (**249g**). Unfortunately, the desired product **250g** was not detected; only 14% yield of reduced product **251** was obtained (Table 2.8, Entry 5).

Table 2.8 Attempted transition metal-catalyzed reaction of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) via Stille and Suzuki–Miyaura couplings.



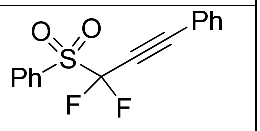
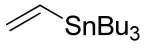
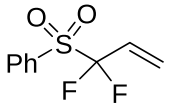
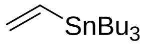
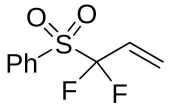
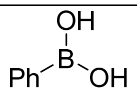
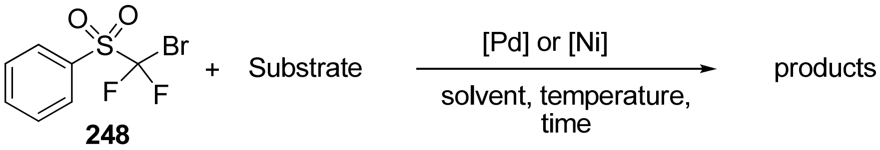
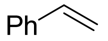
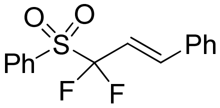
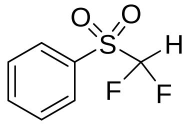
Entry	Substrate (equiv)	[Metal] / additive (equiv)	Solvent	Condition		Product^a
				[*T*] (^{o}C)	Time (h)	
1	$\mathrm{Ph}{-}{\equiv}{-}\mathrm{SnBu_3}$ **274** (1.1)	$Pd(PPh_3)_4$ (0.05)	THF	rt	72	 **275** not detected + $\mathrm{Ph}{-}{\equiv}{-}{\equiv}{-}\mathrm{Ph}$ **276**, 25%
2	 **277** (1.1)	$Pd(PPh_3)_4$ (0.05)	THF	60	24	 **278** not detected
3	 **277** (3.0)	$Pd(PPh_3)_4$ (0.35)	Toluene	100	4	 **278** not detected
4	 **279** (2)	$Pd(PPh_3)_4$/ K_2CO_3 (0.35/1.5)	Toluene	100	4	Complex mixture

Table 2.8 Attempted transition metal-catalyzed reaction of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) via Stille and Suzuki–Miyaura couplings (Continued)



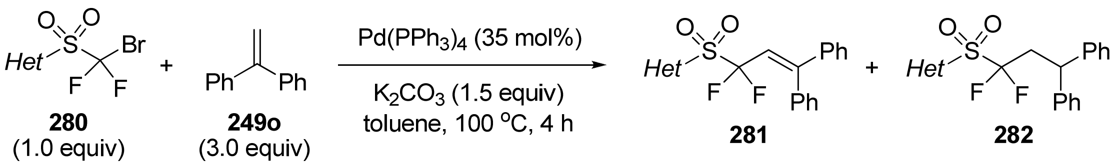
Entry	Substrate (equiv)	[Metal] / additive (equiv)	Solvent	Condition		Product[a]
				[*T*] (°C)	Time (h)	
5	 **249g** (1.5)	$NiCl_2(PPh_3)_2$ /Zn^0 (0.1/3.0)	THF	rt	24	 **250g** not detected +  **251**, 14%

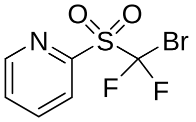
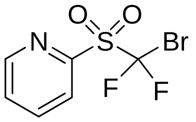
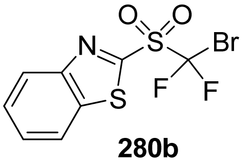
[a]Isolated yields based on **248**.

2.7 The reaction of bromodifluoromethyl(heteroaryl)sulfone 280 in the presence of palladium catalyst

The alternative difluoromethylating reagents such as 2-(bromodifluoromethylsulfonyl)pyridine (**280a**) and 2-(bromodifluoromethylsulfonyl)-benzo[d]thiazole (**280b**) were also evaluate as substrates for Heck-reaction with 1,1-diphenylethylene (**249o**) in the presence of $Pd(PPh_3)_4$ (0.35 equiv), and K_2CO_3 (1.5 equiv) in toluene at 100 °C for 4 h. Unlike [(bromodifluoromethyl)sulfonyl]benzene (**248**), the corresponding product **281** and **282** were not obtained in both cases (Table 2.9)

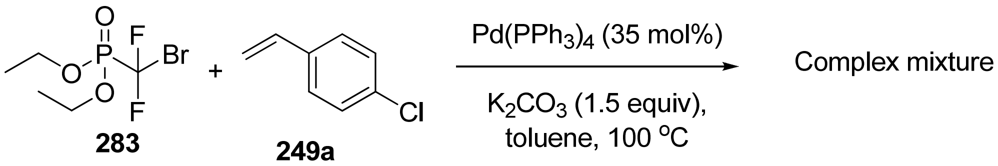
Table 2.9 Palladiun-mediated reaction of bromodifluoromethyl(heteroaryl)sulfone **280** and 1,1-diphenylethylene (**249o**).



Entry	*Het*-SO_2CF_2Br	Additive (equiv)	Product yield (%)	
			281	282
1	 **280a**	-	0	0
2	 **280a**	CuBr, 1.5	0	0
3	 **280b**	-	0	0

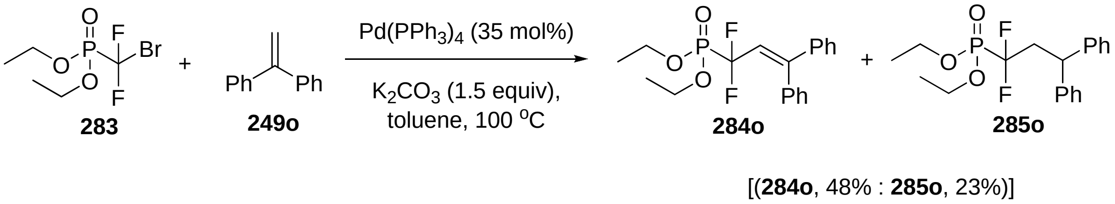
2.8 Pd-catalyzed reaction of diethyl bromodifluoromethylphosphonate (283).

Inspired by the excellent results obtained from Pd-catalyzed reaction of [(bromodifluoromethyl)sulfonyl]benzene (**248**) with styrenes **249**, we envisage that bromodifluoromethylphosphonate (**283**) could be a good reagent for Pd-catalyzed fluoroalkylation reactions as [(bromodifluoromethyl)sulfonyl]benzene (**249**). In the initial exploration of Pd-catalyzed reaction of bromodifluoromethylphosphonate (**283**), *p*-chlorostyrene (**249a**) was chosen as a model substrate for our investigation. Unfortunately, complex mixture was obtained when bromodifluoromethylphosphonate (**283**) and *p*-chlorostyrene (**249a**) were attempted under the standard reaction conditions (3 equiv of **249a**, 1 equiv of **283**, 35 mol% of $Pd(PPh_3)_4$, 1.5 equiv of K_2CO_3 in toluene at 100 °C) (Scheme 2.20).



Scheme 2.20

To our delight, when 1,1-diphenylethylene (**249o**) was used as substrate in the presence of **283** (1 equiv), $Pd(PPh_3)_4$ (35 mol%) and K_2CO_3 (1.5 equiv) in toluene at 100 °C, an inseparable mixture of compounds **284o** and **285o** in 2:1 ratios was obtained in 71% combined yields (Scheme 2.21).



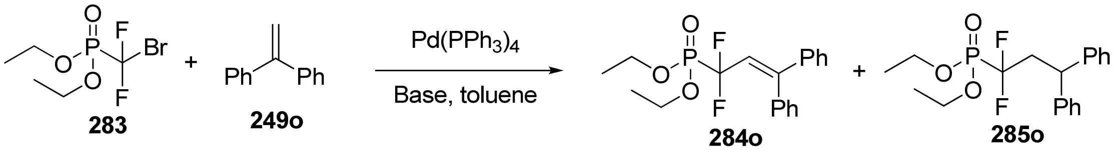
Scheme 2.21

In order to improve the yield and the product ratio of **284o** and **285o**, the reaction parameters were investigated including Pd catalysts, bases, solvents, reaction time and temperature. The results of optimized reaction conditions are summarized in Table 2.10-2.13, respectively.

2.8.1 Optimization of $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (249o) with diethyl bromodifluoromethylphosphonate (283)

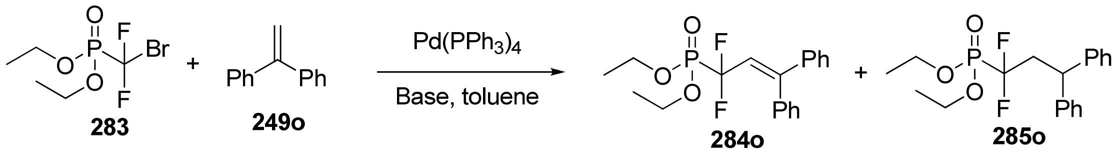
In the initial investigation using bromodifluoromethylphosphonate (**283**) (1 equiv), 1,1-diphenylethylene (**249o**) (3 equiv), $Pd(PPh_3)_4$ and K_2CO_3 in toluene at 100 °C, we quickly identified that 35 mol% of $Pd(PPh_3)_4$ was the optimal catalyst loading (Table 2.10, Entry 4). When the catalyst loading was decreased, inferior results were observed (Table 2.10, Entries 1-3). Performing reaction conditions without base (K_2CO_3), the yields and the product ratios were decreased (Table 2.10, Entry 10). The yield and the product ratio of **284o** and **285o** were further improved to 77% combined yield in 2.4:1 ratios, when the reaction was performed under refluxing temperature of toluene (Table 2.10, Entry 12). The effect of base on the reaction conditions was also examined. Among organic and inorganic bases screening, we found that K_2CO_3, K_3PO_4, Na_2CO_3, $CaCO_3$, $NaHCO_3$, $KHCO_3$, KF, NaOAc and KOAc gave the yield of product over 70% but product ratio of compounds **284o** and **285o** never exceeded 3:1 except for KOAc (3.3:1). Ag_2CO_3 led to the highest product ratio (10:1) but the yields were unsatisfactory (11% yield) (Table 2.10, Entry 17).

Table 2.10 Optimization of $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a]



Entry	249o (equiv)	$Pd(PPh_3)_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b] (284o:285o)
1	3	10	K_2CO_3, 1.5	toluene	100, 20	29, (64:36)
2	3	20	K_2CO_3, 1.5	toluene	100, 20	45, (62:38)
3	3	30	K_2CO_3, 1.5	toluene	100, 5	44, (64:36)
4	3	35	K_2CO_3, 1.5	toluene	100, 5	71, (67:33)
5	3	40	K_2CO_3, 1.5	toluene	100, 5	71, (59:41)
6	3	60	K_2CO_3, 1.5	toluene	100, 5	66, (63:37)
7	1.5	35	K_2CO_3, 1.5	toluene	100, 5	59, (61:39)
8	2	35	K_2CO_3, 1.5	toluene	100, 5	62, (61:39)
9	3	35	K_2CO_3, 3.0	toluene	100, 5	59, (61:39)
10	3	35	-	toluene	100, 20	53, (55:45)
11	3	35	K_2CO_3, 0.5	toluene	100, 5	64, (61:39)
12	3	35	K_2CO_3, 1.5	toluene	Reflux, 5	77, (71:29)
13	3	35	K_3PO_4, 1.5	toluene	Reflux, 5	73, (71:29)

Table 2.10 Optimization of Pd(PPh_3)$_4$ mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a] (Continued)



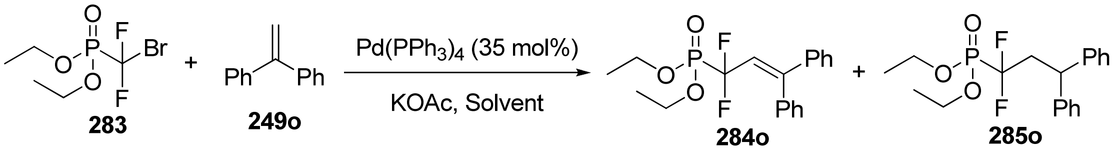
Entry	249o (equiv)	Pd(PPh_3)$_4$ (mol%)	Base (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b] (284o:285o)
14	3	35	Cs_2CO_3, 1.5	toluene	Reflux, 5	25, (69:31)
15	3	35	Na_2CO_3, 1.5	toluene	Reflux, 5	79, (66:34)
16	3	35	$CaCO_3$, 1.5	toluene	Reflux, 5	72, (57:43)
17	3	35	Ag_2CO_3, 1.5	toluene	Reflux, 5	11, (91:9)
18	3	35	$NaHCO_3$, 3.0	toluene	Reflux, 5	78, (64:36)
19	3	35	$KHCO_3$, 3.0	toluene	Reflux, 5	77, (73:27)
20	3	35	Et_3N, 3.0	toluene	Reflux, 5	29, (65:35)
21	3	35	KF, 3.0	toluene	Reflux, 5	77, (69:31)
22	3	35	CsF, 3.0	toluene	Reflux, 5	8, (57:43)
23	3	35	NaOAc, 3.0	toluene	Reflux, 5	76, (75:25)
24	**3**	**35**	**KOAc, 3.0**	**toluene**	**Reflux, 5**	**73, (77:23)**
25	3	35	K_2CO_3, 1.5	toluene	Reflux, 5	54, (63:37)[c]

[a]Reaction conditions: a mixture of **249o**, **283** (1 equiv), Ph(PPh_3)$_4$, base and solvent was heated as temperature indicated. [b]Isolated yields based on **283**. [c]Pivilic acid (0.6 equiv) was used as additive.

2.8.2 Optimization of solvents for $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (249o) with diethyl bromodifluoromethylphosphonate (283)

Solvent effect on the $Pd(PPh_3)_4$-mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**) was studied (Table 2.11). Among the solvents tested, toluene was found to be the best giving the desired products **284o** and **285o** in 73% yield (3.3:1 ratio) (Table 2.11, Entry 1). No the fluoroalkylation products were observed when benzene, THF, MeCN, DMF, and even 15% PTS in water, reported recently as efficient solvent for Pd-catalyzed reaction in mild conditions,[63] were used as the solvents. In the case of 1,4-dioxane employed, a 1.8:1 mixture of compounds **284o** and **285o** was obtained in 12% combined yields (Table 2.11, Entry 3).

Table 2.11 Optimization of solvents for $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a]



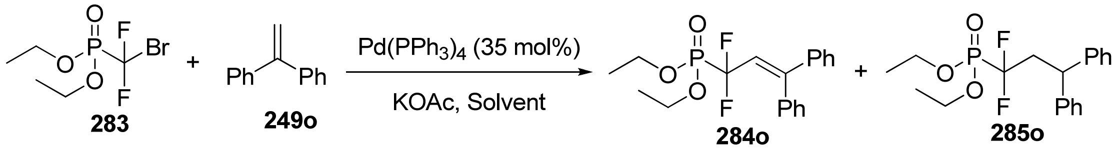
Entry	Solvent	Temp (°C), time (h)	Yield (%)[b] (284o:285o)
1	toluene	Reflux, 5	73, (77:23)
2	benzene	Reflux, 5	0
3	1,4-dioxane	Reflux, 5	12, (64:36)
4	THF	Reflux, 5	0
5	MeCN	Reflux, 5	0
6	DMF	110, 5	0
7	DMSO	110, 5	0
8	15% PTS	Rt, 24	0

[a] Reaction conditions: a mixture of **249o** (3 equiv), **283** (1 equiv), $Ph(PPh_3)_4$ (35 mol%), KOAc (3 equiv) and solvent was heated at temperature indicated. [b] Isolated yields based on **283**.

2.8.3 Evaluation of the effect of additives for $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (249o) with diethyl bromodifluoromethylphosphonate (283)

There were previous reports on the use of phase transfer reagent to facilitate the Heck reaction.[62] It was proposed that it involves in an exchange process between the phase transfer reagent and the inorganic salt prior to deprotonation of the palladium(II)-hydride complex in organic phase, which regenerates the Pd(0) catalyst. Thus, by using bromodifluoromethylphosphonate (**283**) (1 equiv), 1,1-diphenylethylene (**249o**) (3 equiv), $Pd(PPh_3)_4$ (35 mol%) and KOAc (3 equiv) in toluene at reflux as model reaction conditions, the effect of solid-liquid phase transfer including Bu_4NBr, Bu_4NHSO_4 and 18-crown-6 to facilitate Pd-catalyzed reaction was examined (Table 2.12). Unfortunately, the fluoroalkylation products were not observed (Table 2.12, Entries 2-4). The use of transition metal as a co-catalyst for facilitating Pd-mediated reaction was also evaluated. In contrast to the standard reaction conditions, those of which co-catalyzed with the transition metals tested gave the inferior results. For instance, when CuI, a useful heterogeneous co-catalyst for the Heck reaction,[66c,71b] was employed under standard reaction conditions, unfortunately, low yields of the corresponding products were obtained (Table 2.12, Entry 6). Also the reaction did not work well with $Cu(acac)_2$ (Table 2.12, Entry 7). In order to improve the reactivity of the reaction, we envisaged that Zn dust (reducing agent) could help regenerating Pd(0) species form Pd(II) species, which was generated in common Heck reaction, to ensure a catalytic effect. The yields of the corresponding products were obtained in 64% combined yields (Table 2.12, Entry 8). The role of Lewis acids to assist the polarization of the sulfonyl-bromide bond in the Heck reaction was also investigated. When $ZnCl_2$[66b] was employed as co-catalyst, the corresponding products were obtained in 67% combined yields (Table 2.12, Entry 9). The reaction employing $FeCl_3$ as co-catalyst[71c] gave comparable yield of the corresponding products but lower in product ratio comparing to the reaction conditions in the absence of additive (Table 2.12, Entry 5 vs Table 2.11, Entry 1). Reductive Heck conditions[68] was also attempted under this reaction conditions to alter the product ratio from **284o** to **285o** by using 1,1-diphenylethylene (**249o**) (3.0 equiv), bromodifluoromethylphosphonate (**283**) (1.0 equiv), $Pd(PPh_3)_4$ (35 mol%), formic acid (4.5 equiv) and Et_3N (6.0 equiv) in toluene at reflux for 5 h (Table 9, Entry 1). To our disappointed, no desired products were detected.

Table 2.12 . Optimization of additives for $Pd(PPh_3)_4$ mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a]



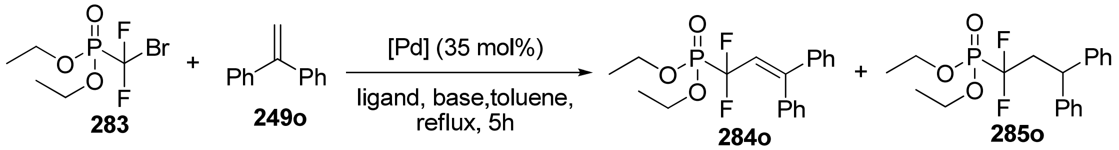
Entry	Base (equiv)	Additive (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[b] (284o:285o)
1	Et_3N, 6.0	HCO_2H, 4.5	toluene	Reflux, 5	0
2	KOAc, 3.0	Bu_4NBr, 0.4	toluene	Reflux, 5	0
3	KOAc, 3.0	Bu_4NHSO_4, 0.4	toluene	Reflux, 5	0
4	KOAc, 3.0	18-crown-6, 0.4	toluene	Reflux, 5	0
5	KOAc, 3.0	$FeCl_3$, 0.35	toluene	Reflux, 5	78, (74:26)
6	KOAc, 3.0	CuI, 0.35	toluene	Reflux, 5	14, (67:33)
7	KOAc, 3.0	$Cu(acac)_2$, 0.35	toluene	Reflux, 5	5, (60:40)
8	KOAc, 3.0	Zn^0, 0.35	toluene	Reflux, 5	64, (74:26)
9	KOAc, 3.0	$ZnCl_2$, 0.2	toluene	Reflux, 5	67, (76:24)

[a] Reaction conditions: a mixture of **249o** (3 equiv), **283** (1 equiv), $Pd(PPh_3)_4$ (35 mol%), KOAc (3 equiv) and toluene was heated at temperature indicated. [b] Isolated yields based on **283**.

2.8.4 Optimization of different Pd precursors and ligands for Pd-mediated fluoroalkylation of 1,1-diphenylethylene (249o) with diethyl bromodifluoromethylphosphonate (283)

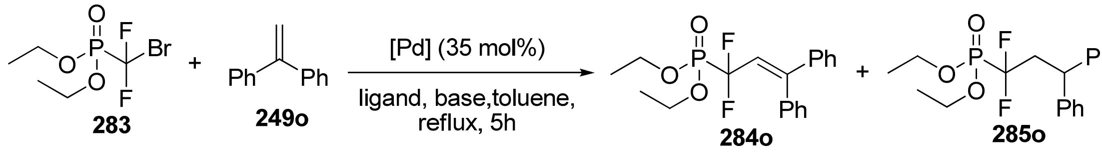
A variety of palladium precursors and ligands were evaluated to understand the effect of the catalyst on the reaction (Table 2.13). Using Pd(II) catalyst (35 mol%) including $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PhCN)_2$ in the presence of PPh_3 (70 mol%) and KOAc (3 equiv) in toluene at reflux gave a mixture of product **284o** and **285o** in moderate yields (not over 65% yield) however with slight improvement in product ratio of **284o** and **285o** (approximately 4:1)) in comparison with the model reaction conditions using $Pd(PPh_3)_4$ as catalyst (3.3:1) (Table 2.13, Entries 3, 9, 10 vs 1). No desired products were observed when the reaction was carried out in the presence of $Pd(OAc)_2$ without PPh_3 ligand. This implied that Pd(0) play an important role in this reaction. Next a variety of phosphine ligands was examined in the presence of $PdCl_2(PhCN)_2$ (35 mol%) and KOAc (3 equiv) in toluene under refluxing temperature for 5h. The use of electron-rich phosphine ligands including Bu_3P, Cy_3P, $(2\text{-furyl})_3P$, $(o\text{-tol})_3P$, and bidentate phosphine ligand (dppp) gave inferior results (Table 2.13, Entries 11–15). In the case of both electron-poor phosphine ligands $P(C_6H_4CF_3)_3$ and $P(C_6H_4F)_3$, the desired products (**284o** and **285o**) were obtained in 66% and 68% combined yields, respectively (Table 2.13, Entries 16 and 17). In contrast with $P(C_6H_4CF_3)_3$, $P(C_6H_4F)_3$ gave higher product ratio of compounds **284o** and **285o** (3.5:1) (Table 2.13, Entries 16 vs 17). When the reported highly-active air- and moisture-stable palladacycles (XPhos)Pd^{II}phenethylamine chloride[65] was employed, a (1.6:1) mixture of compounds **284o** and **285o** was obtained in 44% combined yields (Table 2.13, Entry 18). In the presence of $Pd_2(dba)_3.CHCl_3$, PPh_3, and KOAc in toluene at reflux, a (4.3:1) mixture of compounds **284o** and **285o** was obtained in 68% combined yields (Table 2.13, Entry 19). When the reaction was performed without PPh_3 as ligand, inferior result was observed (Table 2.13, Entries 20 vs 19).

Table 2.13 Optimization of different Pd precursors and ligands for Pd-mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a]



Entry	[Pd] catalyst	Ligand (mol%)	Base (equiv)	Yield (%)[b] (284o:285o)
1	$Pd(PPh_3)_4$	-	KOAc, 3.0	73, (77:23)
2	$Pd(OAc)_2$	Ph_3P, 40	KOAc, 3.0	60, (80:20)
3	$Pd(OAc)_2$	Ph_3P, 70	KOAc, 3.0	57, (83:17)
4	$Pd(OAc)_2$	-	KOAc, 3.0	0
5	$Pd(OAc)_2$	Ph_3P, 70	K_2CO_3, 1.5	38, (69:31)
7	$Pd(OAc)_2$	Ph_3P, 70	NaOAc, 3.0	35, (74:26)
8	$Pd(OAc)_2$	Ph_3P, 70	$KHCO_3$, 3.0	69, (74:26)
9	$PdCl_2$	Ph_3P, 70	KOAc, 3.0	62, (80:20)
10	$PdCl_2(PhCN)_2$	Ph_3P, 70	KOAc, 3.0	63, (84:16)
11	$PdCl_2(PhCN)_2$	Bu_3P, 70	KOAc, 3.0	19, (50:50)
12	$PdCl_2(PhCN)_2$	Cy_3P, 70	KOAc, 3.0	4, (50:50)
13	$PdCl_2(PhCN)_2$	(2-furyl)$_3$P, 70	KOAc, 3.0	8, (60:40)
14	$PdCl_2(PhCN)_2$	(*o*-tol)$_3$P, 70	KOAc, 3.0	0

Table 2.13 Optimization of different Pd precursors and ligands for Pd-mediated fluoroalkylation of 1,1-diphenylethylene (**249o**) with diethyl bromodifluoromethylphosphonate (**283**)[a] (Continued)



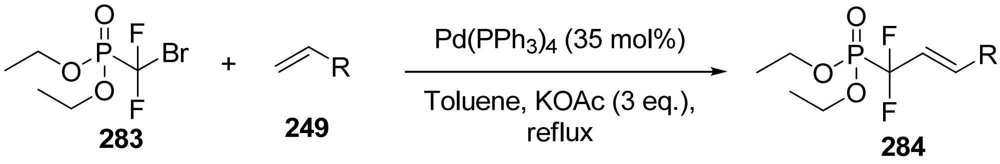
Entry	**[Pd] catalyst**	**Ligand (mol%)**	**Base (equiv)**	**Yield (%)[b] (284o:285o)**
15	$PdCl_2(PhCN)_2$	dppp, 35	KOAc, 3.0	22, (50:50)
16	$PdCl_2(PhCN)_2$	$(F_3CC_6H_4)_3P$, 70	KOAc, 3.0	66, (61:36)
17	$PdCl_2(PhCN)_2$	$(FC_6H_4)_3P$, 70	KOAc, 3.0	68, (78:22)
18	(XPhos)Pd^{II}phenethyl-amine chloride	-	KOAc, 3.0	44, (61:39)
19	$Pd_2(dba)_3.CHCl_3$	Ph_3P, 70	KOAc, 3.0	68, (81:19)[c]
20	$Pd_2(dba)_3.CHCl_3$	-	KOAc, 3.0	19, (51:49)[c]

[a]Reaction conditions: a mixture of **249o** (3 equiv), **283** (1 equiv), Pd catalyst (35 mol%), base, phosphine ligand and toluene was heated at refluxing temperature. [b]Isolated yields based on **283**. [c]17.5 mol% of $Pd_2(dba)_3.CHCl_3$ was employed.

2.8.5 Pd-mediated fluoroalkylation of styrene derivatives with bromodifluoromethylphosphonate (283)

The reaction conditions using bromodifluoromethylphosphonate (**283**) (1 equiv), 1,1-diphenylethylene (**249o**) (3 equiv), $Pd(PPh_3)_4$ (35 mol%) and KOAc (3 equiv) in toluene at reflux for 5h was established as standard reaction conditions. The scope and generality of this transformation using representative substrates including styrene derivatives, vinyl ether and heteroaromatics were investigated. As can be seen from Table 2.14, the reactivity of bromodifluoromethylphosphonate (**283**) with styrene derivatives **249** bearing an electron-withdrawing and electron-donating atom including *p*-chlorostyrene (**249a**), *p*-fluorostyrene (**249b**), *m*-nitrostyrene (**249e**), simple styrene (**249g**), *p*-methylstyrene (**249h**), *p*-acetoxystyrene (**249j**), *p*-methoxystyrene (**249k**) and 4-vinylbenzaldehyde (**249t**) gave inseparable complex mixtures (Table 2.14, Entries 1-7 and 10). According to the crude ^{1}H NMR spectra, we were able to identify the corresponding products **284** existed in the mixtures but that were unable to purify by column or preparative thin layer chromatography. In the case of α-methyl styrene (**249q**) employed, a double bond rearrangement product **286q** was isolated in 26% yield (Table 2.14, Entry 9). When 3,4-dihydro-2*H*-pyran (**254a**) was subjected to the reaction conditions, the corresponding product **287a** was not detected (Table 2.14, Entry 11). The heteroaromatic substrates including 1-methylpyrrole (**257a**) and 1-methyl-1*H*-imidazole (**257m**) were also employed as substrates. Unfortunately, no desired coupling products **288a** and **288m** were observed (Table 2.14, Entries 13-14).

Table 2.14 Pd-mediated fluoroalkylation of styrene derivatives with bromodifluoromethylphosphonate (**283**)[a]



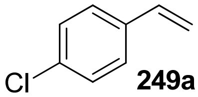
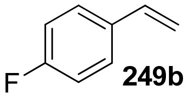
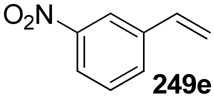
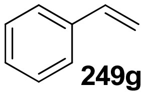
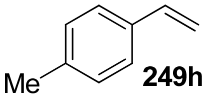
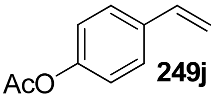
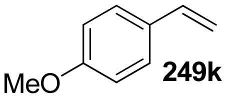
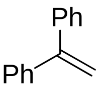
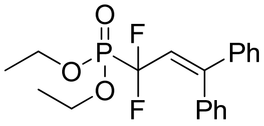
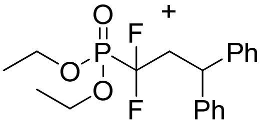
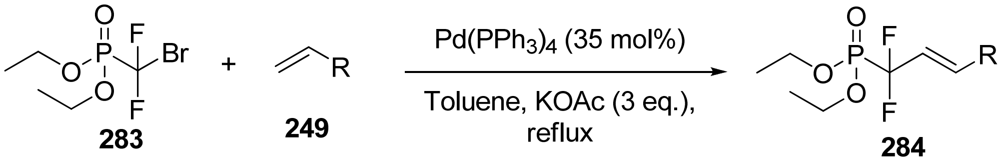
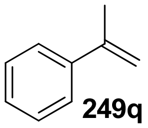
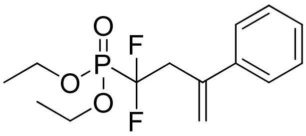
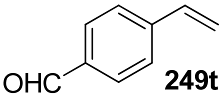
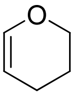
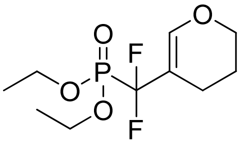
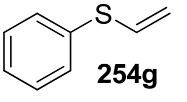
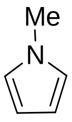
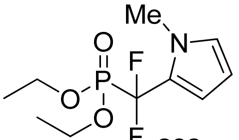
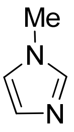
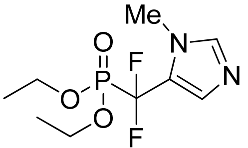
Entry	Substrate	Product	Yield (%)[b]
1	 **249a**	Complex mixtures	-
2	 **249b**	Complex mixtures	-
3	 **249e**	Complex mixtures	-
4	 **249g**	Complex mixtures	-
5	 **249h**	Complex mixtures	-
6	 **249j**	Complex mixtures	-
7	 **249k**	Complex mixtures	-
8	 **249o**	 **284o** +  **285o**	73 (**284o**:**285o**, 77:23)

Table 2.14 Pd-mediated fluoroalkylation of styrene derivatives with bromodifluoromethylphosphonate (**283**)[a] (Continued)



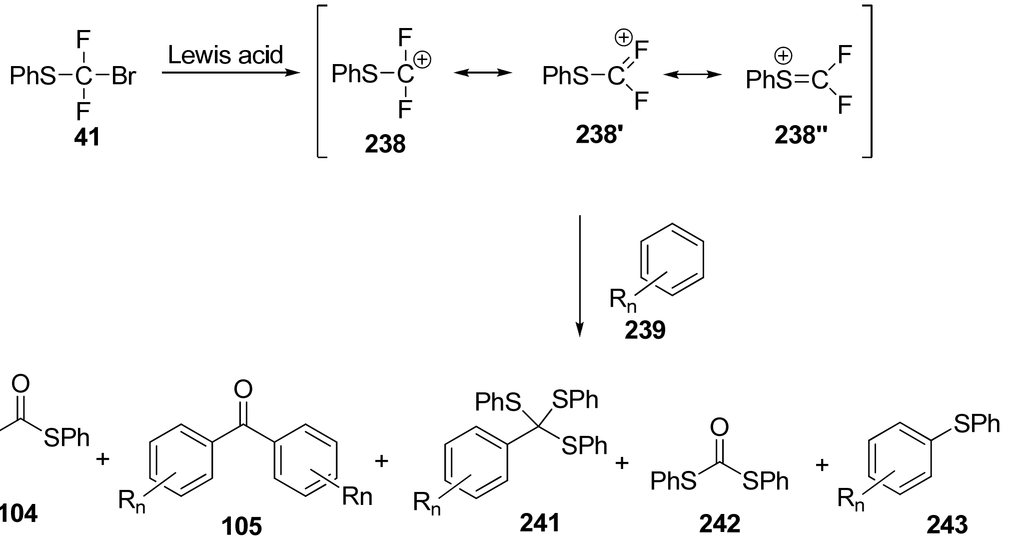
Entry	Substrate	Product	Yield (%)[b]
9	 **249q**	 **286q**	26
10	 **249t**	Complex mixtures	-
11	 **254c**	 **287c**	0
12	 **254g**	Complex mixtures	-
13	 **257a**	 **288a**	0
14	 **257m**	 **288m**	0

[a]Reaction conditions: a mixture of substrate (3 equiv), **283** (1 equiv), Pd(PPh_3)$_4$ (35 mol%), KOAc (3 equiv) in toluene was heated at refluxing temperature. [b]Isolated yields based on **283**.

CHAPTER III

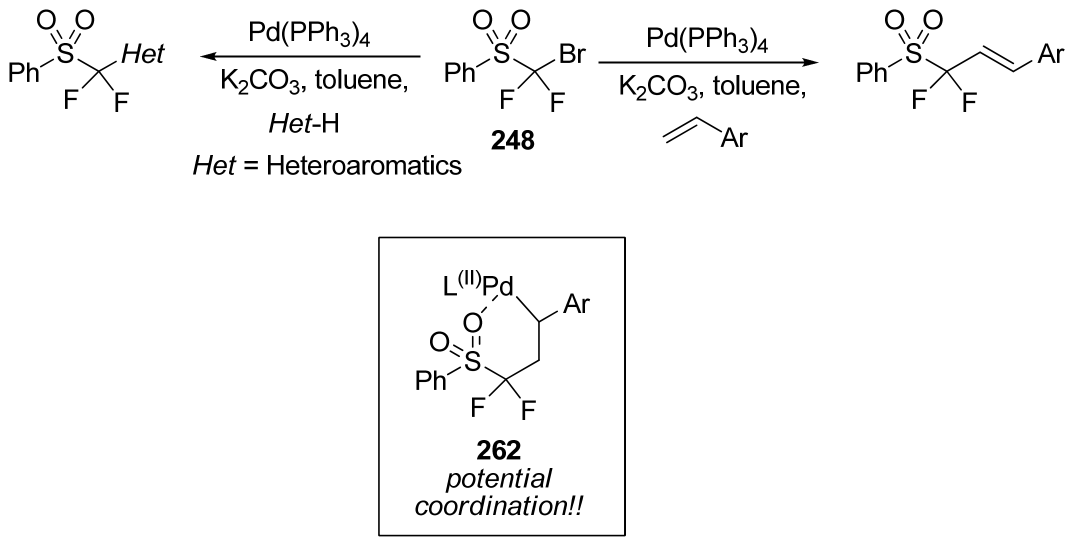
CONCLUSIONS

In conclusion, we have demonstrated the generation and the chemistry of 1,1-difluoro-1-phenylsulfanylmethyl carbocation (**238**) (generated from the reaction of bromodifluoromethyl phenyl sulfide (**41**) with Lewis acids). Upon treatment of a mixture of bromodifluoromethyl phenyl sulfide (**41**) and activated aromatics with Lewis acid, the Friedel–Crafts alkylation of the activated aromatic compound (**239a**) with bromodifluoromethyl phenyl sulfide (**41**) took place providing the corresponding products thioester **104a,** benzophenone **105a**, orthothioester **241a,** *S,S*-diphenyl carbonodithioate (**242**), and phenyl(2,4,5-trimethoxyphenyl)sulfane (**243a)** (Scheme 3.1)**.** The formation of the products depends on the reaction conditions employed including time, temperature, type of Lewis acids, solvents, and mole ratio of substrates. The proposed mechanism for the formation of the thioester **104**, orthothioester **241**, and benzophenone **105** was also discussed which is based, in part, on NMR experiments (^{19}F and ^{13}C NMR).



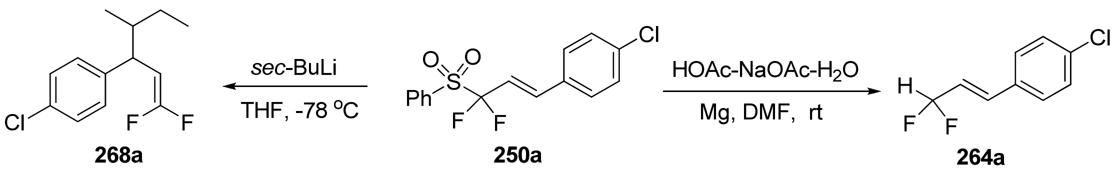
Scheme 3.1

We have also demonstrated the reactivity of [(bromodifluoromethyl)-sulfonyl]benzene (**248**) toward palladium-mediated reaction with the suitable coupling partners including styrene derivatives, vinyl ethers and heteroaromatics. The success of the reaction allows easy synthesis of α-alkenyl- and α-heteroaryl-substituted α,α-difluoromethyl phenyl sulfones. The mechanism for the transformation was proposed via the well-known Heck reaction[66] for styrenes and electrophilic aromatic substitution mechanism (S_EAr) for hetreoaromatics .[69] The coordination of the lone pair oxygen of the sulfonyl group to the palladium metal center is believed being important to stabilize the intermediate formed through the stabilized six-membered palladacycle complex **262** in facilitating the course of the coupling reaction (Scheme 3.2).



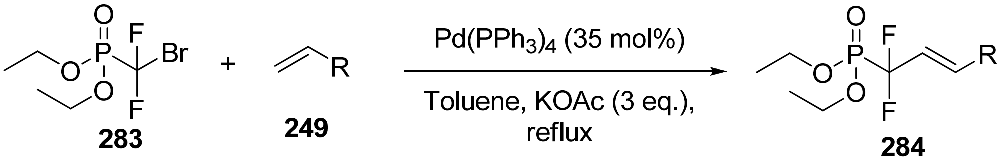
Scheme 3.2

The synthetic application of α-alkenyl-substituted α,α-difluoromethyl phenyl sulfones was also demonstrated. The model substrate (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) could be smoothly converted to the reductive desulfonylation product (**264a**) by using Mg/HOAc/NaOAc desulfonylation system,[12n] and the alkylated desulfonylation product **268a** in moderate yield by employing 2.2 equiv of *sec*-BuLi in THF at -78 °C (Scheme 3.3).



Scheme 3.3

The possible fluoroalkylating reagent bromodifluoromethylphosphonate (**283**) have also been examined under palladium-catalyzed reaction. The reaction was found limited in terms of substrate scope and generality.



Scheme 3.4

CHAPTER IV

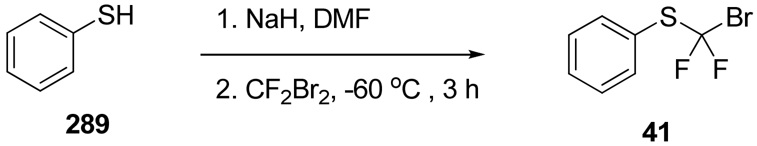
EXPERIMENTAL

4.1 General methods

The ^{1}H and ^{13}C NMR spectra were recorded on either Bruker DPX-300 (300 MHz) spectrometer or Bruker Advance-500 (500 MHz) in $CDCl_3$ and acetone-d_6. ^{1}H NMR chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR chemical shifts are reported in ppm with residual non-deuterated solvent peak as an internal standard. NMR data are reported as follow: ^{1}H NMR chemical shifts, measured in parts per million (ppm) down field from tetramethylsilane (TMS) signal (δ), proton count, multiplicity, observed coupling constant (J) in Hertz (Hz). Multiplicities are reported as singlet (s), broad (br), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quartet (q), quintet (quin) and multiplet (m). The IR spectra were recorded a Perkin Elmer EX FI-IR system spectrometer. The high resolution mass spectra were recorded using a Bruker Micro TOF spectrometer at Faculty of science, Mahidol University. The elemental analysis was performed by a Perkin Elmer Elemental Analyzer 2400 CHN. Melting points were determined on an Electrothermal IA 9000 series and a Gallenkamp Apparatus.

Column chromatography was performed using Merck silica gel 60 (Art. 7734). Preparatory layer chromatography (PLC) was performed using Merck silica gel 60 F_{254} (Art. 7747). Analytical TLC was performed with Merck TLC aluminium sheet silica gel 60 F_{254} (Art. 5554) with 0.2 mm thickness. All chemicals were purchased from Fluka Aldrich and Acros Organics and were used without prior purification.

4.2 Preparation of bromodifluoromethyl phenyl sulfide (41)



To a suspension of sodium hydride (3.6 g, 150.0 mmol) in DMF (200 mL) was slowly added thiophenol (**289**) (10.2 mL, 100.0 mmol) at 0 °C. After the addition was complete, the reaction mixture was warmed to room temperature for 30 min. The reaction mixture was brought to -60 °C (dry ice with $CHCl_3$) for 15 min before dibromodifluoromethane (CF_2Br_2, 28.0 mL, 300.0 mmol) was bubbled into the reaction mixture. The resulting mixture was maintained at -60 °C for 3 h. The reaction flask was cooled in ice-water bath and excess sodium hydride was destroyed by dropwise addition of water (100 mL). The aqueous phase was extracted with Et_2O (3×100 mL). The combined organic layers were washed with water (3×100 mL), brine (50 mL) and dried ($MgSO_4$). Filtration and solvent removal (aspirator, then *vacuo*) afforded a crude product. Purification by flash column chromatography on silica gel using hexanes (R_f = 0.60) as eluent or fractional distillation, b.p. 62–64 °C (2 mmHg) yielded compound **41** (19.6012 g, 82%); colorless liquid; R_f = 0.60 (hexanes).

IR (neat, cm^{-1}): ν_{max} 3064 (C–H of aromatic), 1579, 1476, and 1442 (aromatic), 1062 (C-F), 840, 748, 689.

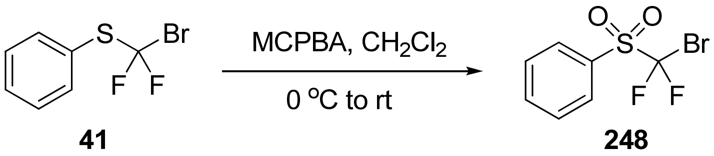
^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2 H), 7.54–7.46 (m, 1 H), 7.45–7.37 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4 (2×CH), 131.0 (CH), 129.4 (2×CH), 127.2 (C), 119.2 (t, J_{CF} = 336.3 Hz, CF_2).

^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ –22.49 (s, CF_2).

MS (EI) [*m/z* (% relative intensity)]: 239 (M^+, 12), 159 (100), 109 (15), 77 (25). HRMS (ESI) Calcd for $C_7H_5BrF_2S$ (M^+), 237.9262; found, 237.9283.

4.3 Preparation of [(bromodifluoromethyl)sulfonyl]benzene (248)[1]



An oven-dried round-bottom flask with a magnetic stir-bar was charged with bromodifluoromethylphenylsulfide (**41**) (10 g, 41.9 mmol) and dry CH_2Cl_2 (100 mL). After cooling to 0 °C, MCPBA (125.7 mmol, 3 equiv.) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated, and dissolved with EtOAc (300 mL). The solution was washed with 10% NaOH (3×200 mL), saturated NaCl solution (200 mL), and dried over anhydrous $MgSO_4$. The combined organic material was dried in vacuo, and purified *via* silica gel column chromatography to yield [(bromodifluoromethyl)sulfonyl]benzene (**248**) (9.5 g, 84% yield) as a white solid: analytical TLC on silica gel: hexanes/EtOAc = 9.0:1.0, $R_f = 0.35$.

IR (KBr, cm^{-1}): ν_{max} 3094 (C–H of aromatic), 1583, and 1453 (aromatic), 1357 and 1111 (SO_2), 1075 (C–F).

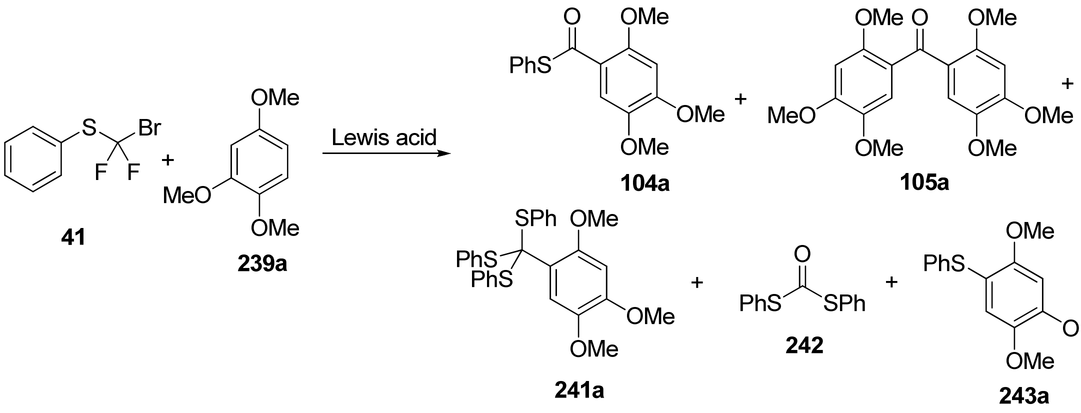
^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$ (d, $J = 7.6$ Hz, 2 H), 7.84 (m, 1 H), 7.69 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 136.2$ (CH), 131.3 (2×CH), 130.1 (C), 129.6 (2×CH), 120.9 (t, $J_{CF} = 346.7$ Hz, CF_2).

^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -57.54$ (s, CF_2).

HRMS (ESI-TOF) *m/z* [(M + Na)$^+$] calcd for $C_7H_5BrF_2O_2SNa$: 292.9059; found: 292.9070.

4.4 Investigation of the reaction of bromodifluoromethyl phenyl sulfide (41) and 1,2,4-trimethoxybenzene (239a) mediated by Lewis acids



General procedure A (a Lewis acid):

In a round-bottomed flask equipped with a stirring bar and rubber septum was placed $PhSCF_2Br$ (**41**). After the reaction flask was evacuated and flushed with argon gas for three times, anhydrous solvent was added. To this solution, were added aromatic compound, followed by Lewis acid. The reaction mixture was allowed to proceed before it was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (3×50 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give a crude product, which was purified by column chromatography.

General procedure B (a Lewis acid):

Lewis acid was weighed into a round-bottomed flask charged with a stirring bar. The reaction flask was fitted with a rubber septum and was evacuated and flushed with argon gas for three times. A solution of $PhSCF_2Br$ (**41**) in anhydrous solvent was added into the reaction flask and the reaction mixture was allowed to stand for 15 min. The solution was added dropwise a solution of aromatic compound. The reaction mixture was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (3×50 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give a crude product, which was purified by column chromatography.

4.4.1 Following the general procedure B, $AlCl_3$ (266.0 mg, 2.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) in CH_2Cl_2 (3.0 mL) and a solution of **239a** (168.1 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) were employed. The reaction mixture was maintained at room temperature for 1 h. Purification by column chromatography afforded **104a** (240.0 mg, 79% yield) and **105a** (7.2 mg, 4% yield).

4.4.2 Following the general procedure A, a 1.8 M solution of $EtAlCl_2$ in toluene (0.61 mL, 1.1 mmol), a solution of **41** (478.0 mg, 2.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in toluene (4.0 mL) were employed. The reaction mixture was maintained at room temperature for 18 h. Purification by column chromatography afforded recovered starting material **239a** (51.8 mg, 30% yield), **104a** (50.0 mg, 16% yield), **105a** (45.0 mg, 12% yield), and **241a** (35.5 mg, 7% yield).

4.4.3 Following the general procedure A, a 2.0 M solution of $AlMe_3$ in hexane (0.55 mL, 1.1 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in hexanes (5.0 mL) were employed. The reaction mixture was maintained at room temperature for 48 h. No product was observed as monitored by TLC analysis.

4.4.4 Following the general procedure A, a 2.0 M solution of $AlMe_3$ in hexane (0.55 mL, 1.1 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. Purification by column chromatography afforded **105a** (3.5 mg, 2% yield).

4.4.5 Following the general procedure A, a 2.0 M solution of $AlMe_3$ in hexane (2.0 mL, 4.0 mmol), a solution of **41** (478.0 mg, 2.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in CH_2Cl_2 (10.0 mL) were employed. The reaction mixture was maintained at room temperature for 15 h. Purification by column chromatography afforded **104a** (27.1 mg, 9% yield).

4.4.6 Following the general procedure B, bis(trimethylaluminun)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3) (256.3 mg, 1.0 mmol), a solution of **41** (478.0 mg, 2.0 mmol) in CH_3CN (3.0 mL) and a solution of **239a** (168.1 mg, 1.0 mmol) in CH_3CN (2.0 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. No product was observed as monitored by TLC analysis.

4.4.7 Following the general procedure B, bis(trimethylaluminun)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3) (256.3 mg, 1.0 mmol), a solution of **41** (478.0 mg, 2.0 mmol) in CH_3CN (3.0 mL) and a solution of **239a** (168.1 mg, 1.0 mmol) in CH_3CN (2.0 mL) were employed. The reaction mixture was maintained at refluxing temperature for 12 h. No product was observed as monitored by TLC analysis.

4.4.8 Following the general procedure B, bis(trimethylaluminun)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3) (512.6 mg, 2.0 mmol), a solution of **41** (478.0 mg, 2.0 mmol) in CH_2Cl_2 (3.0 mL) and a solution of **239a** (168.1 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) were employed. The reaction mixture was maintained at room temperature for 48 h. No product was observed as monitored by TLC analysis.

4.4.9 Following the general procedure A, $BF_3 \cdot OEt_2$ (5.0 mL, 40.0 mmol), a solution of **41** (478.0 mg, 2.0 mmol) and **239a** (168.1 mg, 1.0 mmol) were employed. The reaction mixture was maintained at 70 ^{o}C for 16 h. Purification by column chromatography afforded **105a** (38.0 mg, 21% yield) and **242** (24.5 mg, 10% yield).

4.4.10 Following the general procedure A, $Ag(O_2CCF_3)$ (220.8 mg, 1.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in $CHCl_3$ (7 mL) were employed. The reaction mixture was maintained at room temperature for 18 h. Purification by column chromatography afforded **242** (11.1 mg, 9% yield).

4.4.11 Following the general procedure A, $Zn(BF_4)_2{\cdot}xH_2O$ (406.3 mg, 1.7 mmol), a solution of **41** (478.0 mg, 2.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in $[BMIM][BF_4]$ (3 mL) were employed. The reaction mixture was maintained at room temperature for 72 h. Purification by column chromatography afforded **242** (32.0 mg, 13% yield).

4.4.12 Following the general procedure A, $ZnBr_2$ (225.2 mg, 1.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (336.2 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) were employed. The reaction mixture was maintained at room temperature for 16 h. No product was observed as monitored by TLC analysis.

4.4.13 Trityl tetrakis(pentafluorophenyl)borate (507.3 mg, 0.55 mmol) was placed in An oven-dried round-bottom flask with a magnetic stir-bar which was evacuated and placed under an argon atmosphere. Triethylsilane (3.7 mL, 23.5 mmol) was added via syringe. The yellow solid gradually was replaced with a white powder. After 2 days, the liquid was evacuated and the solid was washed with dry hexanes to remove the triphenyl methane byproduct. The white soled was dried in vacuo and charged with a solution of **41** (143.2 mg, 0.6 mmol) and **239a** (84.1 mg, 0.5 mmol) in dry hexanes (3.0 mL) at room temperature. After stirring for 48 h, the reaction mixture was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (50 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give a crude product, which was purified by column chromatography affording **104a** in 60% yield.

4.4.14 An oven-dried round-bottom flask with a magnetic stir-bar was charged with *N*-butyl-*N*-methylimidazolium chloride (2.85 g, 16.0 mmol) under an argon atmosphere followed by adding aluminium chloride (4.35 g, 32 mmol) in small portions at 0 ^{o}C. After all the aluminium chloride had been added, the cooling was removed and the reaction mixture was warmed to room temperature and stirred at room temperature for 24 h affording [BMIM][Al_2Cl_7] in quantitative yield. The ironic liquid [BMIM][Al_2Cl_7] (16.0 mmol) was added **41** (239.0 mg, 1.0 mmol) at 0 °C. After stirring for 15 min, the reaction mixture was added **239a** (168.1 mg, 1.0 mmol) and stirred at 0 °C for 30 min. the reaction mixture was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (50 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give a crude product, which was purified by column chromatography affording **104a** in 36% yield.

4.4.15 Following the general procedure A, $Sm(OTf)_3$ (597.5 mg, 1.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in a (1:1) solvent mixture of CH_2Cl_2 (5 mL) and THF (5 mL) were employed. The reaction mixture was maintained at room temperature for 2 h. No product was observed as monitored by TLC analysis.

4.4.16 Following the general procedure A, $SmCl_3$ (256.7 mg, 1.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in a (1:1) solvent mixture of CH_2Cl_2 (5 mL) and THF (5 mL) were employed. The reaction mixture was maintained at room temperature for 1 h. No product was observed as monitored by TLC analysis.

4.4.17 Following the general procedure A, $InCl_3$ (221.2 mg, 1.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in a (1:1) solvent mixture of CH_2Cl_2 (5 mL) and THF (5 mL) were employed. The reaction mixture was maintained at room temperature for 16 h. No product was observed as monitored by TLC analysis.

4.4.18 Following the general procedure A, $Bi(OTf)_3$ (131.2 mg, 0.2 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. Purification by column chromatography afforded recovered starting material **239a** (74.0 mg, 56% yield), **104a** (11.0 mg, 4% yield) and **105a** (21.3 mg, 12% yield).

4.4.19 Following the general procedure A, Bi(OTf)$_3$ (131.2 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and [BMIM][BF$_4$] (1.5 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. Purification by column chromatography afforded recovered starting material **239a** (70.9 mg, 42% yield), **104a** (10.0 mg, 3% yield) and **105a** (46.7 mg, 26% yield).

4.4.20 Following the general procedure A, Bi(OTf)$_3$ (131.2 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and [BMIM][BF$_4$] (1.5 mL) were employed. The reaction mixture was maintained at 90 ^{o}C for 2 h. Purification by column chromatography afforded **105a** (22.0 mg, 12% yield).

4.4.21 Following the general procedure A, Bi(OTf)$_3$ (131.2 mg, 0.2 mmol), a mixture of **41** (1.19 g, 5.0 mmol), **239a** (168.1 mg, 1.0 mmol), and [BMIM][BF$_4$] (1.5 mL) were employed. The reaction mixture was maintained at 90 ^{o}C for 24 h. Purification by column chromatography afforded **242** (38.4 mg, 6% yield).

4.4.22 Following the general procedure A, Bi(OTf)$_3$ (131.2 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and [BMIM][PF$_6$] (1.5 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. Purification by column chromatography afforded recovered starting material **239a** (68.5 mg, 41% yield), **104a** (18.5 mg, 6% yield) and **105a** (55.0 mg, 30% yield).

4.4.23 Following the general procedure A, In(OTf)$_3$ (112.4 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and [BMIM][BF$_4$] (2 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. According to TLC analysis, no reaction took place in this reaction conditions.

4.4.24 Following the general procedure A, $Hf(OTf)_4$ (154.0 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and $[BMIM][BF_4]$ (2 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. According to TLC analysis, no reaction took place in this reaction conditions.

4.4.25 Following the general procedure A, $Sm(OTf)_3$ (119.5 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and $[BMIM][BF_4]$ (2 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. According to TLC analysis, no reaction took place in this reaction conditions.

4.4.26 Following the general procedure A, $Yb(OTf)_3$ (124.0 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and $[BMIM][BF_4]$ (3 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. According to TLC analysis, no reaction took place in this reaction conditions.

4.4.27 Following the general procedure A, $Yb(OTf)_3$ (124.0 mg, 0.2 mmol), a solution of **41** (239.0 mg, 1.0 mmol), and **239a** (168.1 mg, 1.0 mmol) in CH_3NO_2 (3 mL) were employed. The reaction mixture was maintained at 100 ^oC for 24 h. According to TLC analysis, no desired products were detected.

4.4.28 Following the general procedure A, $Sc(OTf)_3$ (98.4 mg, 0.2 mmol), a mixture of **41** (239.0 mg, 1.0 mmol), **239a** (168.1 mg, 1.0 mmol), and $[BMIM][BF_4]$ (2 mL) were employed. The reaction mixture was maintained at room temperature for 24 h. Purification by column chromatography afforded recovered starting material **239a** (112.7 mg, 67% yield), and **105a** (6.9 mg, 4% yield).

4.4.29 Following the general procedure A (without Lewis acid), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (84.1 mg, 0.5 mmol) in HFIP (2 mL) was employed. The reaction mixture was maintained at room temperature for 72 h.

Purification by column chromatography afforded **104a** (17.3 mg, 11% yield) and **105a** (8.7 mg, 10% yield).

4.4.30 Following the general procedure A, Bi(OTf)$_3$ (131.2 mg, 0.2 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (84.1 mg, 0.5 mmol) in HFIP (2 mL) were employed. The reaction mixture was maintained at room temperature for 72 h. Purification by column chromatography afforded recovered starting material **239a** (17.7 mg, 21% yield), **104a** (27.6 mg, 18% yield) and **105a** (5.1 mg, 6% yield).

4.4.31 Following the general procedure A, Yb(OTf)$_3$ (124.1 mg, 0.2 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (84.1 mg, 0.5 mmol) in HFIP (2 mL) were employed. The reaction mixture was maintained at room temperature for 72 h. Purification by column chromatography afforded recovered starting material **239a** (5.9 mg, 7% yield), **104a** (35.3 mg, 23% yield) and **105a** (7.2 mg, 8% yield).

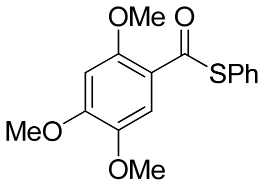
4.4.32 Following the general procedure A, Hf(OTf)$_4$ (155.0 mg, 0.2 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (84.1 mg, 0.5 mmol) in HFIP (2 mL) were employed. The reaction mixture was maintained at room temperature for 72 h. Purification by column chromatography afforded **104a** (50.9 mg, 33% yield) and **105a** (12.4 mg, 14% yield).

4.4.33 Following the general procedure A, FeCl$_3$ (32.4 mg, 2.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in CH$_2$Cl$_2$ (2 mL) were employed. The reaction mixture was maintained at room temperature for 15 h. Purification by column chromatography afforded recovered starting material **239a** (111.5 mg, 66% yield), and 2,2',4,4',5,5'-hexamethoxybiphenyl (**290**) (30.9 mg, 18% yield).

4.4.34 Following the general procedure A, FeCl$_3$ (32.4 mg, 2.0 mmol), a solution of **41** (239.0 mg, 1.0 mmol) and **239a** (168.1 mg, 1.0 mmol) in EtOAc (3 mL) were employed. The reaction mixture was maintained at refluxing temperature for 12

h. Purification by column chromatography afforded recovered starting material **239a** (33.4 mg, 20% yield), and **243a** (82.3 mg, 30% yield).

S-Phenyl 2,4,5-trimethoxybenzenecarbothioate (104a)



104a

Compound **104a**: A white solid, m.p. 86.1–86.5 °C; R$_f$ 0.67 (60% EtOAc/hexanes).

IR (neat, cm^{-1}): $\nu_{\max}$ 1645 (C=O)

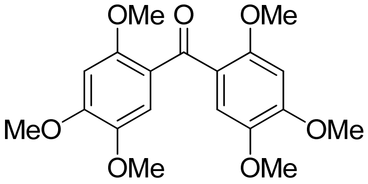
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.53–7.41 (m, 6H, S*Ph* and Ar*H*), 6.56 (s, 1H, Ar*H*), 4.01 (s, 3H, O*CH*$_3$), 3.97 (s, 3H, O*CH*$_3$), 3.85 (s, 3H, O*CH*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ 187.4 (*C*=O), 155.3 (*C*$_q$), 154.2 (*C*$_q$), 143.1 (*C*$_q$), 135.2 (2×*CH*), 129.2 (*C*$_q$), 129.1 (*CH*), 128.9 (2×*CH*), 117.3 (*C*$_q$), 111.9 (*CH*), 96.9 (*CH*), 56.7 (O*CH$_3$*), 56.2 (O*CH$_3$*), 56.1 (O*CH$_3$*).

MS (EI) [*m/z* (% relative intensity)]: 305 (M$^+$+H, 21), 195 (100).

Anal Calcd for $C_{16}H_{16}SO_4$: C, 63.14; H, 5.30; found: C, 63.21; H, 5.64.

Bis(2,4,5-trimethoxyphenyl)methanone (105a)



105a

Compound **105a**: A pale yellow solid, m.p. 152.2–152.5 °C; R$_f$ 0.29 (60% EtOAc/hexanes).

IR (nujol, cm^{-1}): $\nu_{\max}$ 1605 (C=O).

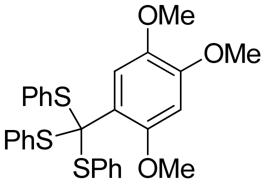
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.14 (s, 2H, Ar*H*), 6.50 (s, 2H, Ar*H*), 3.95 (s, 6H, 2×O*CH*$_3$), 3.87 (s, 6H, 2×O*CH*$_3$), 3.64 (s, 6H, 2×O*CH*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ 192.7 (*C*=O), 154.0 (2×*C*$_q$), 152.5 (2×*C*$_q$), 142.8 (2×*C*$_q$), 122.3 (2×*C*$_q$), 113.2 (2×*CH*), 97.2 (2×*CH*), 56.8 (2×O*CH*$_3$), 56.3 (2×O*CH*$_3$), 56.0 (2×O*CH*$_3$).

MS (EI) [*m/z* (% relative intensity)]: 363 (M$^+$+H, 20), 362 (100).

HRMS (ESI) Calcd for $C_{19}H_{22}O_7Na$ [M+Na]$^+$, 385.1257; found, 385.1259.

1-(Triphenylsulfanylmethyl)-2,4,5-trimethoxybenzene (241a)



241a

Compound **241a**: A pale yellow liquid; R$_f$ 0.21 (20% EtOAc/hexanes).

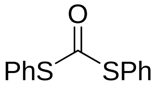
IR (neat, cm^{-1}): ν_{max} 3062, 3004, 1607, 1582, 1509, 1026.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.26–7.08 (m, 15H, 3×S*Ph*), 6.85 (s, 1H, Ar*H*), 6.62 (s, 1H, Ar*H*), 4.07 (s, 3H, O*CH*$_3$), 3.91 (s, 3H, O*CH*$_3$), 3.20 (s, 3H, O*CH*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ 152.0 (*C*$_q$), 149.6 (*C*$_q$), 141.3 (*C*$_q$), 134.2 (3×*C*$_q$), 133.9 (6×*CH*), 127.9 (6×*CH*), 127.8 (3×*CH*), 118.7 (*C*$_q$), 116.1 (*CH*), 99.1 (*CH*), 75.7 (*C* in (*SPh*)$_3$), 57.3 (O*CH*$_3$), 56.0 (O*CH*$_3$), 55.9 (O*CH*$_3$).

HRMS (ESI) Calcd for $C_{28}H_{26}S_3O_3Na$ [M+Na]$^+$, 529.6890; found, 529.0864.

***S,S*-Diphenyl carbonodithioate (242)**



242

Compound **242**: A pale yellow liquid; R$_f$ 0.29 (5% EtOAc/hexanes).

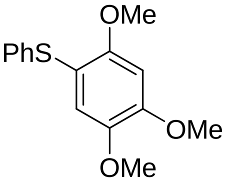
IR (neat, cm^{-1}): ν_{max} 1711 (C=O).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53−7.49 (m, 4H, Ar*H*), 7.43−7.37 (m, 6H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1 (*C*=O), 135.1 (2×*CH*), 130.0 (*CH*), 129.2 (2×*CH*), 127.1 (C_q).

HRMS (ESI) Calcd for $C_{13}H_{10}S_2ONa$ $[M+Na]^+$, 269.0071; found, 269.0016.

Phenyl(2,4,5-trimethoxyphenyl)sulfane (243a)



243a

Compound **243a**: A colorless liquid; R_f 0.28 (20% EtOAc/hexanes).

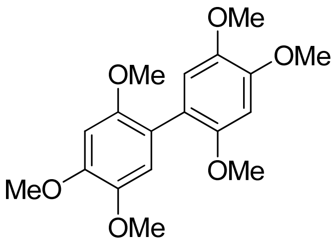
IR (KBr, cm^{-1}): ν_{max} 3059 and 3018 (C–H of aromatic), 1601, 1582, and 1508 (aromatic), and 1214 (C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.23 (m, 2 H), 7.10–7.20 (m, 3 H), 6.97 (s, 1 H), 6.62 (s, 1H), 3.96 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0 (C), 150.7 (C), 143.5 (C), 137.6 (C), 128.7 (2×CH), 127.7 (2×CH), 125.5 (CH), 125.5 (C), 118.6 (CH), 98.2 (CH), 56.9 (OCH_3), 56.5 (OCH_3), 56.1 (OCH_3).

HRMS (ESI-TOF) *m*/*z* $[(M+Na)^+]$ calcd for $C_{15}H_{16}O_3SNa$: 299.0718; found: 299.0701.

2,2',4,4',5,5'-Hexamethoxybiphenyl (290)



Compound **290**: A white solid, m.p. 175.2–177.0 °C; R_f 0.29 (50% EtOAc/hexanes).

IR (KBr, cm^{-1}): ν_{max} 3100, and 3016 (C–H of aromatic), 1608, 1512, and 1464 (aromatic), 1212 (C–O).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 2H, Ar*H*), 6.55 (s, 2H, Ar*H*), 3.95 (s, 6H, 2×O*CH*$_3$), 3.87 (s, 6H, 2×O*CH*$_3$), 3.78 (s, 6H, 2×O*CH*$_3$).

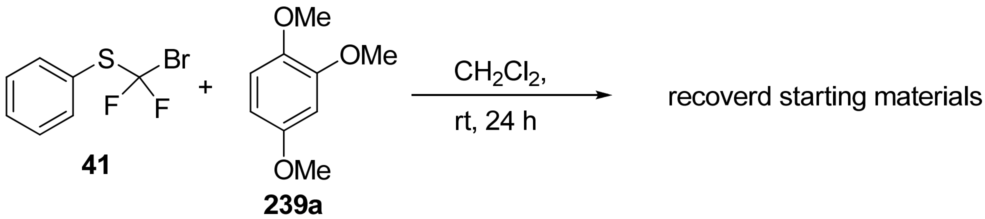
^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2 (2×C_q), 148.8 (2×C_q), 142.9 (2×C_q), 119.0 (2×C_q), 115.4 (2×*CH*), 98.5 (2×*CH*), 56.8 (2×O*CH*$_3$), 56.5 (2×O*CH*$_3$), 56.0 (2×O*CH*$_3$).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{18}H_{22}O_6Na$: 357.1314; found: 357.1319.

4.5 Investigation of the reaction mechanism of the reaction of bromodifluoromethyl phenyl sulfide (41) and 1,2,4-trimethoxybenzene (239a) mediated by Lewis acids

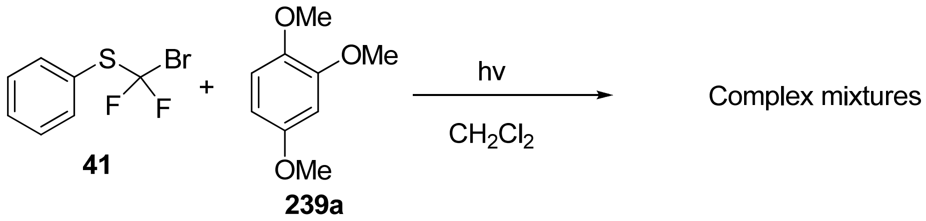
4.5.1 investigation of the electron transfer process (SET)

4.5.1.1 General procedure for the reaction of bromodifluoro(phenylsulfanyl)methane (**41**) and 1,2,4-trimethoxybenzene (**239a**) in the absence of a Lewis acid



In a round-bottomed flask equipped with a stirring bar and rubber septum was placed PhSCF$_2$Br (**41**) (358.4 mg, 1.5 mmol). After the reaction flask was evacuated and flushed with argon gas for three times, anhydrous CH$_2$Cl$_2$ (5.0 mL) was added followed by adding 1,2,4-trimethoxybenzene (**239a**) (126.1 mg, 0.75 mmol). The reaction mixture was allowed to proceed at room temperature for 24 h before it was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (3×50 mL), brine (10 mL), dried (anhydrous MgSO$_4$) and filtered. The filtrate was evaporated (aspirator) to give a crude product, which was purified by column chromatography affording recovered starting material **239a** (123.6 mg, 98% yield), and **41** (340.5 mg, 95% yield).

4.5.1.2 General procedure for the reaction of bromodifluoro(phenylsulfanyl)methane (**41**) and 1,2,4-trimethoxybenzene (**239a**) under photochemical reaction conditions



A 1 L Hanovia photochemical reactor equipped with a 450 W medium-pressure Hg lamp was changed with a solution of bromodifluoro(phenylsulfanyl)methane (**41**) (358.4 mg, 1.5 mmol) and 1,2,4-trimethoxybenzene (**239a**) (126.1 mg, 0.75 mmol) in CH$_2$Cl$_2$ (1.0 L) under argon atmosphere. After 1 h of irradiation, The reaction mixture was evaporated (aspirator) to give a crude product as a complex mixture which was analyzed by means of TLC and ^{1}H NMR analyses.

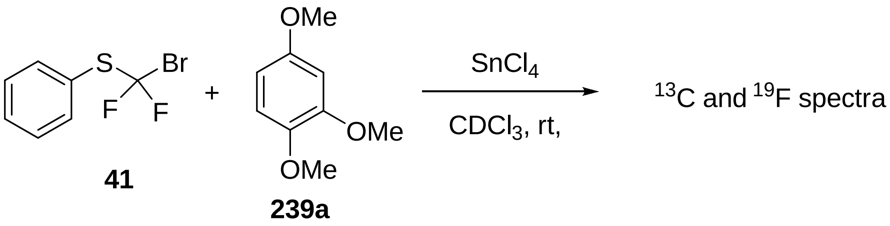
4.5.2 NMR experiments

4.5.2.1 General procedure for the reaction of bromodifluoro(phenylsulfanyl)methane (**41**) in the presence of $SnCl_4$ in $CDCl_3$

$$\underset{\textbf{41}}{\mathrm{PhSCF_2Br}} \xrightarrow[\mathrm{CDCl_3}]{\mathrm{SnCl_4}} {}^{13}\mathrm{C}\text{ and }{}^{19}\mathrm{F}\text{ spectra}$$

In a round-bottomed flask equipped with a stirring bar and rubber septum was placed $PhSCF_2Br$ (**41**) (477.8 mg, 2.0 mmol). After the reaction flask was evacuated and flushed with argon gas for three times, anhydrous $CDCl_3$ (3.0 mL) was added followed by adding a 1 M solution of $SnCl_4$ (4.0 mL, 4.0 mmol) in $CDCl_3$. The reaction mixture was sampled to NMR tube and determined by ^{13}C and ^{19}F NMR spectroscopy as time indicated.

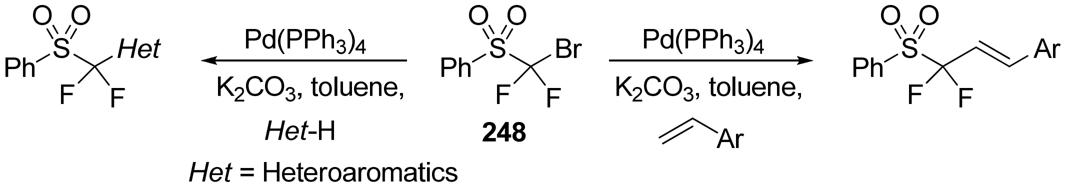
4.5.2.1 General procedure for the reaction of bromodifluoro(phenylsulfanyl)methane (**41**) and 1,2,4-trimethoxybenzene (**239a**) in the presence of $SnCl_4$ in $CDCl_3$



41 **239a**

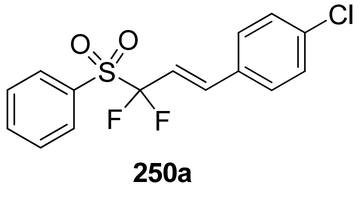
In a round-bottomed flask equipped with a stirring bar and rubber septum was placed $PhSCF_2Br$ (**41**) (358.4 mg, 2.0 mmol) and 1,2,4-trimethoxybenzene (**239a**) (168.1 mg, 1.0 mmol). After the reaction flask was evacuated and flushed with argon gas for three times, anhydrous $CDCl_3$ (3.0 mL) was added followed by adding a 1 M solution of $SnCl_4$ (4.0 mL, 4.0 mmol) in $CDCl_3$. The reaction mixture was sampled to NMR tube and determined by ^{13}C and ^{19}F NMR spectroscopy as time indicated.

4.6 General procedure for palladium-mediated Heck-type reaction of [(bromodifluoromethyl)sulfonyl]benzene (248)



An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol-%), [(bromodifluoromethyl)sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.), and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of styrene derivative (or heteroaromatic) (1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 °C with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography to yield the *gem*-difluorinated compound.

(*E*)-1-Chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (250a)



250a

Compound **250a** was prepared by the general procedure from 4-chlorostyrene (**249a**) (207.9 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.8:0.2) gave the title compound. (*E*)-1-Chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (**250a**) (98.6 mg, 60% yield) was obtained as a white solid, m.p. = 103.0–104.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.8:0.2, $R_f = 0.25$.

IR (KBr, cm^{-1}): ν_{max} 3031 (C–H of aromatic), 1650 (C=C), 1589, 1493, and 1449 (aromatic), 1343 and 1163 (SO_2), 1077 (C–F).

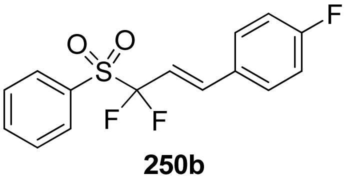
^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 7.6$ Hz, 2 H), 7.80 (m, 1 H), 7.65 (m, 2 H), 7.45 (m, 2 H), 7.40 (m, 2 H), 7.18 (dt, $J = 16.2, 2.2$ Hz, 1 H), 6.39 (dt, $J = 16.2, 11.8$ Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 140.9$ (t, $J_{CF} = 8.7$ Hz, CH), 136.3 (C), 135.3 (CH), 132.8 (C), 132.0 (C), 130.8 (2×CH), 129.3 (2×CH), 129.2 (2×CH), 129.0 (2×CH), 121.3 (t, $J_{CF} = 281.7$ Hz, CF_2), 113.0 (t, $J_{CF} = 22.2$ Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -101.29$ (d, $J_{FH} = 11.7$ Hz, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{15}H_{11}ClF_2O_2SNa$: 351.0034; found: 351.0072.

(*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-fluorobenzene (250b)



250b

Compound **250b** was prepared by the general procedure from 4-fluorostyrene (**249b**) (183.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.8:0.2) gave the title compound. (*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-fluorobenzene (**250b**) (84.2 mg, 54% yield) was obtained as a white solid, m.p. = 107.0–109.1 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.8:0.2, $R_f = 0.22$.

IR (KBr, cm^{-1}): ν_{max} 3058 (C–H of aromatic), 1650 (C=C), 1600, 1578, and 1509 (aromatic), 1341 and 1240 (SO_2), 1090 (C–F).

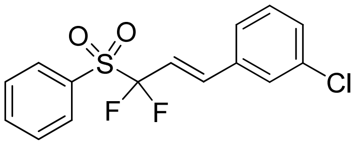
^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.5 Hz, 2 H), 7.79 (m, 1 H), 7.66 (m, 2 H), 7.50 (m, 2 H), 7.19 (dt, J = 16.2, 2.1 Hz, 1 H), 7.11 (m, 2 H), 6.34 (dt, J = 16.3, 11.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7 (d, J_{CF} = 212.5 Hz, CF), 141.0 (t, J_{CF} = 9.0 Hz, CH), 135.3 (CH), 132.9 (C), 130.8 (2×CH), 129.8 (C), 129.7 (d, J_{CF} = 8.6 Hz , 2×CH), 129.2 (2×CH), 121.4 (t, J_{CF} = 281.7 Hz, CF_2), 116.1 (d, J_{CF} = 21.9 Hz, 2×CH), 112.1 (t, J_{CF} = 22.5 Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.15 (d, J_{FH} = 11.8 Hz, CF_2), -109.36 (quin, J_{FH} = 8.5, 4.7 Hz, CF).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{15}H_{11}F_3O_2SNa$: 335.0330; found: 335.0280.

(*E*)-1-Chloro-3-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (250c)



250c

Compound **250c** was prepared by the general procedure from 3-chlorostyrene (**249c**) (207.9 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.8:0.2) gave the title compound. (*E*)-1-Chloro-3-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (**250c**) (65.7 mg, 40% yield) was obtained as a white solid, m.p. = 85.5–86.5 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.8:0.2, R_f = 0.25.

IR (KBr, cm^{-1}): ν_{max} 3077 (C–H of aromatic), 1652 (C=C), 1566, 1473, and 1449 (aromatic), 1345 and 1169 (SO_2), 1093 (C–F).

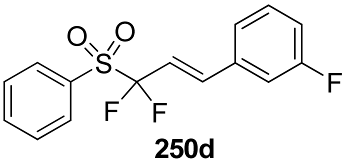
^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.5 Hz, 2 H), 7.80 (m, 1 H), 7.66 (t, J = 7.7 Hz, 2 H), 7.50 (s, 1 H), 7.42–7.34 (m, 3 H), 7.17 (dt, J = 16.2, 2.2 Hz, 1 H), 6.44 (dt, J = 16.2, 11.7 Hz, 1 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 140.8 (t, J_{CF} = 9.0 Hz, CH), 135.38 (C), 135.36 (CH), 135.0 (C), 132.9 (C), 130.8 (2×CH), 130.3 (CH), 130.2 (CH), 129.3 (2×CH), 127.7 (CH), 126.0 (CH), 121.2 (t, J_{CF} = 281.8 Hz, CF$_2$), 114.1 (t, J_{CF} = 22.2 Hz, CH).

^{19}F NMR (470 MHz, CDCl$_3$): δ = -101.49 (d, J_{FH} = 11.7 Hz, CF$_2$).

HRMS (ESI-TOF) *m/z* [(M + Na)$^+$] calcd for $C_{15}H_{11}ClF_2O_2SNa$: 351.0034; found: 351.0111.

(*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-3-fluorobenzene (250d)



250d

Compound **250d** was prepared by the general procedure from 3-fluorostyrene (**249d**) (183.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.8:0.2) gave the title compound. (*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-3-fluorobenzene (**250d**) (39.0 mg, 25% yield) was obtained as a white solid, m.p. = 104.0-105.1 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.8:0.2, R$_f$ = 0.25.

IR (KBr, cm^{-1}): ν_{max} 3089 and 3066 (C–H of aromatic), 1650 (C=C), 1585, 1486, and 1449 (aromatic), 1337 and 1170 (SO$_2$), 1098 (C–F).

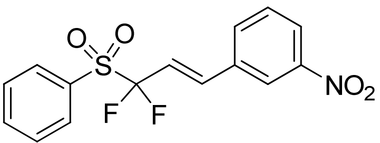
^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.02 (d, J = 7.8 Hz, 2 H), 7.78 (m, 1 H), 7.64 (t, J = 7.8 Hz, 2 H), 7.38 (m, 1 H), 7.27 (d, J = 8.3 Hz, 1 H), 7.18 (br s, 1 H), 7.15–7.07 (m, 3 H), 6.39 (dt, J = 16.2, 11.7 Hz, 1 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 163.0 (d, J_{CF} = 245.5 Hz, CF), 141.0 (t, J_{CF} = 8.8 Hz, CH), 135.7 (d, J_{CF} = 7.8 Hz, C), 135.3 (CH), 132.8 (C), 130.8 (2×CH), 129.3 (2×CH), 123.8 (CH), 121.2 (t, J_{CF} = 282.1 Hz, CF$_2$), 117.2 (d, J_{CF} = 21.1 Hz, CH), 114.3 (d, J_{CF} = 22.1 Hz, CH), 114.0 (t, J_{CF} = 22.1 Hz, CH).

^{19}F NMR (470 MHz, CDCl$_3$): δ = -101.48 (d, J_{FH} = 11.7 Hz, CF$_2$), -112.23 (q, J_{FH} = 8.9, 8.4, 6.1 Hz, CF).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{15}H_{11}F_3O_2SNa$: 335.0330; found: 335.0389.

(*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-3-nitrobenzene (250e)



250e

Compound **250e** was prepared by the general procedure from 3-nitrostyrene (**249e**) (223.7 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 8.5:1.5) gave the title compound. (*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-3-nitrobenzene (**250e**) (13.6 mg, 8% yield) was obtained as a yellow solid, m.p. = 154.2–155.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 8.5:1.5, $R_f = 0.20$.

IR (KBr, cm^{-1}): ν_{max} 3090 (C–H of aromatic), 1650 (C=C), 1528, 1478, and 1448 (aromatic), 1357 and 1160 (SO_2), 1113 (C–F).

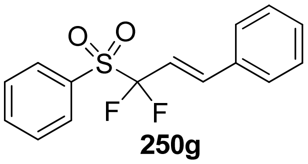
^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.36$ (t, $J = 1.8$ Hz, 1 H), 8.26 (dd, $J = 8.1, 1.4$ Hz, 1 H), 8.03 (d, $J = 7.5$ Hz, 2 H), 7.81–7.77 (m, 2 H), 7.66 (m, 2 H), 7.61 (t, $J = 8.1$ Hz, 1 H), 7.28 (dt, $J = 16.2, 2.1$ Hz, 1 H), 6.55 (dt, $J = 16.2, 11.5$ Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 148.7$ (C), 139.7 (t, $J_{CF} = 8.5$ Hz, CH), 135.5 (CH), 135.2 (C), 133.3 (CH), 132.6 (C), 130.8 (2×CH), 130.0 (CH), 129.4 (2×CH), 124.7 (CH), 122.4 (CH), 120.9 (t, $J_{CF} = 282.5$ Hz, CF_2), 116.1 (t, $J_{CF} = 22.3$ Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -101.67$ (d, $J_{FH} = 11.2$ Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{15}H_{11}F_2NO_4SNa$: 362.0275; found: 362.0327.

(*E*)-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (250g)



250g

Compound **250g** was prepared by the general procedure from styrene (**249g**) (156.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. (*E*)-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (**250g**) (60.0 mg, 41% yield) was obtained as a white solid, m.p. = 112.8–114.4 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R_f = 0.22.

IR (KBr, cm^{-1}): ν_{max} 3071 (C–H of aromatic), 1649 (C=C), 1580, 1499, and 1447 (aromatic), 1338 and 1165 (SO_2), 1092 (C–F).

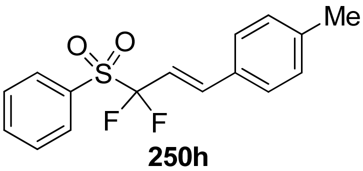
^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.7 Hz, 2 H), 7.79 (m, 1 H), 7.65 (m, 2 H), 7.51 (m, 2 H), 7.42 (m, 3 H), 7.22 (dt, J = 16.2, 2.2 Hz, 1 H), 6.42 (dt, J = 16.2, 11.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3 (t, J_{CF} = 8.5 Hz, CH), 135.2 (CH), 133.5 (C), 132.9 (C), 130.8 (2×CH), 130.3 (CH), 129.2 (2×CH), 128.9 (2×CH), 127.8 (2×CH), 121.5 (t, J_{CF} = 282.0 Hz, CF_2), 112.3 (t, J_{CF} = 22.2 Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.24 (d, J_{FH} = 11.7 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{15}H_{12}F_2O_2SNa$: 317.0424; found: 317.0448.

(*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-methylbenzene (250h)



250h

Compound **250h** was prepared by the general procedure from 4-methylstyrene (**249h**) (177.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. (*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-methylbenzene (**250h**) (80.0 mg, 52% yield) was obtained as a white solid, m.p. = 130.7–132.6 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.25$.

IR (KBr, cm^{-1}): ν_{max} 3071 (C–H of aromatic), 2923 (C–H of aliphatic), 1645 (C=C), 1606, 1514, and 1450 (aromatic), 1334 and 1164 (SO_2), 1075 (C–F).

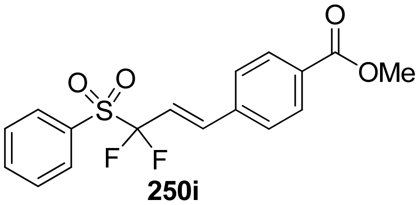
^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.7 Hz, 2 H), 7.78 (m, 1 H), 7.64 (t, J = 7.6 Hz, 2 H), 7.40 (d, J = 8.1 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.17 (dt, J = 16.2, 2.0 Hz, 1 H), 6.35 (dt, J = 16.1, 12.0 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.2 (t, J_{CF} = 8.8 Hz, CH), 140.7 (C), 135.1 (CH), 133.0 (C), 130.8 (C), 130.7 (2×CH), 129.6 (2×CH), 129.2 (2×CH), 127.8 (2×CH), 121.7 (t, J_{CF} = 281.2 Hz, CF_2), 111.1 (t, J_{CF} = 22.0 Hz, CH), 21.4 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.04 (d, J_{FH} = 11.7 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{16}H_{14}F_2O_2SNa$: 331.0580; found: 331.0605.

(*E*)-Methyl 4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzoate (250i)



250i

Compound **250i** was prepared by the general procedure from methyl 4-vinylbenzoate (**249i**) (243.0 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 8:2) gave the title compound. (*E*)-Methyl 4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzoate (**250i**) (29.6 mg, 17% yield) was obtained as a white solid, m.p. = 126.0–127.3 °C: analytical TLC on silica gel: hexanes/EtOAc = 8:2, $R_f = 0.27$.

IR (KBr, cm^{-1}): ν_{max} 3066 (C–H of aromatic), 2958 (C–H of aliphatic), 1720 (C=O), 1646 (C=C), 1449, 1432, and 1415 (aromatic), 1334 and 1162 (SO_2), 1095 (C–O), 1004 (C–F).

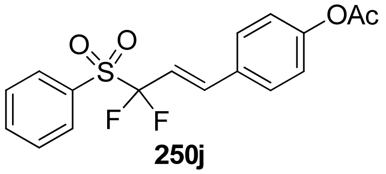
^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.3 Hz, 2 H), 8.04 (d, J = 7.6 Hz, 2 H), 7.81 (m, 1 H), 7.66 (m, 2 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.26 (dt, J = 16.2, 2.2 Hz, 1 H), 6.52 (dt, J = 16.2, 11.8 Hz, 1 H), 3.78 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3 (C), 140.1 (t, J_{CF} = 9.0 Hz, CH), 137.7 (C), 135.3 (CH), 132.8 (C), 131.5 (C), 130.8 (2×CH), 130.1 (2×CH), 129.3 (2×CH), 127.7 (2×CH), 121.2 (t, J_{CF} = 281.7 Hz, CF_2), 115.1 (t, J_{CF} = 22.3 Hz, CH), 52.2 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.53 (d, J_{FH} = 11.7 Hz, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{17}H_{14}F_2O_4SNa$: 375.0479; found: 375.0531.

(*E*)-4-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]phenyl acetate (250j)



250j

Compound **250j** was prepared by the general procedure from 4-vinylphenyl acetate (**249j**) (243.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 8.2:1.8) gave the title compound. (*E*)-4-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]phenyl acetate (**250j**) (30.0 mg, 17% yield) was obtained as a yellow solid, m.p. = 112.0–113.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 8.2:1.8, R_f = 0.20.

IR (KBr, cm^{-1}): ν_{max} 3071 (C–H of aromatic), 1759 (C=O), 1649 (C=C), 1601, 1508, and 1447 (aromatic), 1334 and 1167 (SO_2), 1204 (C–O), 1087 (C–F).

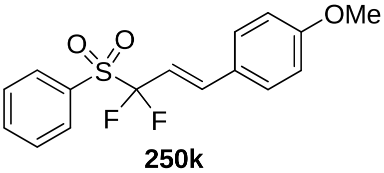
^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.6 Hz, 2 H), 7.78 (m, 1 H), 7.64 (m, 2 H), 7.52 (d, J = 8.6 Hz, 2 H), 7.21–7.13 (m, 3 H), 6.37 (dt, J = 16.1, 11.9 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C=O), 152.1 (C), 141.1 (t, J_{CF} = 8.8 Hz, CH), 135.1 (CH), 132.8 (C), 131.2 (C), 130.7 (2×CH), 129.2 (2×CH), 128.9 (2×CH), 122.1 (2×CH), 121.4 (t, J_{CF} = 281.7 Hz, CF_2), 112.6 (t, J_{CF} = 22.1 Hz, CH), 21.0 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.37 (d, J_{FH} = 11.2 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{17}H_{14}F_2O_4SNa$: 375.0479; found: 375.0503.

(*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-methoxybenze-ne (250k)



250k

Compound **250k** was prepared by the general procedure from 1-methoxy-4-vinylbenzene (**249k**) (201.3 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 8:2) gave the title compound. (*E*)-1-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]-4-methoxybenzene (**250k**) (25.9 mg, 16% yield) was obtained as a white solid, m.p. = 130.0–131.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 8:2, R_f = 0.30.

IR (KBr, cm^{-1}): ν_{max} 3078 (C–H of aromatic), 2937 (C–H of aliphatic), 1646 (C=C), 1605, 1514, and 1449 (aromatic), 1333 and 1161 (SO_2), 1086 (C–O) 1036 (C–F).

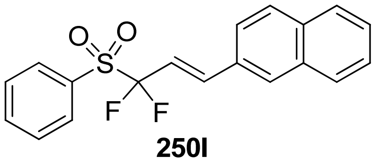
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.2 Hz, 2 H), 7.77 (m, 1 H), 7.64 (m, 2 H), 7.46 (m, 2 H), 7.15 (dt, *J* = 16.1, 2.1 Hz, 1 H), 6.93 (m, 2 H), 6.25 (dt, *J* = 16.2, 12.0 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3 (C), 141.7 (t, J_{CF} = 8.6 Hz, CH), 135.1 (CH), 133.2 (C), 130.7 (2×CH), 129.5 (2×CH), 129.2 (2×CH), 126.4 (C), 121.8 (t, J_{CF} = 281.5 Hz, CF_2), 114.3 (2×CH), 109.6 (t, J_{CF} = 22.0 Hz, CH), 55.3 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -100.70 (d, J_{FH} = 12.2 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{16}H_{14}F_2O_3SNa$: 347.0529; found: 347.0606.

(*E*)-2-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-enyl]naphthalene (250l)



250l

Compound **250l** was prepared by the general procedure from 2-vinylnaphthalene (**249l**) (231.3 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. (*E*)-2-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-enyl]naphthalene (**250l**) (29.2 mg, 17% yield) was obtained as a yellow solid, m.p. = 135.5–137.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R_f = 0.25.

IR (nujol-mull, cm^{-1}): ν_{max} 3061 (C–H of aromatic), 1644 (C=C), 1583, and 1450 (aromatic), 1343 and 1164 (SO_2), 1072 (C–F).

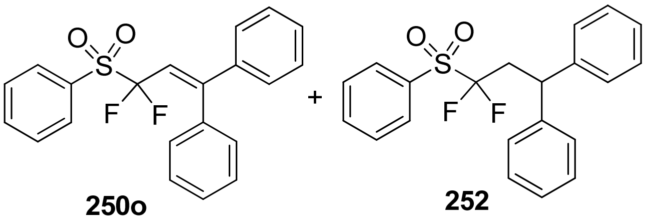
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.3 Hz, 2 H), 7.88–7.82 (m, 4 H), 7.76 (m, 1 H), 7.65–7.61 (m, 3 H), 7.51 (m, 2 H), 7.35 (dt, *J* = 16.1, 2.1 Hz, 1 H), 6.50 (dt, *J* = 16.1, 11.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.3 (t, J_{CF} = 9.0 Hz, CH), 135.2 (CH), 134.2 (C), 133.2 (C), 133.1 (C), 131.0 (C), 130.8 (2×CH), 129.6 (CH), 129.2 (2×CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH), 126.7 (CH), 123.2 (CH), 121.6 (t, J_{CF} = 281.7 Hz, CF_2), 112.5 (t, J_{CF} = 22.1 Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.08 (d, J_{FH} = 11.7 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{19}H_{14}F_2O_2SNa$: 367.0580; found: 367.0643.

[3,3-Difluoro-3-(phenylsulfonyl)prop-1-ene-1,1-diyl]dibenzene (250o) and [3,3-difluoro-3-(phenylsulfonyl)propane-1,1-diyl]dibenzene (252)



250o **252**

Compound **250o** and **252** were prepared by the general procedure from 1,1-diphenylethylene (**249o**) (270.0 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave an 1.2:1 inseparable mixture of **250o** and **252** (152.1 mg, 82% yield) as a white solid: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.25$.

IR (KBr, cm^{-1}): ν_{max} 3066, and 3028 (C–H of aromatic), 1619 (C=C), 1582, 1492, and 1448 (aromatic), 1333 and 1162 (SO_2), 1073 (C–F).

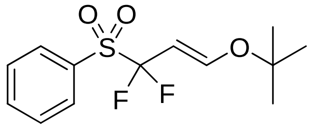
^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 7.5$ Hz, 4 H), 7.75 (m, 2 H), 7.60 (m, 4 H), 7.45–7.22 (m, 20 H), 6.37 (t, $J = 14.8$ Hz, 1 H), 4.52 (t, $J = 7.3$ Hz, 1 H), 3.26 (td, $J = 18.2$, 7.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 156.1$ (t, $J_{CF} = 4.5$ Hz, C), 142.8 (C), 140.5 (C), 137.2 (C), 135.2 (CH), 135.0 (CH), 133.0 (C), 132.0 (C), 130.7 (CH), 129.6 (CH), 129.2 (CH), 129.15 (CH), 129.13 (CH), 129.10 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.7 (CH), 124.1 (t, $J_{CF} = 287.5$ Hz, CF_2), 121.2 (t, $J_{CF} = 284.0$ Hz, CF_2), 110.6 (t, $J_{CF} = 19.6$ Hz, CH), 44.1 (CH), 34.1 (t, $J_{CF} = 18.7$ Hz, CH_2).

^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -94.39$ (d, $J_{FH} = 15.0$ Hz, CF_2), -102.06 (t, $J_{FH} = 18.3$ Hz, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{21}H_{16}F_2O_2SNa$: 393.0737; found: 393.0700, and *m/z* [$(M + Na)^+$] calcd for $C_{21}H_{18}F_2O_2SNa$: 395.0893; found: 395.0848.

(*E*)-(3-*tert*-Butoxy-1,1-difluoroallylsulfonyl)benzene (255a)



255a

Compound **255a** was prepared by the general procedure from *tert*-butylvinyl ether (**254a**) (500.8 mg, 5.0 mmol, 10 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. (*E*)-(3-*tert*-Butoxy-1,1-difluoroallylsulfonyl)benzene (**255a**) (65.8 mg, 45% yield) was obtained as a yellow liquid: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.25$.

IR (KBr, cm^{-1}): ν_{max} 3071 (C–H of aromatic), 2977 (C–H of aliphatic), 1657 (C=C), 1584, 1478, and 1449 (aromatic), 1337 and 1163 (SO_2), 1115 (C–O), 1070 (C–F).

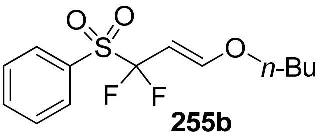
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05(d, J = 7.2 Hz, 2 H), 7.75 (m, 1 H), 7.61 (m, 2 H), 7.03 (dt, J = 12.1, 2.0 Hz, 1 H), 5.17 (td, J = 12.7, 12.2 Hz, 1 H), 1.35 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3 (t, J_{CF} = 10.2 Hz, CH), 134.8 (CH), 133.3 (C), 130.6 (2×CH), 129.1 (2×CH), 122.8 (t, J_{CF} = 280.6 Hz, CF_2), 91.7 (t, J_{CF} = 22.7 Hz, CH), 79.8 (C), 27.9 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -97.80 (d, J_{FH} = 12.7 Hz, CF_2).

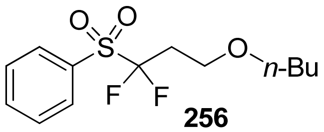
HRMS (APCI-TOF) *m*/*z* [(M + *t*BuOH) + H)$^+$] calcd for $C_{17}H_{27}F_2O_4S$: 365.1593; found: 365.1578.

(*E*)-(3-butoxy-1,1-difluoroallylsulfonyl)benzene (255b) and (3-butoxy-1,1-difluoropropylsulfonyl)benzene (256)



255b

\+



256

Compound **255b** and **256** were prepared by the general procedure from *n*-butylvinyl ether (**254b**) (150.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave an 2.3:1 inseparable mixture of **255b** and **256** (82.2 mg, 56% yield) as a yellow liquid: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.27$.

IR (neat, cm^{-1}): ν_{max} 3069 (C–H of aromatic), 2959, and 2933 (C–H of aliphatic), 1614 (C=C), 1584, 1478, and 1450 (aromatic), 1364 and 1134 (SO_2), 1113 (C–O), 1078 (C–F).

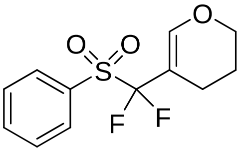
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 4 H), 7.88–7.60 (m, 6 H), 7.07 (dt, J = 12.7, 1.7 Hz, 1 H,), 5.04 (q, J = 12.4 Hz, 1 H), 3.88 (t, J = 6.5 Hz, 2 H), 3.77 (t, J = 6.8 Hz, 2 H), 3.46 (t, J = 6.5 Hz, 2 H), 2.66 (m, 2 H), 1.72(m, 2 H), 1.56 (m, 2 H), 1.43 (m, 2 H), 1.37 (m, 2 H), 0.97 (t, J = 7.4, 3 H), 0.92 (t, J = 7.4, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0 (t, J_{CF} = 10.2 Hz, CH), 135.3 (CH), 134.9 (CH), 133.1 (C), 132.2 (C), 130.7 (2×CH), 130.6 (2×CH), 129.2 (2×CH), 129.1 (2×CH), 123.7 (t, J_{CF} = 283.3 Hz, CF_2), 122.7 (t, J_{CF} = 280.0 Hz, CF_2), 88.9 (t, J_{CF} = 22.6 Hz, CH), 70.9 (CH_2), 70.6 (CH_2), 62.9 (t, J_{CF} = 4.0 Hz, CH_2), 31.6 (CH_2), 30.7 (CH_2), 30.0 (t, J_{CF} = 19.6 Hz, CH_2), 19.1 (CH_2), 18.9 (CH_2), 13.8 (CH_3), 13.6 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -97.92 (d, J_{FH} = 12.3 Hz, CF_2), -102.62 (t, J_{FH} = 17.8 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{13}H_{16}F_2O_3SNa$: 313.0686; found: 313.0621, and *m*/*z* [(M + Na)$^+$] calcd for $C_{13}H_{18}F_2O_3SNa$: 315.0842; found: 315.0777.

5-[Difluoro(phenylsulfonyl)methyl]-3,4-dihydro-2*H*-pyran (255c)



255c

Compound **255c** was prepared by the general procedure from 3,4-dihydro-2*H*-pyran (**254c**) (126.2 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. 5-[difluoro(phenylsulfonyl)methyl]-3,4-dihydro-2*H*-pyran (**255c**) (56.6 mg, 41% yield) was obtained as a white solid, m.p. = 85.8–86.9 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.20$.

IR (KBr, cm^{-1}): ν_{max} 3068 (C–H of aromatic), 2999, and 2923 (C–H of aliphatic), 1649 (C=C), 1581, 1475, and 1446 (aromatic), 1328 and 1164 (SO_2), 1087 (C–F).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01(m, 2 H), 7.76 (m, 1 H), 7.63 (m, 2 H), 6.98 (t, J = 1.4 Hz, 1 H), 4.11 (t, J = 5.3 Hz, 2 H), 2.41 (t, J = 6.2 Hz, 2 H), 1.97 (quin, J = 6.2, 5.3 Hz, 1 H).

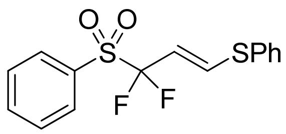
^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0 (t, J_{CF} = 10.6 Hz, CH), 134.8 (CH), 133.4 (C), 130.6 (2×CH), 129.1 (2×CH), 122.7 (t, J_{CF} = 283.6 Hz, CF_2), 100.6 (t, J_{CF} = 21.2 Hz, C), 66.4 (CH_2), 21.0 (CH_2), 19.0 (t, J_{CF} = 2.8 Hz, CH_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -101.79 (s, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{12}H_{12}F_2O_3SNa$: 297.0373; found: 297.0439.

(*E*)-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (*trans*-255g) and (*Z*)-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (*cis*-255g): Compound (***trans*-255g**) and (***cis*-255g**) was prepared by the general procedure from phenyl(vinyl)sulfane (**254g**) (204.3 mg, 1.5 mmol, 3 equiv.). The crude product was purified by preparative thin-layer chromatography (hexanes/EtOAc, 9.2:0.8) to give (*E*)-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (***trans*-255**g) (70.7 mg, 43% yield) as a yellow liquid and (*Z*)-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (***cis*-255g**) (43.3 mg, 26% yield) as a yellow liquid: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R_f = 0.25 and 0.17, respectively.

(*E*)-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (*trans*-255g)



trans-**255g**

IR (neat, cm^{-1}): ν_{max} 3062 (C–H of aromatic), 1600 (C=C), 1583, 1478, and 1448 (aromatic), 1338 and 1164 (SO_2), 1091 (C–F).

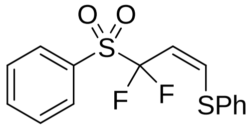
^1H NMR (500 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.76 (m, 1 H), 7.62 (m, 2 H), 7.51–7.43 (m, 5 H), 7.25 (dt, J = 15.2, 1.9 Hz, 1 H), 5.57 (dt, J = 15.2, 11.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.2 (t, J_{CF} = 9.0 Hz, CH), 135.1 (CH), 133.1 (C), 133.1 (2×CH), 130.7 (2×CH), 130.0 (C), 129.8 (2×CH), 129.3 (CH), 129.2 (2×CH), 120.9 (t, J_{CF} = 282.7 Hz, CF_2), 109.2 (t, J_{CF} = 23.5 Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -99.85 (d, J_{FH} = 12.2 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{15}H_{12}F_2O_2S_2Na$: 349.0144; found: 349.0013.

(*Z*)-[3,3-Difluoro-3-(phenylsulfonyl)prop-1-enyl](phenyl)sulfane (*cis*-255g)



cis-**255g**

IR (KBr, cm^{-1}): ν_{max} 3062 (C–H of aromatic), 1698 (C=C), 1478, and 1447 (aromatic), 1342 and 1155 (SO_2), 1085 (C–F).

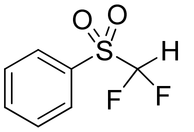
^1H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.4 Hz, 2 H), 7.78 (m, 1 H), 7.65 (m, 2 H), 7.44–7.36 (m, 5 H), 7.15 (dt, J = 11.1, 2.7 Hz, 1 H), 5.75 (td, J = 15.5, 11.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1 (t, J_{CF} = 4.8 Hz, CH), 135.2 (CH), 134.2 (t, J_{CF} = 2.7 Hz, C), 133.0 (C), 131.2 (2×CH), 130.9 (2×CH), 129.4 (2×CH), 129.2 (2×CH), 128.4 (CH), 121.8 (t, J_{CF} = 283.8 Hz, CF_2), 109.2 (t, J_{CF} = 23.2 Hz, CH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -99.83 (d, J_{FH} = 15.0 Hz, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{15}H_{12}F_2O_2S_2Na$: 349.0144; found: 349.0189.

(Difluoromethylsulfonyl)benzene (251)



251

IR (KBr, cm^{-1}): ν_{max} 3070 (C–H of aromatic), 2989, and 2927 (C–H of aliphatic), 1584, 1490, and 1449 (aromatic), 1349 and 1163 (SO_2), 1078 (C–F).

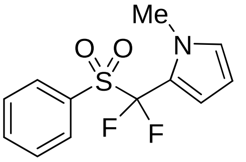
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.8 Hz, 2 H), 7.82 (m, 1 H), 7.68 (m, 2 H), 6.22 (t, J_{HF} = 53.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.7 (CH), 131.7 (C), 130.6 (2×CH), 129.5 (2×CH), 114.6 (t, J_{CF} = 284.0 Hz, CF_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -121.6 (d, J_{FH} = 53.1 Hz, CF_2H).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_7H_6F_2O_2SNa$: 214.9954; found: 214.9923.

2-[Difluoro(phenylsulfonyl)methyl]-1-methyl-1*H*-pyrrole (258a)



258a

Compound **258a** was prepared by the general procedure from 1-methyl-1*H*-pyrrole (**257a**) (121.7 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 8.5:1.5) gave the title compound. 2-[Difluoro(phenylsulfonyl)methyl]-1-methyl-1*H*-pyrrole (**258a**) (99.1 mg, 73% yield) was obtained as a yellow solid, m.p. = 102.9–104.0 °C: analytical TLC on silica gel: hexanes/EtOAc = 8.5:1.5, $R_f = 0.27$.

IR (KBr, cm^{-1}): ν_{max} 3130, and 3093 (C–H of aromatic), 1581, 1534, and 1485 (aromatic), 1337 and 1162 (SO_2), 1065 (C–F).

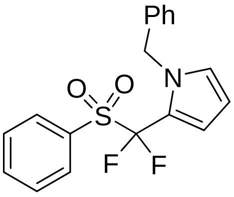
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.76 (m, 1 H), 7.62 (m, 2 H), 6.81 (t, J = 2.2 Hz, 1 H), 6.57 (m, 1 H), 6.18 (m, 1 H), 3.86 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.0 (CH), 133.1 (C), 132.8 (C), 130.6 (2×CH), 129.2 (CH), 129.1 (2×CH), 120.0 (t, J_{CF} = 282.3 Hz, CF_2), 116.7 (t, J_{CF} = 24.6 Hz, C), 116.4 (t, J_{CF} = 4.8 Hz, CH), 108.3 (CH), 36.0 (CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -96.8 (s, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{12}H_{11}F_2NO_2SNa$: 294.0376; found: 294.0362.

1-Benzyl-2-[difluoro(phenylsulfonyl)methyl]-1*H*-pyrrole (258b)



258b

Compound **258b** was prepared by the general procedure from 1-benzyl-1*H*-pyrrole (**257b**) (235.8 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. 1-Benzyl-2-[difluoro(phenylsulfonyl)methyl]-1*H*-pyrrole (**258b**) (119.8 mg, 69% yield) was obtained as a brown solid, m.p. = 75.7–76.8 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.30$.

IR (KBr, cm^{-1}): ν_{max} 3127, and 3060 (C–H of aromatic), 1584, 1536, 1487, and 1446 (aromatic), 1325 and 1159 (SO_2), 1016 (C–F).

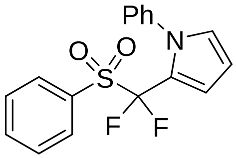
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.0 (d, J = 7.5 Hz, 2 H), 7.77 (m, 1 H), 7.62 (m, 2 H), 7.38–7.30 (m, 3 H), 7.16 (d, J = 7.1 Hz, 2 H), 6.84 (t, J = 2.2 Hz, 1 H), 6.64 (m, 1 H), 6.26 (m, 1 H), 5.40 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.4 (C), 135.0 (CH), 133.1 (C), 130.7 (2×CH), 129.2 (CH), 128.7 (2×CH), 128.4 (CH), 127.7 (CH), 127.1 (2×CH), 120.0 (t, J_{CF} = 282.8 Hz, CF_2), 117.0 (t, J_{CF} = 29.6 Hz, C), 116.5 (t, J_{CF} = 4.8 Hz, CH), 109.1 (CH), 52.3 (CH_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -95.85 (s, CF_2).

HRMS (ESI-TOF) *m/z* [$(M + Na)^+$] calcd for $C_{18}H_{15}F_2NO_2SNa$: 370.0689; found: 370.0667.

2-[Difluoro(phenylsulfonyl)methyl]-1-phenyl-1*H*-pyrrole (258c)



258c

Compound **258c** was prepared by the general procedure from 1-phenyl-1*H*-pyrrole (**257c**) (214.8 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. 2-[Difluoro(phenylsulfonyl)methyl]-1-phenyl-1*H*-pyrrole (**258c**) (63.0 mg, 38% yield) was obtained as a white solid, m.p. = 117.4–118.5 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R_f = 0.30.

IR (KBr, cm^{-1}): ν_{max} 3123, and 3104 (C–H of aromatic), 1596, 1531, 1496, and 1448 (aromatic), 1341 and 1169 (SO_2), 1073 (C–F).

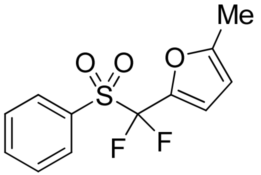
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.8 Hz, 2 H), 7.69 (m, 1 H), 7.53 (m, 2 H), 7.41 (m, 5 H), 6.93 (t, J = 2.1 Hz, 1 H), 6.83 (m, 1 H), 6.36 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.6 (C), 134.9 (CH), 133.1 (C), 130.7 (2×CH), 129.8 (t, J_{CF} = 1.8 Hz, CH), 129.0 (2×CH), 128.5 (CH), 128.4 (2×CH), 127.7 (2×CH), 119.7 (t, J_{CF} = 284.0 Hz, CF_2), 117.7 (t, J_{CF} = 27.8 Hz, C), 117.2 (t, J_{CF} = 5.6 Hz, CH), 109.3 (CH).

^{19}F NMR (470 MHz, CDCl$_3$): δ = -92.60 (s, CF$_2$).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{17}H_{13}F_2NO_2SNa$: 356.0533; found: 356.0550.

2-[Difluoro(phenylsulfonyl)methyl]-5-methylfuran (258d)



258d

Compound **258d** was prepared by the general procedure from 2-methylfuran (**257d**) (410.5 mg, 5.0 mmol, 10 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. 2-[difluoro(phenylsulfonyl)methyl]-5-methylfuran (**258d**) (39.3 mg, 29% yield) was obtained as a yellow solid, m.p. = 83.8–85.4 °C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R$_f$ = 0.17.

IR (KBr, cm^{-1}): ν_{max} 3132 (C–H of aromatic), 1580, 1546, and 1448 (aromatic), 1343, and 1171 (SO$_2$), 1124 (C–O), 1081 (C–F).

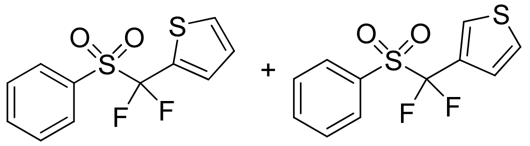
^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.01 (m, 2 H), 7.79 (m, 1 H), 7.64 (m, 2 H), 6.86 (m, 1 H), 6.16 (m, 1 H), 2.37 (m, 3 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 157.2 (C), 137.5 (t, J_{CF} = 28.9 Hz, C), 135.2 (CH), 132.9 (C), 130.7 (2×CH), 129.2 (2×CH), 117.3 (t, J_{CF} = 282.7 Hz, CF$_2$), 117.1 (t, J_{CF} = 3.1 Hz, CH), 107.8 (CH), 13.6 (CH$_3$).

^{19}F NMR (470 MHz, CDCl$_3$): δ = -102.15 (s, CF$_2$).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{12}H_{10}F_2O_3SNa$: 295.0216; found: 295.0177.

2-[Difluoro(phenylsulfonyl)methyl]thiophene (258e) and 3-[difluoro-(phenylsulfonyl)-methyl]thiophene (258e′)



258e **258e'**

Compound **258e** and **258e′** were prepared by the general procedure from thiophene (**257e**) (841.4 mg, 10.0 mmol, 10 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave an 5.2:1 inseparable mixture of **258e**and **258e′** (85.0 mg, 31% yield) as a yellow solid: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, R_f = 0.25.

IR (KBr, cm^{-1}): ν_{max} 3113, and 3065 (C–H of aromatic), 1581, 1526, and 1447 (aromatic), 1339 and 1170 (SO_2), 1094 (C–F).

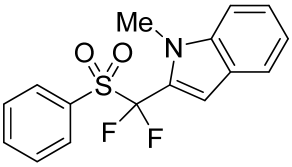
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (m, 4 H), 7.82–7.77 (m, 2 H), 7.67–7.62 (m, 6 H), 7.57 (m, 1 H), 7.47 (m, 1 H), 7.34 (dd, J = 5.2, 1.3 Hz, 1 H), 7.19 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.3 (CH), 135.2 (CH), 132.7 (C), 132.5 (C), 131.9 (t, J_{CF} = 5.0 Hz, CH), 131.4 (CH), 130.9 (2×CH), 130.8 (2×CH), 129.7 (t, J_{CF} = 6.1 Hz, CH), 129.3 (2×CH), 129.2 (2×CH), 127.6 (CH), 127.1 (CH), 127.0 (t, J_{CF} = 27.0 Hz, C), 126.2 (t, J_{CF} = 3.5 Hz, CH), 120.7 (t, J_{CF} = 283.7 Hz, CF_2), 120.3 (t, J_{CF} = 282.8 Hz, CF_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -92.6 (s, CF_2), -97.5 (s, CF_2).

HRMS (ESI-TOF) m/z [$(M + Na)^+$] calcd for $C_{11}H_8F_2O_2S_2Na$: 296.9831; found: 296.9922.

2-[Difluoro(phenylsulfonyl)methyl]-1-methyl-1*H*-indole (258f)



258f

Compound **258f** was prepared by the general procedure from 1-methyl-1*H*-indole (**257f**) (196.8 mg, 1.5 mmol, 3 equiv.). Column chromatography (silica gel; hexanes/EtOAc, 9.2:0.8) gave the title compound. 2-(Difluoro(phenylsulfonyl)methyl)-1-methyl-1*H*-indole (**258f**) (38.5 mg, 24% yield) was obtained as a white solid, m.p. = 127.5–129.0 ^{o}C: analytical TLC on silica gel: hexanes/EtOAc = 9.2:0.8, $R_f = 0.22$.

IR (KBr, cm^{-1}): ν_{max} 3058 (C–H of aromatic), 2925 (C–H of aliphatic), 1580, 1529, and 1470 (aromatic), 1337 and 1167 (SO_2), 1054 (C–F).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.7 Hz, 2 H), 7.8 (m, 1 H), 7.69–7.62 (m, 3 H), 7.42 (m, 2 H), 7.21 (m, 1 H), 6.96 (s, 1 H), 4.01 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.7 (C), 135.3 (CH), 132.8 (C), 130.8 (2×CH), 129.2 (2×CH), 126.0 (C), 124.7 (CH), 123.7 (t, J_{CF} = 27.5 Hz, C), 122.1 (CH), 120.7 (CH), 120.0 (t, J_{CF} = 277.5 Hz, CF_2), 110.0 (CH), 109.1 (t, J_{CF} = 5.5 Hz, CH), 31.7 (t, J_{CF} = 3.6 Hz, CH_3).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -96.8 (s, CF_2).

HRMS (ESI-TOF) *m*/*z* [$(M + Na)^+$] calcd for $C_{16}H_{13}F_2NO_2SNa$: 344.0533; found: 344.0531.

4.7 The investigation of the role of the sulfonyl moiety of [(bromodifluoromethyl)sulfonyl]benzene (248) in Pd(0)-catalyzed Heck type reactions

4.7.1 General procedure for pd-catalyzed reaction of *p*-chlorostyrene (249a) with bromodifluoromethyl phenyl sulfide (41)

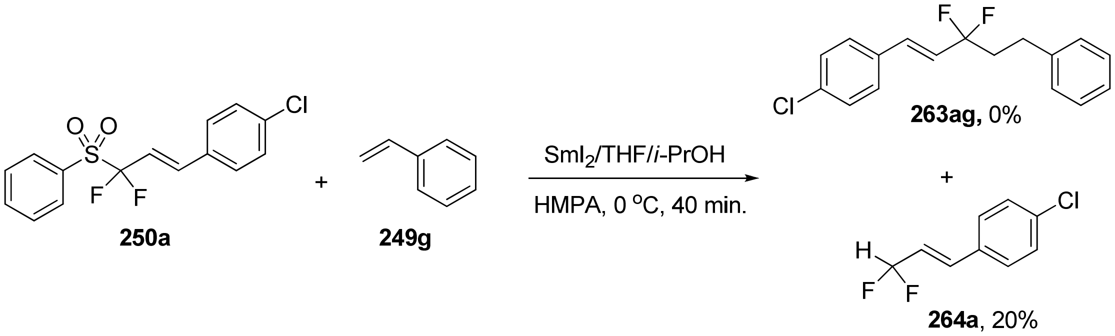
An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol-%), bromodifluoromethyl phenyl sulfide (**41**) (119.5 mg, 0.5 mmol, 1.0 equiv.), and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of *p*-chlorostyrene (**249a**) (207.9 mg, 1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 ^{o}C with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. According to TLC and ^{1}H NMR analyses, no desired product **259a** was detected.

4.7.2 General procedure for pd-catalyzed reaction of *p*-chlorostyrene (249a) with [(bromodifluoromethyl)sulfinyl]benzene (260)

An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol-%), [(bromodifluoromethyl)sulfinyl]benzene (**260**) (127.5 mg, 0.5 mmol, 1.0 equiv.), and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of *p*-chlorostyrene (**249a**) (207.9 mg, 1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 ^{o}C with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. According to TLC and ^{1}H NMR analyses, no desired product **261a** was detected.

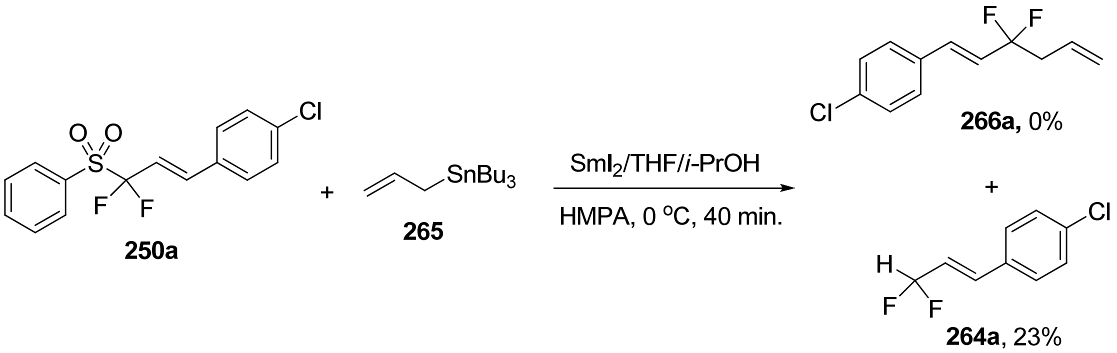
4.8 The synthetic application of allyl sulfones containing $PhSO_2CF_2$-moiety

4.8.1 General procedure for the radical addition reaction between (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (250a) and styrene (249g) using SmI_2/THF/*i*-PrOH/HMPA conditions



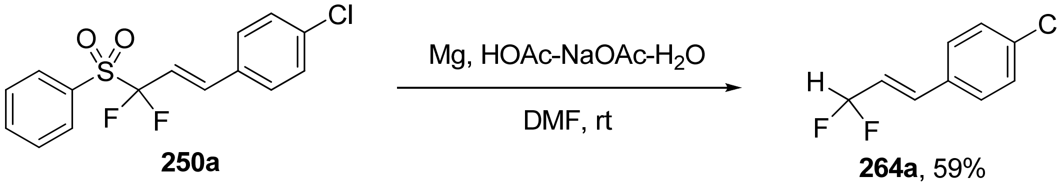
An oven-dried round-bottom flask with a magnetic stir-bar was charged with samarium (40 mesh, 0.32 g, 2.08 mmol). After the flask was evacuated and flushed with argon gas (three times), anhydrous THF (3.0 mL) was added. The slurry of samarium powder in THF was cooled to 0 °C and CH_2I_2 (0.10 mL, 1.25 mmol) was added to give a deep blue-green solution. The mixture was stirred at 0 °C for 15 min and allowed to warm to room temperature for an additional 2 h. To a deep blue-green SmI_2 solution at 0 °C, were added a solution of (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) (82.1 mg, 0.25 mmol), styrene (**249g**) (130 mg, 1.25 mmol), and isopropanol (0.10 mL, 1.25 mmol) in THF (2.0 mL), followed by HMPA (1.0 mL). The reaction mixture was stirred at 0 °C for 40 min. Saturated sodium bicarbonate solution (10.0 mL) was added and organic layer was separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined EtOAc extracts were washed with water (3×20 mL), brine (20 mL), dried (anh. $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give the crude product, which was purified by silica gel column chromatography to yield (*E*)-1-chloro-4-(3,3-difluoroprop-1-en-1-yl)benzene (**264a**) (9.3 mg, 20% yield) as colorless liquid: analytical TLC on silica gel: hexanes, $R_f = 0.37$.

4.8.2 General procedure for the radical addition reaction between (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (250a) and allyltributylstannane (265) using SmI_2/THF/*i*-PrOH/HMPA conditions



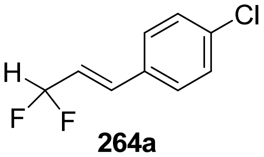
An oven-dried round-bottom flask with a magnetic stir-bar was charged with samarium (40 mesh, 0.32 g, 2.08 mmol). After the flask was evacuated and flushed with argon gas (three times), anhydrous THF (3.0 mL) was added. The slurry of samarium powder in THF was cooled to 0 °C and CH_2I_2 (0.10 mL, 1.25 mmol) was added to give a deep blue-green solution. The mixture was stirred at 0 °C for 15 min and allowed to warm to room temperature for an additional 2 h. To a deep blue-green SmI_2 solution at 0 °C, were added a solution of (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-enyl]benzene (**250a**) (82.1 mg, 0.25 mmol), allyltributylstannane (**265**) (413.9 mg, 1.25 mmol), and isopropanol (0.10 mL, 1.25 mmol) in THF (2.0 mL), followed by HMPA (1.0 mL). The reaction mixture was stirred at 0 °C for 40 min. Saturated sodium bicarbonate solution (10.0 mL) was added and organic layer was separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined EtOAc extracts were washed with water (3×20 mL), brine (20 mL), dried (anh. $MgSO_4$) and filtered. The filtrate was evaporated (aspirator) to give the crude product, which was purified by silica gel column chromatography to yield (*E*)-1-chloro-4-(3,3-difluoroprop-1-en-1-yl)benzene (**264a**) (1.1 mg, 23% yield) as colorless liquid: analytical TLC on silica gel: hexanes, $R_f = 0.37$.

4.8.3 General procedure for the reductive desulfonylation reaction of (*E*)-1-chloro-4-[3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl]benzene (250a) using Mg/HOAc/NaOAc desulfonylation system



A round-bottom flask with a magnetic stir-bar was charged with compound **250a** (105.7 mg, 0.32 mmol), and DMF (5 mL) followed by adding 2.5 mL of HOAc/NaOAc (1:1) buffer solution (8 mol/L). Magnesium turnings (115.5 mg, 4.8 mmol) were added in portions. After stirring at room temperature for 5 h, 15 mL of water was added and extracted with EtOAc (20 mL × 3). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography using hexanes as eluent to give product **264a** (35.5 mg, 59%) as colorless liquid.

(*E*)-1-chloro-4-(3,3-difluoroprop-1-en-1-yl)benzene (264a)



264a

IR (neat, cm^{-1}): ν_{max} 3031 (C–H of aromatic), 1658 (C=C), 1589, 1490, and 1448 (aromatic), 1138 (C–F).

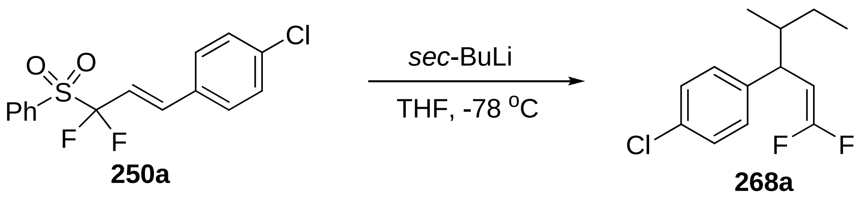
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.6 Hz, 2 H), 7.34 (d, J = 8.6 Hz, 2 H), 6.83 (m, 1 H), 6.23 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.7 (t, J_{CF} = 11.8 Hz, CH), 135.2 (C), 132.9 (C), 129.0 (2×CH), 128.4 (2×CH), 121.5 (t, J_{CF} = 23.7 Hz, CH), 115.0 (t, J_{CF} = 232.7 Hz, CF_2).

^{19}F NMR (470 MHz, $CDCl_3$): δ = -110.04 (m, CF_2).

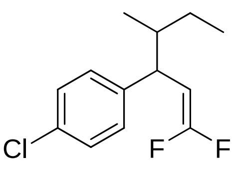
HRMS (ESI-TOF) *m*/*z* [(M + H)$^+$] calcd for $C_9H_8ClF_2$: 189.0283; found: 189.0306.

4.8.4 General procedure for synthesis of 1-chloro-4-(1,1-difluoro-4-methylhex-1-en-3-yl)benzene (268a)



To a solution of (*E*)-1-chloro-4-(3,3-difluoro-3-(phenylsulfonyl)prop-1-en-1-yl)benzene (**250a**) (80.5 mg, 0.24 mmol, 1 equiv.) in THF (3 mL) was added a solution of *sec*-BuLi (1.4 M) in cyclohexane (the number of equivalents of this reagent and the reaction temperature are indicated in Table 5). After stirring for 1 h, the mixture was hydrolyzed with aq. NH_4Cl solution, and extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl solution and dried over $MgSO_4$. The solvents were removed and the crude residue was purified by column chromatography (silica gel; hexanes) to yield the 1-chloro-4-(1,1-difluoro-4-methylhex-1-en-3-yl)benzene (**268a**).

1-Chloro-4-(1,1-difluoro-4-methylhex-1-en-3-yl)benzene (268a)



268a

An approximately 2 : 1 inseparable mixture of two diasteriomers **268a** was obtained as colorless liquid; : analytical TLC on silica gel: hexanes, $R_f = 0.57$.

IR (KBr, cm^{-1}): ν_{max} 3029 (C–H of aromatic), 2966, and 2932 (C–H of aliphatic), 1742 (C=C), 1490, and 1463 (aromatic), 1092 (C–F).

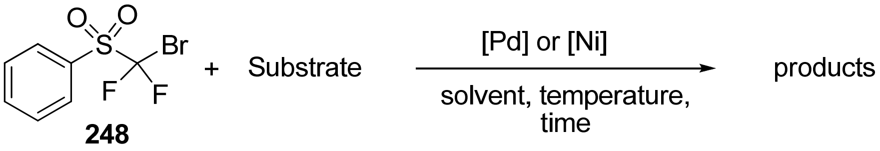
^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.4$ Hz, 4 H), 7.0 (m, 4 H), 4.41–4.33 (m, 2 H), 3.30, and 3.19 (t, $J = 9.8$, 8.4 Hz, 2 H), 1.65 (m, 2 H), 1.28 (m, 1 H), 1.02 (m, 2 H), 0.84 (m, 11 H), 0.73 (d, $J = 6.6$ Hz 2 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 156.3 (t, J_{CF} = 285.2 Hz, CF$_2$), 156.2 (t, J_{CF} = 285.3 Hz, CF$_2$), 141.9 (C), 141.7 (C), 132.1 (C), 132.0 (C), 128.9 (2×CH), 128.8 (2×CH), 128.5 (4×CH), 80.9 (t, J_{CF} = 20.5 Hz, CH), 79.8 (t, J_{CF} = 20.5 Hz, CH), 45.0 (d, J_{CF} = 4.2 Hz, CH), 44.2 (d, J_{CF} = 3.9 Hz, CH), 40.1 (CH), 39.9 (CH), 27.2 (CH$_2$), 26.2 (CH$_2$), 16.7 (CH$_3$), 15.6 (CH$_3$), 11.3 (CH$_3$), 11.1 (CH$_3$).

^{19}F NMR (470 MHz, CDCl$_3$): δ = -87.9 (d, J_{FF} = 44.6 Hz, CF$_2$), -88.2 (d, J_{FF} = 45.6 Hz, CF$_2$), -89.6 (dd, J_{FF} = 45.1, J_{FH} = 24.4 Hz, CF$_2$), -89.9 (dd, J_{FF} = 45.6, J_{FH} = 24.4 Hz, CF$_2$).

HRMS (APCI-TOF) *m/z* [(M + H$_3$O)$^+$] calcd for C$_{13}$H$_{15}$ClF$_2$H$_3$O: 263.1014; found: 263.1058.

4.9 General procedure for the investigation of [(bromodifluoromethyl)sulfonyl]benzene (248) under various reaction conditions.



4.9.1 An oven-dried round-bottom flask with a magnetic stir-bar was charged with Pd(PPh$_3$)$_4$ (28.9 mg, 0.025 mmol), and [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of tributyl(phenylethynyl)stannane (**274**) (214.5 mg, 0.55 mmol, 1.1 equiv.) in THF (2.5 mL) was added through the septum *via* syringe. The resulting mixture was stirred at room temperature for 72 h. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was concentrated, diluted with saturated NaF (10 mL) and filtered. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (3×20 mL), brine (10 mL), dried (anhydrous MgSO$_4$) and filtered. The filtrate was dried in vacuo, and purified *via* silica gel column chromatography to yield 1,4-diphenylbuta-1,3-diyne (**276**) (14.0 mg, 25% yield).

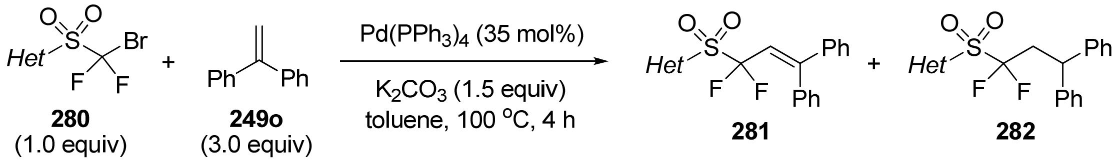
4.9.2 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), and [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of tributyl(vinyl)stannane (**277**) (174.3 mg, 0.55 mmol, 1.1 equiv.) in THF (2.5 mL) was added through the septum *via* syringe. The resulting mixture was stirred at 60 ^{o}C for 24 h. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was concentrated, diluted with saturated NaF (10 mL) and filtered. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (3×20 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was dried in vacuo, and purified *via* silica gel column chromatography. According to ^{1}H NMR and MS analyses, the desired product **278** was not detected.

4.9.3 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (28.9 mg, 0.175 mmol), and [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of tributyl(vinyl)stannane (**277**) (174.3 mg, 1.5 mmol, 3.0 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was stirred at 100 ^{o}C for 4 h. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was concentrated, diluted with saturated NaF (10 mL) and filtered. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (3×20 mL), brine (10 mL), dried (anhydrous $MgSO_4$) and filtered. The filtrate was dried in vacuo, and purified *via* silica gel column chromatography. According to ^{1}H NMR and MS analyses, the desired product **278** was not detected.

4.9.4 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol-%), [(bromodifluoromethyl)sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (**279**) (122.0 mg, 1.0 mmol, 2 equiv.) and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas followed by adding toluene (2.5mL) through the septum *via* syringe. The resulting mixture was heated at 100 °C with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. Unidentified products were obtained in this reaction conditions.

4.9.5 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $NiCl_2(PPh_3)_2$ (32.7 mg, 0.05 mmol, 10 mol%), [(bromodifluoromethyl)-sulfonyl]benzene (**248**) (135.7 mg, 0.5 mmol, 1.0 equiv.), and Zn^0 (97.5 mg, 1.5 mmol, 3.0 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of styrene **249g** (78.0 mg, 0.75 mmol, 1.5 equiv.) in THF (2.5 mL) was added through the septum *via* syringe. The resulting mixture was stirred at room temperature for 24 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography to yield (difluoromethylsulfonyl)benzene (**251**) (13.5 mg, 14% yield).

4.10 General procedure for the reaction of bromodifluoromethyl-(heteroaryl)sulfone (280) in the presence of palladium catalyst

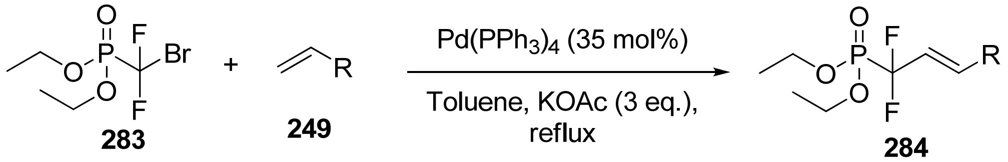


4.10.1 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol%), 2-(bromodifluoromethylsulfonyl)pyridine (**280a**) (136.0 mg, 0.5 mmol, 1.0 equiv.), and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of 1,1-diphenylethylene (**249o**) (270.0 mg, 1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 ^oC with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. No desired products **281** and **282** were obtained in the reaction conditions.

4.10.2 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol%), 2-(bromodifluoromethylsulfonyl)pyridine (**280a**) (136.0 mg, 0.5 mmol, 1.0 equiv.), CuBr (107.6 mg, 0.75 mmol, 1.5 equiv) and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of 1,1-diphenylethylene (**249o**) (270.0 mg, 1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 ^oC with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. No desired products **281** and **282** were obtained in the reaction conditions.

4.10.3 An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol%), 2-(bromodifluoromethylsulfonyl)benzo[*d*]thiazole (**280b**) (164.1 mg, 0.5 mmol, 1.0 equiv.), and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of 1,1-diphenylethylene (**249o**) (270.0 mg, 1.5 mmol, 3 equiv.) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at 100 °C with vigorous stirring for 4 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified *via* silica gel column chromatography. No desired products **281** and **282** were obtained in the reaction conditions.

4.11 General procedure for Pd-mediated fluoroalkylation of styrene derivatives with bromodifluoromethylphosphonate (283)



An oven-dried round-bottom flask with a magnetic stir-bar was charged with $Pd(PPh_3)_4$ (202.2 mg, 0.17 mmol, 35 mol%), and KOAc (147.2 mg, 1.5 mmol, 3.0 equiv.). The reaction flask was capped with a rubber septum and then evacuated and backfilled with argon gas. A solution of styrene derivative **249** (or heteroaromatic **257**) (1.5 mmol, 3 equiv.) and diethyl bromodifluoromethylphosphonate (**283**) (133.5 mg, 0.5 mmol, 1.0 equiv) in toluene (2.5 mL) was added through the septum *via* syringe. The resulting mixture was heated at reflux with vigorous stirring for 5 h. The mixture was then allowed to cool to room temperature. The reaction was filtered through a plug of Celite and eluted with ethyl acetate (50 mL). The solution was dried in vacuo, and purified via silica gel column chromatography.

4.11.1 Accordance with the general procedure, 4-chlorostyrene (**249a**) (207.9 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0, $R_f = 0.20$) gave the inseparable complex mixture (40.2 mg).

4.11.2 Accordance with the general procedure, 4-fluorostyrene (**249b**) (183.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0, R_f = 0.22) gave the inseparable complex mixture (32.1 mg).

4.11.3 Accordance with the general procedure, 3-nitrostyrene (**249e**) (223.7 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 5.0:5.0, R_f = 0.35) gave the inseparable complex mixture (36.7 mg)

4.11.4 Accordance with the general procedure, styrene (**249g**) (156.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0, R_f = 0.22) gave the inseparable complex mixture (34.1 mg).

4.11.5 Accordance with the general procedure, 4-methylstyrene (**249h**) (177.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0, R_f = 0.30) gave the inseparable complex mixture (21.0 mg).

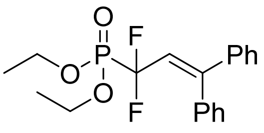
4.11.6 Accordance with the general procedure, 4-vinylphenyl acetate (**249j**) (243.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 5.0:5.0, R_f = 0.25) gave the inseparable complex mixture (33.9 mg).

4.11.7 Accordance with the general procedure, 1-methoxy-4-vinylbenzene (**249k**) (201.3 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 6.0:4.0, R_f = 0.25) gave the inseparable complex mixture (29.8 mg).

4.11.8 Accordance with the general procedure, 1,1-diphenylethylene (**249o**) (270.0 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0) gave an 3.3:1 inseparable mixture of **284o** and

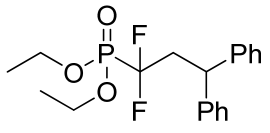
285o (133.7 mg, 73% yield) as a brown liquid: analytical TLC on silica gel: hexanes/EtOAc = 7.0:3.0, R_f = 0.20.

Diethyl 1,1-difluoro-3,3-diphenylallylphosphonate (284o) and diethyl 1,1-difluoro-3,3-diphenylpropylphosphonate (285o) (284o:285o, 2:1)



284o

+



285o

IR (neat, cm^{-1}): ν_{max} 3058, and 3028 (C–H of aromatic), 2985, and 2932 (C–H of aliphatic), 1633 (C=C), 1577, 1493, and 1445 (aromatic), 1270 (P=O), 1029 (P−OEt).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42−7.22 (m, 30 H), 6.19 (td, J = 16.2, 2.2 Hz, 2 H), 4.55 (t, J = 6.9 Hz, 1 H), 4.35−4.19 (m, 12 H), 2.94 (tdd, J = 19.7, 6.9, 4.3 Hz, 2 H), 1.37 (m, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0 (dt, J_{CP} = 7.7 Hz, J_{CF} = 6.2 Hz, C), 143.9 (C), 141.4 (C), 138.1 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 126.4 (CH), 121.2 (C), 119.5 (C), 117.3 (td, J_{CF} = 259.3 Hz, J_{CP} = 219.2 Hz, CF_2), 117.0 (td, J_{CF} = 19.4 Hz, J_{CP} = 13.7 Hz, CH), 64.5 (d, J_{CP} = 6.7 Hz, CH_2), 64.4 (d, J_{CP} = 6.8 Hz, CH_2), 43.8 (m, CH), 39.2 (td, J_{CF} = 19.4 Hz, J_{CP} = 14.2 Hz, CH_2), 16.3 (m, CH_3).

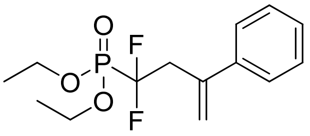
^{19}F NMR (470 MHz, $CDCl_3$): δ = -102.15 (dd, J_{FP} = 113.7 Hz, J_{FH} = 16.2 Hz, CF_2), -110.8 (dt, J_{FP} = 107.6 Hz, J_{FH} = 19.7 Hz, CF_2).

HRMS (ESI-TOF) *m*/*z* [(M + Na)$^+$] calcd for $C_{19}H_{21}F_2O_3PNa$: 389.1089; found: 389.0888, and *m*/*z* [(M + Na)$^+$] calcd for $C_{19}H_{23}F_2O_3PNa$: 391.1245; found: 391.1030.

4.13.9 Accordance with the general procedure, α-methyl styrene (**249q**) (177.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0) gave diethyl 1,1-difluoro-3-phenylbut-3-

enylphosphonate (**286q**) (40.7 mg, 26% yield) as a brown liquid: analytical TLC on silica gel: hexanes/EtOAc = 7.0:3.0, $R_f = 0.25$.

Diethyl 1,1-difluoro-3-phenylbut-3-enylphosphonate (286q)



286q

IR (neat, cm^{-1}): ν_{max} 3085 (C–H of aromatic), 2985, and 2934 (C–H of aliphatic), 1627 (C=C), 1575, 1495, and 1445 (aromatic), 1271 (P=O), 1037 (P−OEt).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.10 (m, 5 H), 5.59 (s, 1 H), 5.34 (s, 1 H), 4.35–4.15 (m, 4 H), 3.28 (t, J = 19.8, 2 H), 1.34 (t, J = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8 (C), 128.2 (2×CH), 127.7 (CH), 126.1 (2×CH), 119.4 (CH_2), 64.4 (d, J_{CP} = 7.0 Hz, CH_2), 38.7 (m, CH_2), 16.3 (d, J_{CP} = 5.0 Hz, CF_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -110.5 (dt, J_{FP} = 107.9 Hz, J_{FH} = 19.5 Hz, CF_2).

HRMS (ESI-TOF) m/z [$(M + Na)^+$] calcd for $C_{14}H_{19}F_2O_3PNa$: 327.0938; found: 327.0933.

4.11.10 Accordance with the general procedure, 4-vinylbenzaldehyde (**249t**) (198.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 5.0:5.0, $R_f = 0.35$) gave the inseparable complex mixture (36.7 mg).

4.11.11 Accordance with the general procedure, 3,4-dihydro-2*H*-pyran (**254c**) (126.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. No desired product **287c** was detected.

4.11.12 Accordance with the general procedure, phenyl(vinyl)sulfane (**254g**) (204.3 mg, 1.5 mmol, 3 equiv.) was used as substrate. Column chromatography (silica gel; hexanes/EtOAc, 7.0:3.0, $R_f = 0.25$) gave the inseparable complex mixture (26.4 mg).

4.11.13 Accordance with the general procedure, 1-methyl-1*H*-pyrrole (**257a**) (121.7 mg, 1.5 mmol, 3 equiv.) was used as substrate. No desired product **288a** was detected.

4.11.13 Accordance with the general procedure, 1-methyl-1*H*-imidazole (**257m**) (123.2 mg, 1.5 mmol, 3 equiv.) was used as substrate. No desired product **288m** was detected.

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PUBLICATION	**Surapanich**, **N**., Kuhakarn, C., Pohmakotr, M., Reutrakul, V. *Eur. J. Org. Chem.* **2012**, 5943–5952.