Top Curr Chem (2012) 308: 25–44
DOI: 10.1007/128_2011_246

Published online: 7 September 2011

Selective Fluoroalkylation of Organic Compounds by Tackling the "Negative Fluorine Effect"

Wei Zhang, Chuanfa Ni, and Jinbo Hu

Abstract The presence of fluorine on a carbanion center will dramatically influence the nucleophilic alkylation reactions. Based on our own experience, we noticed that the fluorine substitution on the carbanionic carbon poses a negative effect in many nucleophilic fluoroalkylation reactions [we propose this effect as "negative fluorine effect (NFE)"]. Two factors were believed to contribute to the NFE: (1) thermal instability of fluorinated carbanions caused by α-elimination (self-decomposition) and (2) the intrinsic nucleophilicity of fluorinated carbanion influenced by the fluorine atoms (such as hard/soft nature of the fluorinated carbanions). By tackling the NFE, our research group has attempted to design nucleophilic fluoroalkylation reactions with fluorinated sulfones and related reagents. These results were summarized as four methods to modulate the fluoroalkylation reactions: (1) changing the number of fluorine atoms, (2) slightly changing the neighboring groups, (3) changing the metal counterion, including using carbon-metal covalent bond to tune the reactivity, and (4) enhancing the generation of carbene species.

Keywords Difluorocarbene · Fluorinated sulfones · Fluorinated sulfoximines · Fluoroalkylations · Negative fluorine effect

Contents

1 Introduction 26
2 The "Negative Fluorine Effect" in Fluoroalkylation Reactions 28
2.1 The Unique Effect of Fluorine Substitution on the Carbanions 28
2.2 The "Negative Fluorine Effect" 29

W. Zhang, C. Ni, and J. Hu (✉)
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
e-mail: jinbohu@sioc.ac.cn

3 Modulating the Fluoroalkylation Reactions by Tackling the "Negative Fluorine Effect" . 30
3.1 Modulating the Fluoroalkylation Reactions by Changing the Number of Fluorine Atoms 31
3.2 Modulating the Fluoroalkylation Reactions by Slightly Changing the Neighboring Groups 33
3.3 Modulating the Fluoroalkylation Reactions by Changing the Metal Counterion 37
3.4 Modulating the Fluoroalkylation Reactions by Enhancing the Generation of Carbene Species 39
4 Conclusion 41
References 42

Abbreviations

Bn	Benzyl
DFT	Density functional theory
dr	Diastereomeric ratio
ee	Enantiomeric excess
i-Pr	*iso*-Propyl
KHMDS	Potassium *bis*(trimethylsilyl)amide
LiHMDS	Lithium *bis*(trimethylsilyl)amide
NaHMDS	Sodium *bis*(trimethylsilyl)amide
Ph	Phenyl
Py	Pyridine
TBAT	Tetrabutylammonium triphenyldifluorosilicate
t-Bu	*tert*-Butyl
TMS	Trimethylsilyl
Ts	Tosyl (*p*-toluenesulfonyl)

1 Introduction

Due to the high electronegativity and small size of fluorine, the replacement of hydrogen atoms by fluorine in organic compounds often results in a profound change in their physical and chemical properties, including the stability, high lipophilicity, and bioavailability [1–4]. In the past decades, organofluorine compounds have found broad applications in both life sciences and material sciences, and around 20% of all pharmaceuticals and 30–40% of all agrochemicals on the market contain fluorine [5, 6]. Among nearly 3,200 known naturally occurring organohalogen compounds, only very few (around 13) are organofluorine compounds (all of them are mono-fluorinated) [7]. However, despite their rarity in nature, till 2010 about four million organic compounds which contain at least one C−F bond have been artificially synthesized by chemists, and those occupied about 55% of the approximate 7.2 million man-made organohalogen compounds [a SciFinder search (October, 2010) revealed >4,000,000 structures containing at least one C–F bond and >7,200,000 structures containing at least one C–X (X = F, Cl, Br, I) bond].

Many fluorinated compounds can be constructed by using simple fluorine-containing building blocks. However, some desired fluorinated molecules are complex and, therefore, selective fluorination and fluoroalkylation synthetic methodologies are preferred for the synthesis of these molecules [8, 9]. In the field of fluoroalkylation chemistry, although both free radical fluoroalkylation and electrophilic fluoroalkylation are well known, nucleophilic fluoroalkylation often bring about many advantages and thus it has become one of the most important methods for incorporation of fluorinated moieties into organic molecules [10]. Nucleophilic fluoroalkylation typically features the transfer of a fluoroalkyl group (such as perfluoroalkyl, CF_3, CF_2H, and CH_2F) to an electrophile, in which either a free α-fluoro carbanion, an equivalent of α-fluoro carbanion (i.e., a species that has similar reactivity character to an α-fluoro carbanion, such as pentacoordinate silicon species) or a fluoroalkyl metal species (R_fM) is involved.

During the past decades, nucleophilic perfluoroalkylation using organometallic reagents of lithium, magnesium, and zinc, among others, has been extensively studied, but these reagents do not have attractive profiles of reactivity, selectivity, stability, and convenience, and do not generally apply to the trifluoromethylation case [11, 12]. In 1989 Prakash and Olah reported the first nucleophilic trifluoromethylation reactions of carbonyls by using the stable organosilicon reagent (trifluoromethyl)trimethylsilane ($TMSCF_3$) under the initiation of a fluoride [13], then nucleophilic trifluoromethylation was creatively solved and perfluoroalkyl silanes have become the most widely used reagents in nucleophilic perfluoroalkylation. Compared to trifluoromethylation chemistry, the analogous difluoromethylation and monofluoromethylation (selective introduction of a CF_2H or CH_2F group into organic molecules) are less studied. It is found that difluoromethyl- and monofluoromethyl-containing compounds often exhibit unique biological properties, and there is a growing interest in developing new synthetic methods for nucleophilic di- and monofluoromethylation. Due to the lower polarization of the C−Si bond, initial results showed that nucleophilic difluoromethylation with compound $R_3Si{-}CF_2H$ had to be conducted under harsh conditions, which made it less likely to become a widely used difluoromethylation reagent [14]. Similarly, the analogous $R_3Si{-}CH_2F$ is even more stable and less likely to be a viable monofluoromethylation reagent.

Selective di- and monofluoromethylation are generally accomplished by two strategies: one is the direct transfer of a "CF_2H" or "CH_2F" moiety into organic molecules [15]; the other is the transfer of a functionalized moiety (such as "CF_2R" or "CFR_2"), followed by removal of the functional or auxiliary groups [16]. The introduction of functional groups to fluorinated carbanions can facilitate the nucleophilic fluoroalkylation reactions. In this review we will discuss the negative effect of fluorine substitution on the reactivity of carbanions, and summarize our research results as four methods to modulate the fluoroalkylation reactions by tackling the "negative fluorine effect."

2 The "Negative Fluorine Effect" in Fluoroalkylation Reactions

On the basis of the nature of the substituents on the anionic or metal-bearing fluorinated carbon atom, the fluoroalkyl anions can be classified as activated and unactivated. When an electron-withdrawing group (such as sulfonyl, sulfinyl, sulfanyl, carbonyl, phosphinyl, perfluoroalkyl, ester, cyano, nitro, etc.) is present on the anionic carbon, the fluoroalkyl anion is activated; otherwise, in the absence of such groups, it is unactivated. In the case of an activated fluoroalkyl anion, it is usually stabilized by one or two neighboring functional groups, and the negative charge on the anionic carbon is usually delocalized to the neighboring groups. However, for the unactivated fluoroalkyl anions (such as CF_3^-, CHF_2^-, CH_2F^-, etc.), the negative charge has to be more localized on the carbanionic carbon.

2.1 The Unique Effect of Fluorine Substitution on the Carbanions

In order to understand better the fluorine effect in nucleophilic fluoroalkylation reactions, the unique effect of fluorine substitution on the carbanions (R_f^-) can be discussed from three aspects: the acidity (for the generation of the anion), thermodynamic stability, and kinetic stability (lifetime of the anion).

First, for the formation of a fluorinated carbanion (R_f^-) by deprotonation of its conjugate acid (R_fH), the inductive effect of fluorine substitution can increase the acidity of a hydrofluorocarbon, thus favoring the production of the carbanion. The calculated enthalpy values of C−H ionization (ΔH_{calcd}, kcal/mol) in the gas phase are as follows: 368.9 (CF_3−H) < 391.3 (CHF_2−H) < 406.3 (CH_2F−H) < 416.8 (CH_3−H), which reveals that the production of CF_3^- by deprotonation will be much easier than CH_3^- [2].

Second, for the thermodynamic stability of a fluorinated carbanion itself, fluorine substitution is more effective in α-stabilization of a methyl anion than other halogen atoms and hydrogen substitution itself. The calculated enthalpy values by Bickelhaupt and coworkers for homolytic cleavage of the C−F bonds in CH_2F^- (117.0 kcal/mol) is higher than the cleavage of C−H bonds in CH_3^- (103.2 kcal/mol), which indicates that CH_2F^- is thermodynamically more stable than CH_3^- [17].

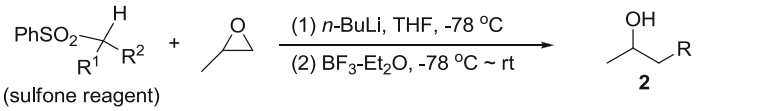
Third, for the decomposition of a fluorinated carbanion via α-elimination of a fluoride (kinetic aspect) in the presence of a hard metal cation, despite the fact that α-fluorine substitution on the carbanion has a certain stabilization influence through inductive effect, the strong repulsion between the electron lone pair on the anionic carbon and those on fluorine atom can decrease the stability of the carbanion [18]. These fluoromethyl metal species display carbenoid reactivity [19, 20]. The formation of carbene and metal fluoride species will act as a substantial driving force for its decomposition. In this regard, the kinetic stability (lifetime) of the carbanions decreases in the following order: $CH_3^- > CH_2F^- > CHF_2^- > CF_3^-$.

2.2 *The "Negative Fluorine Effect"*

Due to the lack of systematic study of per-, poly-, tri-, di-, and mono-fluoroalkylation reactions, the chemical reactivities of various fluorinated methyl anions in nucleophilic fluoroalkylation reactions were not well summarized. As the "chemical chameleon" in organic synthesis, the sulfone functionality (such as $PhSO_2R$) possesses strong electron-withdrawing ability and is ideal for various types of reactions, and the versatile transformations of the sulfone functionality make the subsequent intermediates suitable for the generation of a range of important products which are otherwise difficult to obtain. For instance, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$, **1**) has been extensively employed as a difluoromethylation reagent [21, 22]. The (phenylsulfonyl)difluoromethyl group has been introduced to a series of electrophiles with reagent **1**, and the (phenylsulfonyl) difluoromethyl substituted intermediates so obtained could undergo many further transformations [10, 23].

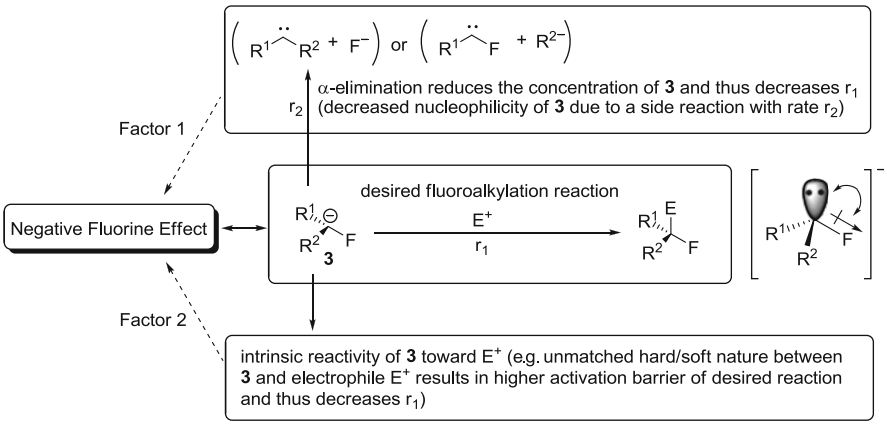
In recent years, our research group studied the nucleophilic ring-opening fluoroalkylation of epoxides with di- and monofluoro(phenylsulfonyl)-methyllithium (Scheme 1) [24]. It was found that α-fluorine substitution on the carbanion dramatically decreases the carbanion's reactivity towards epoxides. According to the product yields, we can see that the nucleophilicity of halogenated sulfone reagents toward propylene oxide decreases in the following order: (1) for fluorinated carbanions $(PhSO_2)_2CF^- > PhSO_2CHF^- > PhSO_2CF_2^-$ and (2) for different halogen-substituted carbanions $PhSO_2CCl_2^- > PhSO_2CF_2^-$. The difficulty of the ring-opening reaction between a fluorinated carbanion and an epoxide can be attributed to (1) the low thermal stability of fluorinated carbanion (R_f^-) caused by its high tendency to undergo α-elimination of a fluoride ion (or another leaving group) and (2) its intrinsic low nucleophilicity towards epoxides.

This negative (unfavorable) influence of fluorine substitution on the reactivity of the carbanions was proposed as "Negative Fluorine Effect (NFE)" (Scheme 2) [24, 25]. The word "negative" implies both the *negative* (unfavorable) influence and the *negatively* charged species (carbanion). For the desired nucleophilic reaction between fluorinated carbanion **3** (R^1, R^2 = H, halogen, alkyl, aryl, etc.) and electrophile E^+, two factors are involved. Factor 1 is the α-elimination reaction



2a	R = $PhSO_2CF_2$	0%
2b	R = $PhSO_2CCl_2$	72%
2c	R = $PhSO_2CHF$	67%
2d	R = $PhSO_2CHCl$	71%
2e	R = $(PhSO_2)CF$	91%

Scheme 1 Nucleophilic ring-opening fluoroalkylation of epoxides



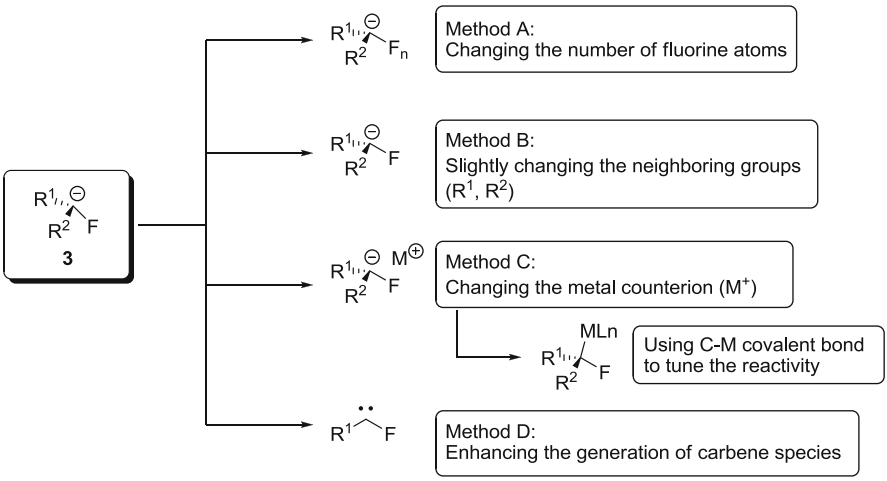
Scheme 2 The "negative fluorine effect" in nucleophilic fluoroalkylation reaction

(with reaction rate r_2) which acts as a competitive side reaction of the desired fluoroalkylation reaction (with reaction rate r_1), and the former reaction reduces the concentration of carbanion **3** and thus decreases r_1. Factor 2 is the intrinsic reactivity of fluorinated carbanion **3** toward electrophile E^+. This can be influenced by many factors, such as the match of the hard/soft nature between **3** and electrophile E^+. For instance, the increased hardness of **3** arising from more fluorine substitution can result in a higher activation barrier of the desired reaction with soft electrophiles (such as alkyl iodides) [26, 27], and thus decreases the desired reaction rate r_1.

It should be noted that Factor 1 (self-decomposition of carbanion **3**) should always have a negative (unfavorable) influence on the desired nucleophilic fluoroalkylation reaction, no matter what kind of electrophile is applied. However, the influence of Factor 2 is independent from Factor 1, which depends on the intrinsic reactivity of **3** toward an electrophile. Combining Factors 1 and 2 together, we can understand that there often exists a unique and quite subtle fluorine effect in many nucleophilic fluoroalkylation reactions involving a fluorinated carbanion.

3 Modulating the Fluoroalkylation Reactions by Tackling the "Negative Fluorine Effect"

As mentioned above, the presence of fluorine on the carbanion center will dramatically influence the nucleophilic alkylation reactions. Although the "NFE" could not be used to summarize all reactivity aspects of fluoroalkyl carbanion in nucleophilic fluoroalkylation reactions, it is at least helpful to understand many nucleophilic fluoroalkylation reactions. During the past several years, our group has attempted to design nucleophilic fluoroalkylation reactions by tackling the NFE with fluorinated



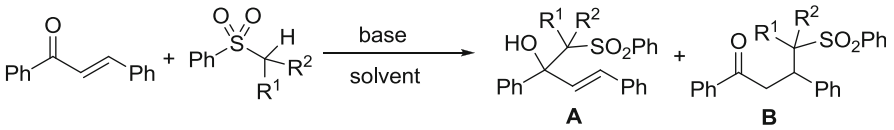
Scheme 3 Methods to modulate the fluoroalkylation reactions

sulfones and related reagents. Our research results were summarized as four methods to modulate the fluoroalkylation reactions: (1) changing the number of fluorine atoms, (2) slightly changing the neighboring groups (R^1, R^2), (3) changing the metal counterion, including using carbon−metal (C−M) covalent bond to tune the reactivity, and (4) enhancing the generation of carbene species (Scheme 3).

3.1 Modulating the Fluoroalkylation Reactions by Changing the Number of Fluorine Atoms

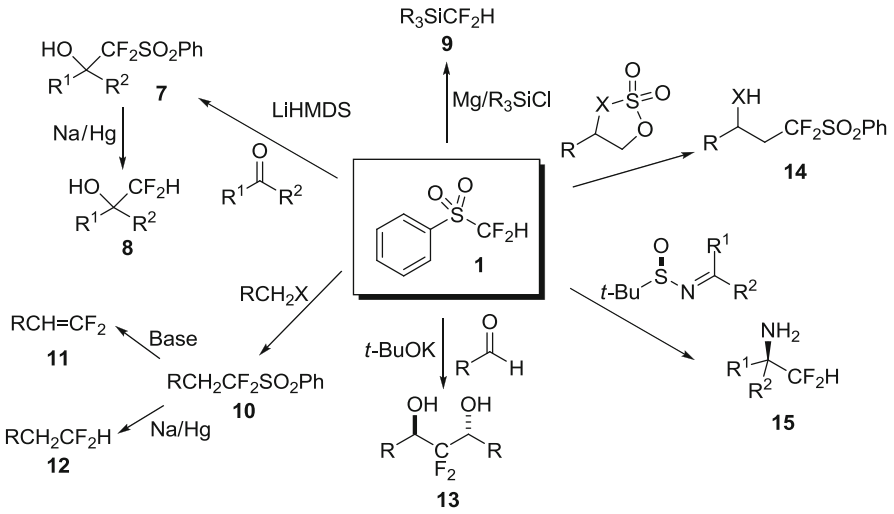
As shown in Scheme 2, the unmatched hard/soft nature between fluorinated carbanion **3** and electrophile E^+ will decrease the desired reaction rate. Recently, we studied the nucleophilic fluoroalkylation reaction of α,β-enones with different fluorinated carbanion (Scheme 4) [28]. It was found that the two fluorines substituted sulfone (**1**) gave the 1,2-addition product solely, while the one fluorine substituted sulfone (**4**) gave the mixture of 1,2- and 1,4-addition products. The number of α-fluorine atoms in carbanions affects its hard/soft nature, which made the 1,2- and 1,4-addition product ratio significantly different. This disclosed the order of softness of halogenated carbanions, which can be given as follows: $(PhSO_2)_2CF^- \approx PhSO_2CCl_2^- > PhSO_2CHF^- > PhSO_2CF_2^-$ ($\geq CF_3^-$).

The introduction of an electron-withdrawing sulfonyl group to the fluoroalkyl anions can stabilize the fluorinated carbanion via electron-delocalization, and reduce the electron repulsion between the electron pairs on the carbanionic carbon and those on the fluorine atoms. The sulfonyl group also acts as a good auxiliary group that can be readily removed by reductive desulfonylation after desired transformations.



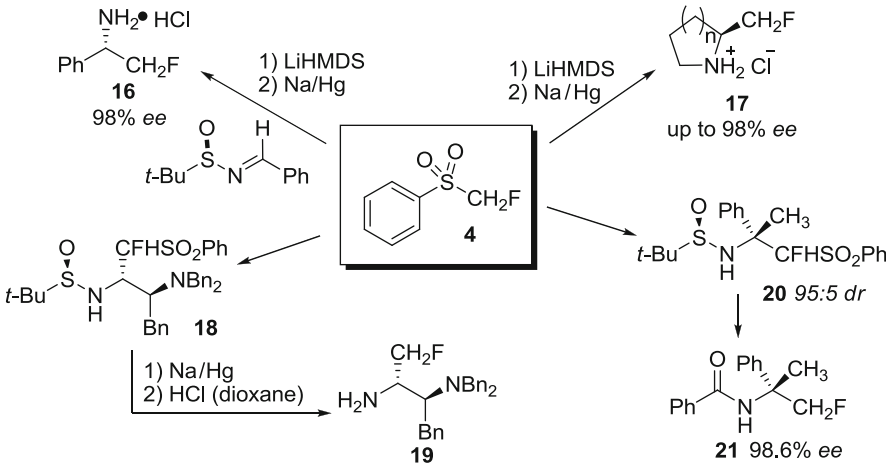
Sulfone	R^1	R^2	Yield (**A**+**B**)	**A**:**B**
1	F	F	97	100:0
4	F	H	98	42:58
5	F	SO_2Ph	98	0:100
6	Cl	Cl	95	0:100

Scheme 4 1,2- and 1,4-additions to α,β-enones with carbanions



Scheme 5 Nucleophilic difluoromethylation reactions with $PhSO_2CF_2H$ (**1**)

Difluoromethyl phenyl sulfone (**1**) was first prepared by Hine in 1960 [22], and in 1989 Stahly reported the preparation of difluoromethylated alcohol from aldehyde by using the nucleophilic reaction with $PhSO_2CF_2H$, followed by reductive desulfonylation (Scheme 5) [21]. In 2003 Prakash and coworkers reported that $PhSO_2CF_2H$ could be used as a nucleophilic difluoromethylation reagent in the presence of a reducing metal (such as magnesium). By using this protocol, chlorotrialkylsilanes was successfully difluoromethylated to give difluoromethylsilanes **9** in practically useful yields (Scheme 5) [29]. Thereafter, $PhSO_2CF_2H$ reagent was extensively used as a robust "CF_2H^-" synthetic equivalent, and the reagent has been efficiently applied to react with a wide range of substrates, such as primary alkyl halides [30, 31], aldehydes, ketones and esters [28, 32–35], imines [36, 37], cyclic sulfates and sulfamidates [25] (Scheme 5).

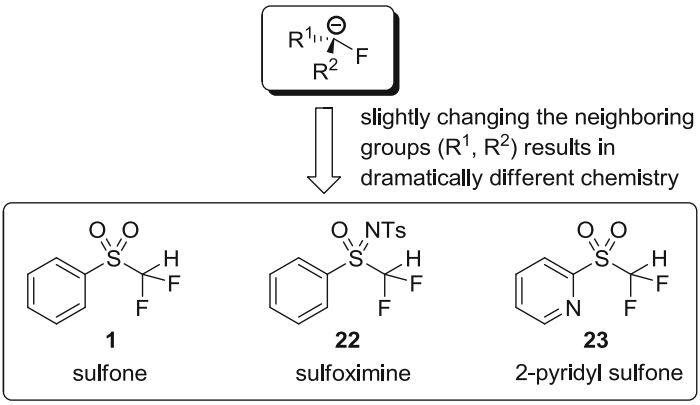


Scheme 6 Nucleophilic monofluoromethylation reactions with $PhSO_2CH_2F$ (**4**)

By decreasing the number of fluorine atoms substituted on the fluorinated carbanion center, the nucleophilic monofluoromethylation is relatively easier than difluoromethylation. According to our study on the reactivity difference of mono- and difluoromethyl anions in nucleophilic fluoroalkylation reactions, the $PhSO_2CHF^-$ anion (generated from $PhSO_2CH_2F$, **4**) possesses higher thermal stability than $PhSO_2CF_2^-$anion and is suitable for pregeneration. In 2006 we reported the first stereoselective nucleophilic monofluoromethylation with the reagent $PhSO_2CH_2F$ (Scheme 6) [38]. It turned out that the reaction between homochiral *N-tert*-butylsulfinyl aldimines and **4** in the presence of LiHMDS readily gave (phenylsulfonyl) fluoromethylated products, which could be converted to monofluoromethylated chiral amines **16** and **17** (via removal of both phenylsulfonyl and *tert*-butylsulfinyl groups) in good yields with excellent optical purity (Scheme 6). The reagent **4** was also successfully used by us in the stereoselective synthesis of monofluoromethylated vicinal ethylenediamine **19** (Scheme 6) [37], as well as in the nucleophilic monofluoromethylation of α,β-unsaturated ketones [28]. Recently we achieved the highly stereoselective monofluoromethylation of *N-tert*-butylsulfinyl ketimines by using the pregenerated $PhSO_2CHF^-$ anion [39], and this stereocontrol mode of the diastereoselective monofluoromethylation of ketimines is opposite to the other known fluoroalkylation of *N-tert*-butylsulfinyl aldimines, which suggests that a cyclic six-membered transition state is involved in the reaction.

3.2 *Modulating the Fluoroalkylation Reactions by Slightly Changing the Neighboring Groups*

For a long time, the phenylsulfonyl group at the α-position of fluorinated carbanions is the most frequently used neighboring group due to its versatility. Recently

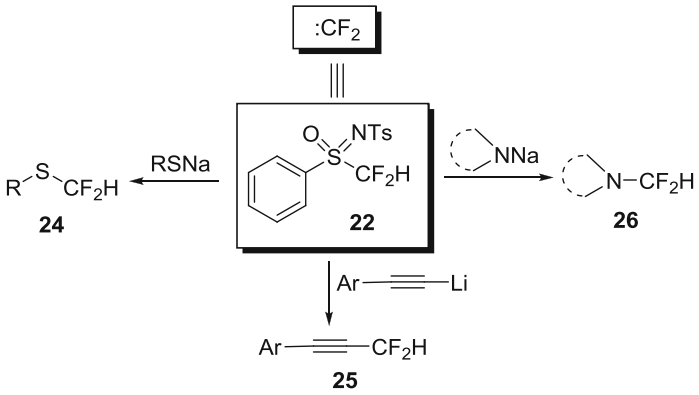


Scheme 7 Slightly changing the neighboring groups of fluorinated carbanions

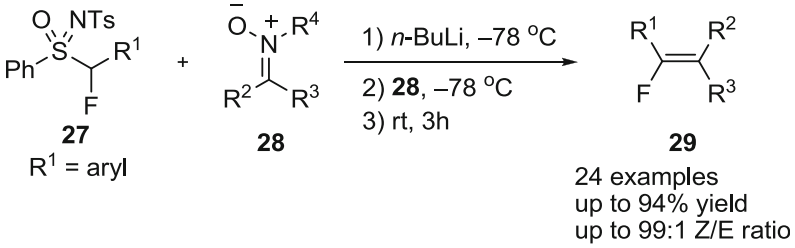
we found that when one oxygen atom in compound **1** was replaced by the NTs group, the chemical reactivity of the resulting compound *N*-tolyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**22**) is significantly different from **1** (Scheme 7). Also, by careful modification of the aryl group of reagent **1**, difluoromethyl 2-pyridyl sulfone (**23**) was developed (Scheme 7). These slight changes of neighboring groups of fluorinated carbanions result in dramatically different and very interesting chemistry.

Sulfoximines have been widely used in organic synthesis [40], but the fluorinated sulfoximines are poorly studied. In 1988 Finch and coworkers reported that monofluorinated sulfoximines could react with carbonyl compounds to yield hydroxyl adducts, which can be converted into fluoroolefins (but with poor Z/E-selectivity) by reduction with aluminum amalgam [41]. In 2009 we successfully prepared the first α-difluoromethyl sulfoximine compound **22** by using the copper-catalyzed nitrene transfer reaction, and the compound **22** was found to be a novel and efficient electrophilic difluoromethylation reagent for transferring CF_2H group to S-, N-, and C-nucleophiles (Scheme 8) [42]. According to the deuterium-labeling experiments, a difluorocarbene mechanism was proposed in this difluoromethylation reaction with reagent **22**. Under the same reaction conditions, the reagent $PhSO_2CF_2H$ (**1**) does not react with the S-nucleophiles to give electrophilic fluoroalkylation products. In addition, by using the sulfoximine **22** and aldehyde, the nucleophilic fluoroalkylation reaction does not occur, while the reagent **1** readily gives adduct products. This remarkably different reactivity pattern between reagent **22** and the $PhSO_2CF_2H$ (**1**) provides important insights into the unique chemical reactivities of fluorinated sulfones and sulfoximines.

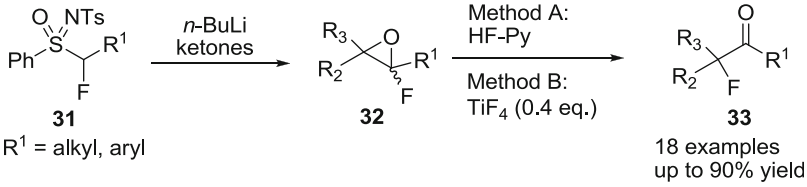
The trifluoromethylated sulfoximine derivative (fluorinated Johnson reagent) was developed by Shibata and coworkers for the electrophilic trifluoromethylation of carbon nucleophiles [43]. Recently, by using monofluoromethylsulfoxinium salts, the electrophilic monofluoromethylation reaction was developed, and the unique inherent preference of the CH_2F cation for the oxygen atom in the alkylation of enolates was observed [44].



Scheme 8 Difluoromethylation of S-, N-, and C-nucleophiles with reagent **22**



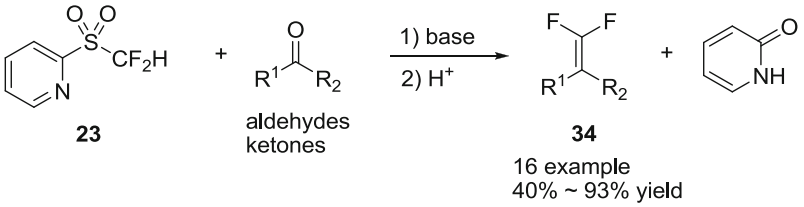
Scheme 9 Synthesis of fluorinated alkenes by using fluorinated sulfoximines **27** and nitrones



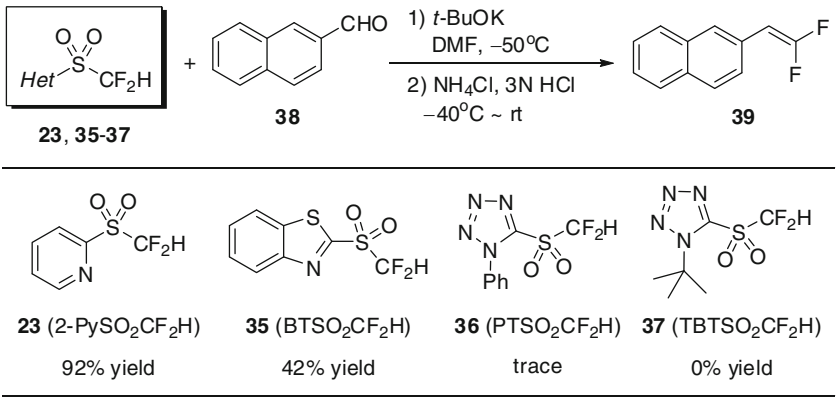
Scheme 10 O-Cyclization reaction with α-fluorosulfoximines **31** and relative ring-opening reactions

In 2009 we successfully prepared α-monofluorinated sulfoximines **27** (Scheme 9) [45]. By using the reagent **27** and nitrones **28**, monofluoroalkenes **29** were synthesized with excellent Z/E stereoselectivity (Scheme 9) [45]. This novel fluoroolefination reaction between a sulfoximine and a nitrone proceeds via an addition– elimination pathway. When fluorinated sulfone compound $PhSO_2CF_2TMS$ (**30**, in place of a sulfoximine) was used to react with a nitrone, a fluoroalkylated hydroxylamine product was obtained, and no alkene product was formed, which demonstrates a remarkable reactivity difference between fluorinated sulfoximines and sulfones.

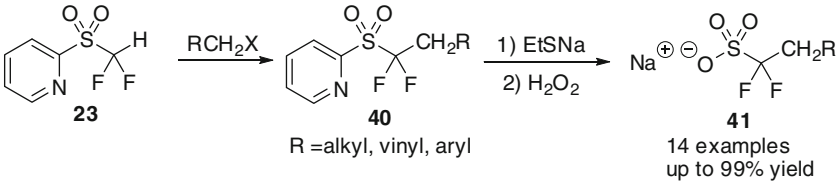
In 2010 we reported an O-cyclization reaction between α-fluorosulfoximines **31** and ketones to synthesize monofluorinated epoxides **32** (Scheme 10) [46]. The obtained fluoroepoxides **32** were found to undergo readily an interesting



Scheme 11 *gem*-Difluoroolefination reactions with difluoromethyl 2-pyridyl sulfone



Scheme 12 *gem*-Difluoroolefination with different sulfones



Scheme 13 Synthesis of various α,α-difluorosulfonates with reagent **23**

ring-opening process (involving both a C−F bond cleavage and another C−F bond formation) in the presence of titanium tetrafluoride or pyridinium poly(hydrogen fluoride) to afford α-fluorinated ketones **33**. The sulfoximinyl group of compound **31** not only retains the strong electron-withdrawing ability to stabilize the carbanion, but also displays better leaving group ability for further transformations.

By slightly changing the phenyl group, difluoromethyl 2-pyridyl sulfone (**23**) was developed by us, which was found to act as a novel and efficient *gem*-difluoroolefination reagent for both aldehydes and ketones (Scheme 11) [47]. In this Julia-Kocienski olefination reaction, the fluorinated sulfinate salt intermediate in the reaction is relatively stable under basic conditions, and it decomposes after protonolysis.

Difluoromethyl heteroaryl sulfones **35**–**37** were also prepared to investigate their reactivities in difluoroolefination reactions [47]. It was found that heteroaryl

sulfones **35**–**37** show lower reactivity in the difluoroolefination reaction with 2-naphthaldehyde **38**. The high reactivity of 2-pyridyl sulfone **23** (compared with other sulfones **35**–**37**) may be due to the fact that 2-Py$SO_2CF_2^-$ anion possesses the best nucleophilicity (among four Het$SO_2CF_2^-$ anions, Het = 2-Py, BT, PT, and TBT) toward carbonyl compounds (Scheme 12).

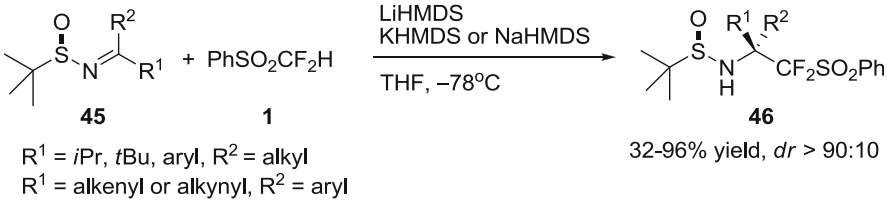
Another important application of difluoromethyl 2-pyridyl sulfone (**23**) was reported by Prakash and coworkers (Scheme 13) [48]. Alkyl α,α-difluorosulfonates **41** were efficiently synthesized from the reagent **23** and halides. This result not only extends the synthetic application of fluorinated sulfones but also provides a unique solution for the long-standing challenge in the nucleophilic difluoro(sulfonato) methylation reaction.

3.3 *Modulating the Fluoroalkylation Reactions by Changing the Metal Counterion*

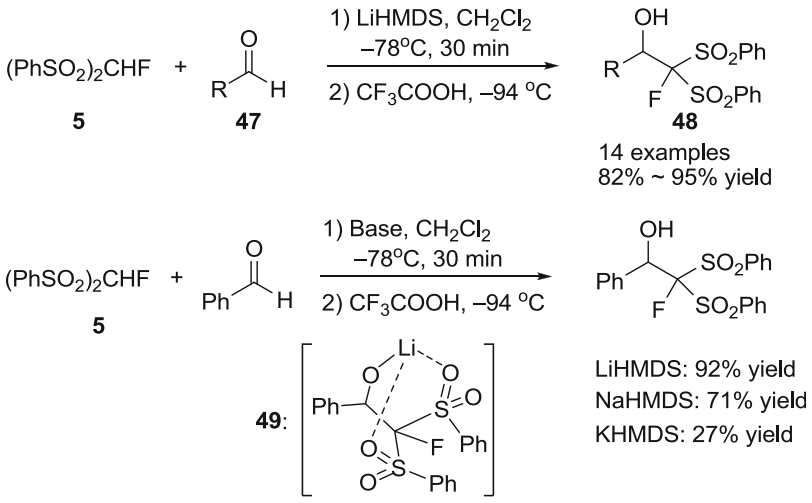
Based on our understanding of the proposed "NFE," the nucleophilic fluoroalkylation reactions can be improved by attaching an electron-withdrawing group, which makes the fluorinated carbanions thermally more stable and "softer." Moreover, during the past few years, our research results have showed that the metal counterion (M^+) of the fluorinated carbanions may play an important role in C_F–C bond formation reaction.

In 2010 we reported that the in situ generated $PhSO_2CF_2^-$ anion can react with a variety of structurally diverse *N-tert*-butylsulfinyl ketimines, which will give a variety of structurally diverse homochiral α-difluoromethyl tertiary carbinamines, including α-difluoromethyl allylic amines and α-difluoromethyl propargylamines in excellent yields and with very high diastereoselectivity (Scheme 14) [49].

The reaction between the $PhSO_2CF_2^-$ anion and α-unsaturated *N-tert*-butylsulfinyl ketimines is highly dependent on the metal counterions, which is different from aldimines and β-acetylenic *N-tert*-butylsulfinyl ketimines. The former preferred potassium base to other metal bases, while the later showed little base preference. It is believed that the kinetically preferred generation of the $PhSO_2CF_2^-$ anion by KHMDS and nucleophilic addition of the $PhSO_2CF_2^-$ anion to ketimines over the undesired aza-enolization of ketimines are the key factors for the success of difluoromethylation of simple ketimines.



Scheme 14 Nucleophilic difluoromethylation of ketimines

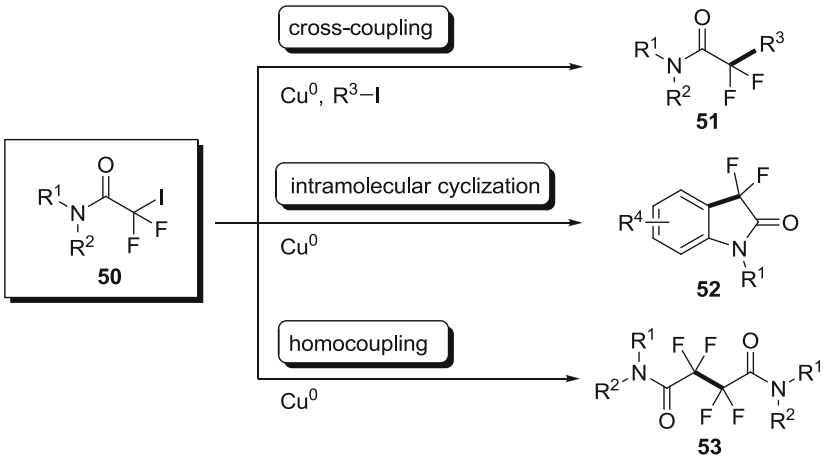


Scheme 15 Nucleophilic additions to aldehyde with $(PhSO_2)_2CFH$

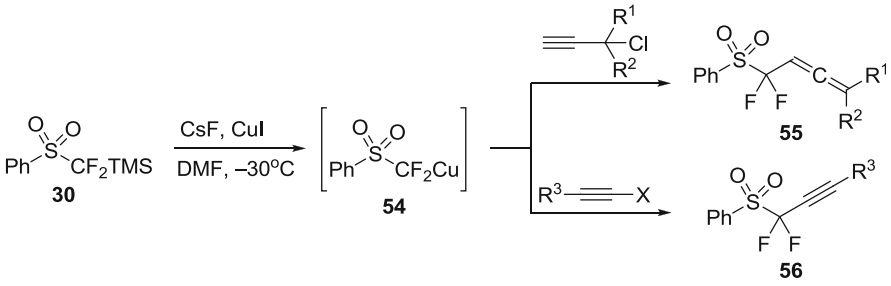
The nucleophilic addition reaction between $(PhSO_2)_2CFH$ (**5**) and an aldehyde, a reaction that was previously believed to be unattainable, was recently accomplished by us (Scheme 15) [50]. Among the lithium, sodium, and potassium hexamethyldisilazides, LiHMDS serves as the best base for this addition reaction, which indicates that the strong Li–O coordination in the carbinolate intermediate **49** plays a very important role in the success of the reaction (Scheme 15). Furthermore, under the same reaction conditions, the similar nucleophilic addition reactions between $(PhSO_2)_2CHX$ (X = Cl or H) and PhCHO were unsuccessful. That means the fluorine substitution is also very important for the nucleophilic fluoroalkylation reaction, which was further supported by DFT calculations.

The copper-mediated perfluoroalkyl (or trifluoromethyl) cross-coupling reaction, involving an "R_f-Cu" species, are well documented; however, corresponding difluoromethylation involving a "RCF_2-Cu" intermediate was less studied. It is believed that the carbon–metal covalent bond in fluorinated carbanion will tune its reactivity. Recently, we systematically studied the Cu-mediated fluoroalkylation reactions with iododifluoroacetamides **50** (Scheme 16) [51]. It was found that three types of reactions (cross-coupling, intramolecular cyclization, and homocoupling reactions) may coexist in this Cu-mediated reaction between the reagent **50** and aryl/alkenyl iodides. The selectivity among these three types of reactions could be controlled by tuning the substituents on the nitrogen atom of iododifluoroacetamides, and/or by removing the cross-coupling reaction partner (aryl/alkenyl halides).

By using $PhSO_2CF_2TMS$/CuI/CsF in DMF, $PhSO_2CF_2Cu$ (**54**) was successfully prepared, which was found to undergo efficiently cross-coupling reactions with propargyl chlorides and alkynyl halides to give relative allenes (**55**) and alkynes (**56**) (Scheme 17) [52].



Scheme 16 Cu-mediated fluoroalkylation reactions with iododifluoroacetamides **50**

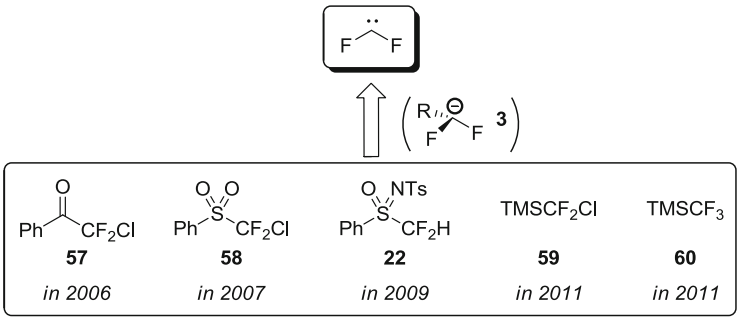


Scheme 17 Cross-coupling reactions with $PhSO_2CF_2Cu$

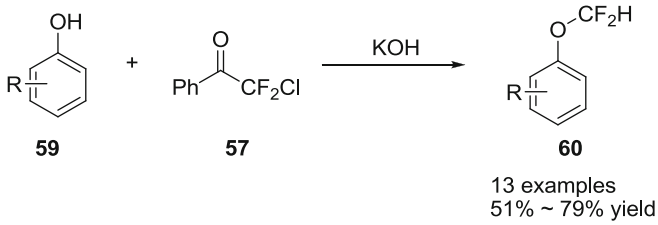
3.4 Modulating the Fluoroalkylation Reactions by Enhancing the Generation of Carbene Species

As mentioned in the discussion of "NFE," the Factor 1 (self-decomposition of carbanion **3**) should always have a negative effect for nucleophilic fluoroalkylation reactions; however, by enhancing this decomposition, novel and efficient difluorocarbene reagents were successfully developed by our research group (Scheme 18) [42, 53–56]. Difluorocarbene is the most stable dihalocarbene due to the interaction of the carbene center with the lone pairs of fluorine [57]. Typical synthetic applications of difluorocarbene include (1) homocoupling at very high temperature to produce tetrafluoroethylene [58], (2) reacting with O-, S-, N-, P-, and C-nucleophiles to give difluoromethylated products, and (3) undergoing [2 + 1] cycloaddition with alkynes or alkenes [57].

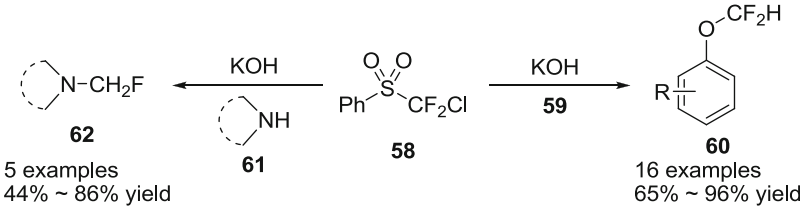
In 2006 we reported a novel and non-ODS-based (ODS = ozone-depleting substance) difluorocarbene reagent **57** (Scheme 19) [53]. 2-Chloro-2,2-



Scheme 18 New difluorocarbene reagents



Scheme 19 Difluoromethylation with carbene reagent **57**

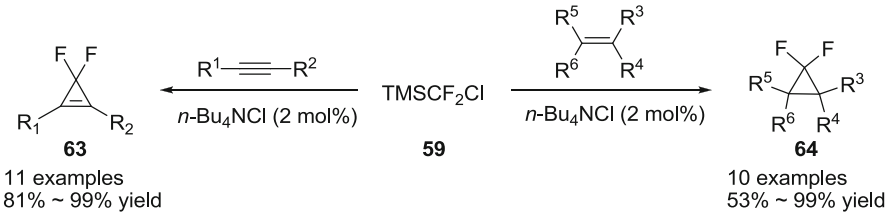


Scheme 20 Difluoromethylation with carbene reagent **58**

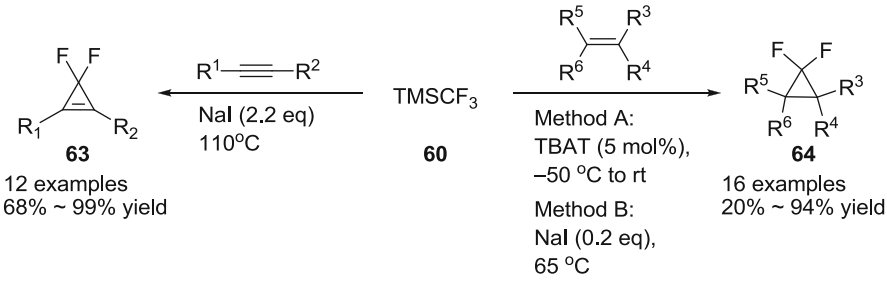
difluoroacetophenone (**57**) was found to react readily with a variety of structurally diverse phenol derivatives (**59**) to produce aryl difluoromethyl ethers (**60**) in good yields.

In 2007 another environmentally friendly difluorocarbene reagent was developed by us (Scheme 20) [54]. Chlorodifluoromethyl phenyl sulfone (**58**) was prepared with non-Freon- or Halon-based procedures, and the compound was found to be an efficient difluorocarbene reagent for O- and N-difluoromethylation of phenols and N-heterocycles.

As mentioned above, the reagent **22** ($PhSO(NTs)CF_2H$) can be used to transfer the CF_2H group to S-, N-, and C-nucleophiles with a difluorocarbene mechanism [42]. However, besides the reagent **22**, $PhCOCF_2Cl$ (**57**) and $PhSO_2CF_2Cl$ (**58**) were found to be incapable of undergoing [2 + 1] cycloaddition reactions with alkynes or alkenes.



Scheme 21 Difluoromethylation with carbene reagent **59**



Scheme 22 [2 + 1] Cycloaddition by using $TMSCF_3$ as a difluorocarbene reagent

In 2011 we reported that $TMSCF_2Cl$ (**59**) can be used as a relatively nontoxic difluorocarbene precursor (Scheme 21) [55]. Under mild and neutral conditions, by using chloride ion as a catalyst, difluorocarbene can be efficiently generated from $TMSCF_2Cl$ (**59**), which will undergo [2 + 1] cycloaddition reactions with alkynes and alkenes to give *gem*-difluorocyclopropenes (**63**) and difluorocyclopropanes (**64**).

Trifluoromethyltrimethylsilane ($TMSCF_3$ **60**), known as Ruppert–Prakash reagent, is the most widely used nucleophilic trifluoromethylating agent for a variety of applications. Recently, an efficient method for the generation of difluorocarbene from $TMSCF_3$ (**60**) was successfully developed (Scheme 22) [56]. It was found that TBAT was able to initiate decomposition of **60** to generate difluorocarbene at low temperatures to give corresponding *gem*-difluorocyclopropane (**64**) in good yields (Method A) and, promoted by NaI, the [2 + 1] cycloaddition reactions of alkenes and alkynes at higher temperatures were also successful (Method B).

4 Conclusion

The incorporation of fluorine atom(s) into organic compounds has become a useful strategy in drug design and new functional material development. The presence of fluorine on a carbanion center will dramatically influence the nucleophilic alkylation reactions. Based on our research, we noticed that, in many cases, the fluorine substitution on the carbanionic carbon poses a negative effect in nucleophilic

fluoroalkylation reactions. We proposed this effect as "NFE." At least two factors were believed to contribute to the NFE: (1) thermal instability of fluorinated carbanions caused by α-elimination (self-decomposition) and (2) the intrinsic nucleophilicity of fluorinated carbanion influenced by the fluorine atoms (such as hard/soft nature of the fluorinated carbanions). Although a comprehensive understanding of the unusual reactivity of fluorinated carbanions needs more investigations and insights, our discussion in terms of NFE is hoped to be helpful to understand many nucleophilic fluoroalkylation reactions. During the past several years, our group has attempted to design nucleophilic fluoroalkylation reactions by tackling the NFE with fluorinated sulfones and related reagents. Our research results were summarized as four methods to modulate the fluoroalkylation reactions: (1) changing the number of fluorine atoms, (2) slightly changing the neighboring groups, (3) changing the metal counterion, including using carbon–metal covalent bond to tune the reactivity, and (4) enhancing the generation of carbene species.

Acknowledgments We are grateful to the following agencies for financial support: the National Natural Science Foundation of China (20825209, 20772144, 20832008) and the Chinese Academy of Sciences.

References

1. Müller K, Faeh C, Diederich F (2007) Fluorine in pharmaceuticals: looking beyond intuition. Science 317:1881
2. Bégué J-P, Bonnet-Delpon D (2008) Bioorganic and medicinal chemistry of fluorine. Wiley, Hoboke
3. Hagmann WK (2008) The many roles for fluorine in medicinal chemistry. J Med Chem 51:4359
4. Prakash GKS, Chacko S (2008) Novel nucleophilic and electrophilic fluoroalkylation methods. Curr Opin Drug Discov Dev 11:793
5. Kirsch P (2004) Modern fluoroorganic chemistry: synthesis, reactivity, applications. Wiley-VCH, Weinheim
6. Banks RE, Smart BE, Tatlow JC (1994) Organofluorine chemistry: principles and commercial applications. Plenum, New York
7. O'Hagan D, Schaffrath C, Cobb SL, Hamilton JTG, Murphy CD (2002) Biochemistry: biosynthesis of an organofluorine molecule. Nature 416:279
8. Uneyama K (2006) Organofluorine chemistry. Blackwell, Oxford
9. Chambers RD (2004) Fluorine in organic chemistry. Blackwell, Oxford
10. Prakash GKS, Hu J (2007) Selective fluoroalkylations with fluorinated sulfones, sulfoxides, and sulfides. Acc Chem Res 40:921
11. Farnham WB (1996) Fluorinated carbanions. Chem Rev 96:1633
12. Prakash GKS, Yudin AK (1997) Perfluoroalkylation with organosilicon reagents. Chem Rev 97:757
13. Prakash GKS, Krishnamurti R, Olah GA (1989) Synthetic methods and reactions. 141. Fluoride-induced trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane (TMS-CF_3). A trifluoromethide equivalent. J Am Chem Soc 111:393
14. Hagiwara T, Fuchikami T (1995) Difluoroalkylation of carbonyl compounds with (1,1-difluoroalkyl)silane derivatives. Synlett 7:717

15. Hu J, Zhang W, Wang F (2009) Selective difluoromethylation and monofluoromethylation reactions. Chem Commun 7465
16. Ni C, Hu J (2011) Selective nucleophilic fluoroalkylations facilitated by removable activation groups. Synlett 6:770
17. Bickelhaupt FM, Hermann HL, Boche G (2006) α-Stabilization of carbanions: fluorine is more effective than the heavier halogens. Angew Chem Int Ed 45:823
18. Faustov VI, D'yachenko AI, Nefedov OM (1979) Unstable organolithium halide compounds. Communication 7. Thermodynamic calculations of the mechanism of decomposition of organolithium halide compounds. Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya 2183
19. Boche G, Lohrenz JCW (2001) The electrophilic nature of carbenoids, nitrenoids, and oxenoids. Chem Rev 101:697
20. Capriati V, Florio S (2010) Anatomy of long-lasting love affairs with lithium carbenoids: past and present status and future prospects. Chem Eur J 16:4152
21. Stahly GP (1989) Nucleophilic addition of difluoromethyl phenyl sulfone to aldehydes and various transformations of the resulting alcohols. J Fluor Chem 43:53
22. Hine J, Porter JJ (1960) Formation of difluoromethylene from difluoromethyl phenyl sulfone and sodium methoxide. J Am Chem Soc 82:6178
23. Hu J (2009) Nucleophilic, radical, and electrophilic (phenylsulfonyl) difluoromethylations. J Fluor Chem 130:1130
24. Ni C, Li Y, Hu J (2006) Nucleophilic fluoroalkylation of epoxides with fluorinated sulfones. J Org Chem 71:6829
25. Ni C, Liu J, Zhang L, Hu J (2007) A remarkably efficient fluoroalkylation of cyclic sulfates and sulfamidates with $PhSO_2CF_2H$: facile entry into β-difluoromethylated or β-difluoromethylenated alcohols and amines. Angew Chem Int Ed 46:786
26. Fleming I (1976) Frontier orbitals and organic chemical reactions. Wiley, New York
27. Ho T-L (1977) Hard and soft acids and bases principle in organic chemistry. Academic, New York
28. Ni C, Zhang L, Hu J (2008) Nucleophilic fluoroalkylation of α, β-enones, arynes, and activated alkynes with fluorinated sulfones: probing the hard/soft nature of fluorinated carbanions. J Org Chem 73:5699
29. Prakash GKS, Hu J, Olah GA (2003) Preparation of tri- and difluoromethylsilanes via an unusual magnesium metal-mediated reductive tri- and difluoromethylation of chlorosilanes using tri- and difluoromethyl sulfides, sulfoxides, and sulfones. J Org Chem 68:4457
30. Prakash GKS, Hu J, Wang Y, Olah GA (2004) Nucleophilic difluoromethylation of primary alkyl halides using difluoromethyl phenyl sulfone as a difluoromethyl anion equivalent. Org Lett 6:4315
31. Prakash GKS, Hu J, Wang Y, Olah GA (2004) Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: use in the synthesis of 1,1-difluoro-1-alkenes. Angew Chem Int Ed 43:5203
32. Prakash GKS, Hu J, Mathew T, Olah GA (2003) Difluoromethyl phenyl sulfone as a selective difluoromethylene dianion equivalent: one-pot stereoselective synthesis of anti-2, 2-difluoropropane-1,3-diols. Angew Chem Int Ed 42:5216
33. Prakash GKS, Hu J, Wang Y, Olah GA (2005) Convenient synthesis of difluoromethyl alcohols from both enolizable and non-enolizable carbonyl compounds with difluoromethyl phenyl sulfone. Eur J Org Chem 2218
34. Ye J-D, Liao X, Piccirilli JA (2005) Synthesis of 2′-C-difluoromethylribonucleosides and their enzymatic incorporation into oligonucleotides. J Org Chem 70:7902
35. Liu J, Ni C, Wang F, Hu J (2008) Stereoselective synthesis of α-difluoromethyl-β-amino alcohols via nucleophilic difluoromethylation with $Me_3SiCF_2SO_2Ph$. Tetrahedron Lett 49:1605
36. Li Y, Hu J (2005) Facile synthesis of chiral α-difluoromethyl amines from N-(tert-butylsulfinyl)aldimines. Angew Chem Int Ed 44:5882

37. Liu J, Li Y, Hu J (2007) Stereoselective synthesis of di- and monofluoromethylated vicinal ethylenediamines with di- and monofluoromethyl sulfones. J Org Chem 72:3119
38. Li Y, Ni C, Liu J, Zhang L, Zheng J, Zhu L, Hu J (2006) Stereoselective nucleophilic monofluoromethylation of N-(tert-butanesulfinyl)imines with fluoromethyl phenyl sulfone. Org Lett 8:1693
39. Liu J, Zhang L, Hu J (2008) Stereoselective monofluoromethylation of N-tert-butylsulfinyl ketimines using pregenerated fluoro(phenylsulfonyl)methyl anion. Org Lett 10:5377
40. Reggelin M, Zur C (2000) Sulfoximines. Structures, properties, and synthetic applications. Synthesis 1:1
41. Boys ML, Collington EW, Finch H, Swanson S, Whitehead JF (1988) α-Fluoromethyl-n-methyl-phenylsulfoximine: a new fluoromethylenation reagent. Tetrahedron Lett 29:3365
42. Zhang W, Wang F, Hu J (2009) N-Tosyl-S-difluoromethyl-S-phenylsulfoximine: A new difluoromethylation reagent for S-, N-, and C-nucleophiles. Org Lett 11:2109
43. Noritake S, Shibata N, Makamura S, Toru T, Shiro M (2008) Fluorinated Johnson reagent for transfer-trifluoromethylation to carbon nucleophiles. Eur J Org Chem 3465
44. Nomura Y, Tokunaga E, Shibata N (2011) Inherent oxygen preference in enolate monofluoromethylation and a synthetic entry to monofluoromethyl ethers. Angew Chem Int Ed 50:1885
45. Zhang W, Huang W, Hu J (2009) Highly stereoselective synthesis of monofluoroalkenes from α-fluorosulfoximines and nitrones. Angew Chem Int Ed 48:9858
46. Zhang W, Hu J (2010) Efficient synthesis and ring-opening reactions of monofluorinated epoxides derived from α-fluorosulfoximines. Adv Synth Catal 352:2799
47. Zhao Y, Huang W, Zhu L, Hu J (2010) Difluoromethyl 2-pyridyl sulfone: a new gem-difluoroolefination reagent for aldehydes and ketones. Org Lett 12:1444
48. Prakash GKS, Ni C, Wang F, Hu J, Olah GA (2011) From difluoromethyl 2-pyridyl sulfone to difluorinated sulfonates: a protocol for nucleophilic difluoro(sulfonato)methylation. Angew Chem Int Ed 50:2559
49. Liu J, Hu J (2010) Highly diastereoselective synthesis of α-difluoromethyl amines from N-tert-butylsulfinyl ketimines and difluoromethyl phenyl sulfone. Chem Eur J 16:11443
50. Shen X, Zhang L, Zhao Y, Zhu L, Li G, Hu J (2011) Nucleophilic fluoromethylation of aldehydes with fluorobis(phenylsulfonyl)methane: the importance of strong Li-O coordination and fluorine substitution for C-C bond formation. Angew Chem Int Ed 50:2588
51. Zhu J, Zhang W, Zhang L, Liu J, Zheng J, Hu J (2010) Copper-mediated fluoroalkylation reactions with iododifluoroacetamides: controlling the selectivity among cross-coupling, intramolecular cyclization, and homocoupling reactions. J Org Chem 75:5505
52. Zhu J, Wang F, Huang W, Zhao Y, Ye W, Hu J (2011) Copper-mediated fluoroalkylation reactions with [(phenylsulfonyl)-difluoromethyl] trimethylsilane: synthesis of $PhSO_2CF_2$-containing allenes and alkynes. Synlett 7:899
53. Zhang L, Zheng J, Hu J (2006) 2-Chloro-2,2-difluoroacetophenone: a non-ODS-based difluorocarbene precursor and its use in the difluoromethylation of phenol derivatives. J Org Chem 71:9845
54. Zheng J, Li Y, Zhang L, Hu J, Meuzelaar GJ, Federsel H-J (2007) Chlorodifluoromethyl phenyl sulfone: a novel non-ozone-depleting substance-based difluorocarbene reagent for O- and N-difluoromethylations. Chem Commun 48:5149
55. Wang F, Zhang W, Zhu J, Li H, Huang K-W, Hu J (2011) Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of gem-difluorinated cyclopropenes and cyclopropanes. Chem Commun 47:2411
56. Wang F, Luo T, Hu J, Wang Y, Krishnan HS, Jog PV, Ganesh SK, Prakash GKS, Olah GA (2011) Synthesis of gem-difluorinated cyclopropanes and cyclopropenes using $TMSCF_3$ as a difluorocarbene source. Angew Chem Int Ed. 50:7153
57. Brahms LS, Dailey WP (1996) Fluorinated carbenes. Chem Rev 96:1585
58. Hudlicky M, Pavlath AE (1995) Chemistry of organic fluorine compounds II. American Chemical Society, Washington DC