

Selective Nucleophilic Fluoroalkylations Facilitated by Removable Activation Groups

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Received 3 November 2010

Abstract: Selective incorporation of fluorine atoms or fluorine-containing moieties into organic molecules has become a routine and powerful strategy in drug design and new functional-material development. Nucleophilic fluoroalkylation, typically involving the transfer of a fluorinated carbanion or carbanion equivalent to an electrophile, is one of the most important and frequently used methods to synthesize fluorinated organic molecules. In this Account, we introduce some recent achievements in the field of nucleophilic di- and monofluoroalkylation chemistry with functionalized fluoroalkylation reagents. In particular, the effect of fluorine substitution on the reactivity of carbanions is discussed, and several strategies for improving nucleophilic fluoroalkylations are proposed and successfully applied in various new nucleophilic fluoroalkylation reactions. It was found that attaching a removable activation group (such as the phenylsulfonyl group) to a fluorinated carbanion is an important approach to improve the latter's reactivity.

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Key words: fluorine, nucleophilic fluoroalkylation, activation group, sulfone, fluorine effect

1 Introduction

Fluorine, characterized by its small size and high electronegativity, can impart fabulous chemical and biological properties to an organic molecule, including the stability, high lipophilicity, and bioavailability that can favorably change in vivo drug transport and absorption rates.¹ As a small atom with a big ego, fluorine has become an ubiquitous element in pharmaceutical-, agrochemical- and material-related applications.^{1,2} Although there are only very few (around 13) organofluorine compounds among nearly 3200 known naturally occurring organohalogen compounds,³ till 2010 about 55% of the approximate 7.2 million man-made organohalogen compounds contain at least one carbon–fluorine bond.⁴ Among all these documented fluorinated structures, many of them can be constructed from simple fluorine-containing starting materials in virtue of the building-block methodology. However, fluorination and fluoroalkylation, as the two major synthetic methods to prepare selectively fluorinated organic compounds, will prevail over the former when the desired fluorinated molecules are complex and the incorporation of the fluorine or fluoroalkyl groups must occur at a late stage of their synthesis.

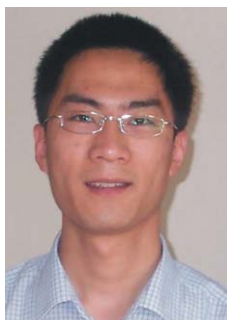
In the field of fluoroalkylation chemistry, although both free-radical fluoroalkylation and electrophilic fluoroalkylation are well known, nucleophilic fluoroalkylation possesses a number of advantages and thus has become one of the most important methods for incorporation of fluorinated moieties into organic molecules.⁵ Nucleophilic fluoroalkylation typically features the transfer of a fluoroalkyl group 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. The major known preparative methods for nucleophilic fluoroalkylating species include: (a) addition of nucleophiles (especially fluoride ion) to fluorinated olefins, (b) deprotonation of hydrofluorocarbons with a proper base, (c) metal–halogen exchange reaction (such as the reaction between methyl lithium and perfluoroalkyl iodide), (d) reduction of fluoroalkyl halides by metals (such as Mg, Zn, etc.), and (e) Lewis base activated generation using organosilicon reagents.^{2c,6,7}

During the past half century, nucleophilic perfluoroalkylation using organometallic reagents of lithium, magne-

sium, and zinc, among others, have 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.⁶ Since Prakash and Olah's first report of nucleophilic trifluoromethylation of carbonyls using stable organosilicon reagent (trifluoromethyl)trimethylsilane (TMSCF₃, now known as Ruppert–Prakash reagent) under the initiation of a fluoride in 1989,^{6b} nucleophilic trifluoromethylation was creatively solved and perfluoroalkyl silanes have become the most widely used reagents in nucleophilic perfluoroalkylation.^{5,6} More recently, due to the many findings that difluoromethyl- and monofluoromethyl-containing compounds often exhibit unique biological properties, there is a growing interest in developing new synthetic methods for nucleophilic difluoromethylation and monofluoromethylation. However, due to the lower polarization of C–Si bond, initial results showed that nucleophilic difluoromethylation with compound R₃Si–CF₂H had to be conducted under harsh conditions, which made it less likely to become a widely used difluoromethylation reagent.⁸ Similarly, the analogous R₃Si–CH₂F compound is even more stable and less likely to be a viable monofluoromethylation reagent.

The introduction of removable activation groups (RAG) to fluoromethyl anions can facilitate the nucleophilic difluoromethylation and monofluoromethylation reactions. In this Account, we will introduce the recent synthetic achievements in this field from both our laboratory and some others. Particularly, the negative effect of the fluorine substitution on the reactivity of carbanions and our rationalization for its solution with RAG method will be discussed.

Biographical Sketches



Chuanfa Ni was born in Shandong, P. R. of China in 1982. He obtained his BSc degree in chemistry from Shandong Normal University in 2003. After receiving his PhD degree in 2009

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Jinbo Hu was born in Zhejiang, P. R. of China in 1973. After he completed his BSc (Hangzhou University) and MSc (Chinese Academy of Sciences) degrees, he did his PhD work during 1997 to 2002 at the University of Southern California (USC), USA, with

Professors G. K. S. Prakash and G. A. Olah. After his postdoctoral work at USC, he accepted the Research Professorship at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early 2005, where he is currently the Head of the CAS

Key Laboratory of Organofluorine Chemistry. He is the recipient of the RSC Fluorine Prize 2009. His current research interests include selective fluorination, defluorination, fluoroalkylation methodologies, and fluorinated materials.

2 The Fluorine Effect in Nucleophilic Fluoroalkylation Reactions

Similar to the classification of aziridinylium anions,⁹ on the basis of the nature of the substituent on the anionic or metal-bearing fluorinated carbon atom, the fluoroalkyl anions can be classified as activated, when an electron-withdrawing group (such as sulfonyl, sulfinyl, sulfanyl, phosphinyl, carbonyl, perfluoroalkyl, ester, cyano, nitro, etc.) is present on the anionic carbon and unactivated in the absence of such groups. 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 CF₃[–], CHF₂[–], CH₂F[–], etc.), the negative charge has to be more localized on the anionic carbon.

2.1 Unique Properties of Fluorinated Carbanions

For a better understanding of the fluorine effect in nucleophilic fluoroalkylation reactions, the unique effect of fluorine substitution on the carbanions (R_f[–]) can be discussed in three aspects: (1) the acidity (the generation of the anion), (2) the thermodynamic stability, and (3) the kinetic stability (lifetime of the anion).

When we consider 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^{1a} of C–H ionization (ΔH_{calcd} , kcal/mol) in the gas phase are as

follows: 368.9 (CF₃–H) < 391.3 (CHF₂–H) < 406.3 (CH₂F–H) < 416.8 (CH₃–H), which reveals that the production of CF₃[–] by deprotonation will be much easier than CH₃[–].

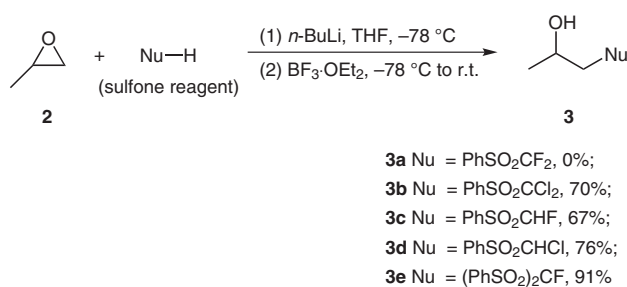
When we consider the thermodynamic stability of a fluorinated carbanion itself, fluorine substitution is more effective in α -stabilization of a methyl carbanion than other halogen atoms and hydrogen substitution itself. The calculated enthalpy values by Bickelhaupt and co-workers¹⁰ for homolytic cleavage of the C–F bonds in CH₂F[–] (117.0 kcal/mol) is higher than the cleavage of C–H bonds in CH₃[–] (103.2 kcal/mol), which indicates that CH₂F[–] is thermodynamically more stable than CH₃[–].¹⁰

When we consider 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 certain stabilization influence through the 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.¹¹ These fluoromethyl metal species display carbenoid reactivity.¹² 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: CH₃[–] > CFH₂[–] > CF₂H[–] > CF₃[–].

2.2 Factors Influencing the Reactivity of Fluorinated Carbanions towards the Electrophiles

Although the unique stability issue of fluorinated carbanions has been discussed previously,^{1a,5–7,10–12} the chemical reactivities of various fluorinated methyl anions in nucleophilic fluoroalkylation reactions were not well summarized. This was mainly due to the lack of systematic study of per-, poly-, tri-, di-, and monofluoroalkylation reactions. As the ‘chemical chameleon’ in organic synthesis, the sulfone functionality (such as PhSO₂R) possesses strong electron-withdrawing ability and is ideal for various types of reactions: 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. In 1989, Stahly reported the use of difluoromethyl phenyl sulfone (PhSO₂CF₂H, **1**) as a difluoromethylation reagent.¹³ The reaction between **1** and excess amount of aldehydes in the presence of aqueous NaOH and a phase-transfer catalyst gave the (phenylsulfonyl)difluoromethyl carbinols in good yields. In the subsequent research, it was found that (phenylsulfonyl)difluoromethyl group could be introduced to a series of electrophiles with **1** as the reagent and the so-obtained (phenylsulfonyl)difluoromethyl-substituted intermediates could undergo many further transformations.^{5b,13d}

In 2006, during our study of nucleophilic ring-opening fluoroalkylation of epoxides with di- and monofluoro-(phenylsulfonyl)methyl lithium, we found that α -fluorine substitution on the carbanion dramatically decreases the



Scheme 1 Nucleophilic ring-opening fluoroalkylation of epoxides

carbanion's reactivity towards epoxides (Scheme 1).¹⁴ From the product yields, we can see that the nucleophilicity of halogenated sulfone anions (Nu[–]) toward propylene oxide (**2**) decreases in the following order: (a) for fluorinated anions: (PhSO₂)₂CF[–] > PhSO₂CHF[–] > PhSO₂CF₂[–]; (b) for different halogen-substituted anions: PhSO₂CCl₂[–] > PhSO₂CF₂[–].

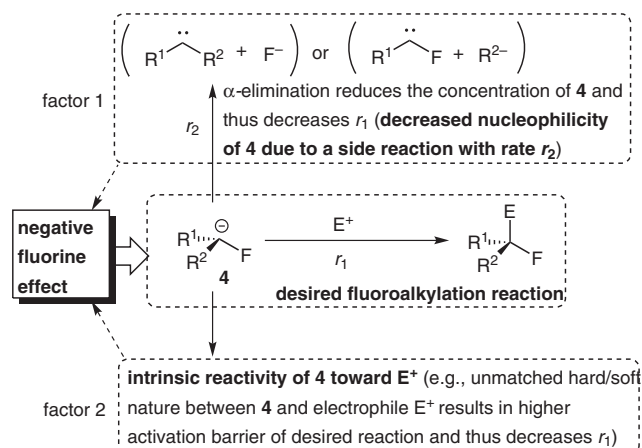
We described this negative (unfavorable) influence of fluorine substitution on the reactivity of the carbanions as ‘negative fluorine effect (NFE)’.^{14,15} The difficulty of the ring-opening reaction between an epoxide and a fluorinated carbanion can be attributed to (a) the unique properties of the fluorine-bearing carbanion (R_F[–]), that is, its low thermal stability caused by its high tendency to undergo α -elimination of a fluoride ion (or another leaving group) due to the strong electron repulsion between the 2s- or 2p-electron pairs on the small fluorine atom(s) and the electron lone pair occupying the 2p-orbital (or an sp³-hybridized orbital) of the carbanionic carbon, as well as (b) its intrinsic low nucleophilicity towards epoxides.^{14a} The schematic depiction of NFE is shown in Scheme 2. For the desired nucleophilic reaction between fluorinated carbanion **4** (R¹, R² = H, F, Alk, Ar, etc.) and electrophile E⁺, two factors are involved:

Factor 1: the α -elimination reaction (with reaction rate r_2) acts as a competitive side reaction of the desired fluoroalkylation reaction (with r_1), and the former reaction reduces the concentration of carbanion **4** and thus decreases r_1 .

Factor 2: the intrinsic reactivity of fluorinated carbanion **4** toward electrophile E⁺. This can be influenced by many factors, such as the match of the hard/soft nature between **4** and E⁺. For instance, the increased hardness of **4** – arising from more fluorine substitution – can result in a higher activation barrier of the desired reaction with soft electrophiles (such as alkyl iodides),^{16,17} and thus decreases the desired reaction rate r_1 (we call this ‘intrinsic low nucleophilicity’ just to differentiate the factor 2 from factor 1).

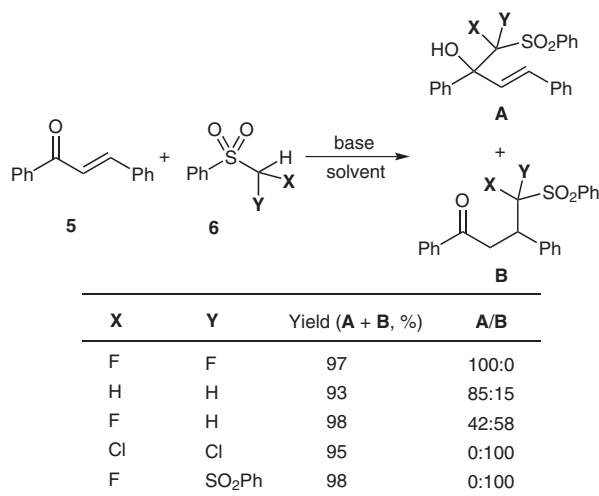
It should be pointed out that, no matter what kind of electrophile E⁺ is applied, factor 1 (self-decomposition of carbanion **4**) should always have a negative (unfavorable) influence on the desired nucleophilic fluoroalkylation reaction. However, the influence of factor 2 depends on the intrinsic reactivity of **4** toward an electrophile E⁺, which is independent from factor 1. Combining factor 1 and 2 together, we can understand that there often exists a signif-

icant but quite subtle fluorine effect in many nucleophilic fluoroalkylation reactions involving a fluorinated carbanion.



Scheme 2 Schematic depiction of the 'negative fluorine effect'

By using the 1,2- and 1,4-addition-product ratio as a probe to determine the hard/soft nature of different carbanions (Scheme 3), our recent studies on the nucleophilic (phenylsulfonyl)methylation of α,β -enones^{14b,18} disclosed the order of softness of halogenated carbanions and can be given as follows: $(PhSO_2)_2CF^- \approx PhSO_2CCl_2^- > PhSO_2CHF^- > PhSO_2CF_2^- (\geq CF_3^-)$.^{14b,18}



Scheme 3 1,2- and 1,4-Additions to α,β -enones with carbanions

2.3 Possible Strategies to Improve the Nucleophilic Fluoroalkylations

Based on the above discussions of factors influencing the nucleophilic fluoroalkylation with fluorinated carbanions, we can accordingly propose three strategies to improve the nucleophilic fluoroalkylations as follows:

Strategy 1: to make the fluorinated carbanions thermally more stable. This can be achieved by attaching an electron-withdrawing group (such as sulfonyl, sulfinyl, sulfonyl, phosphinyl, carbonyl, perfluoroalkyl, ester, cyano,

nitro, etc.) that is able to stabilize the fluorinated carbanion via electron delocalization. As a result, the factor 1 in Scheme 2 (the self-decomposition of the anion via α -elimination) can be significantly diminished, and the desired nucleophilic fluoroalkylation reaction is improved. Such functional groups can also facilitate the formation of the carbanions by deprotonation.

Strategy 2: to make the fluorinated carbanions 'softer'. Since many carbon electrophiles (such as alkyl iodides and activated alkenes and alkynes) are 'soft', they favor reacting with soft fluorinated carbanions. This strategy can be achieved by applying 'softening' functional groups such as phenylsulfonyl, carbonyl, and phenylthio groups. Since softening groups also can stabilize the fluorinated carbanions, in many cases strategies 1 and 2 can be applied jointly.

Strategy 3: to make the electrophiles (the substrates for nucleophilic fluoroalkylation) more electrophilic. Since the fluorinated carbanions are generally less nucleophilic due to the NFE, the enhanced electrophilicity of the substrates will offset the NFE and make the desired fluoroalkylation reaction proceed smoothly.

During the past several years, we have attempted to apply these three strategies in understanding and design nucleophilic fluoroalkylation reactions with fluorinated sulfones and related reagents. Besides the arylsulfonyl group, some other functional groups, such as phosphinyl and ester group, can also be removed under certain conditions, so they are also used for this purpose. Due to the tremendous growth in the field of asymmetric organocatalysis,¹⁹ fluorinated carbon acids displayed impressive profiles in asymmetric fluoroalkylations. Although negative fluorine effect (NFE) could not be used to summarize all reactivity aspects of fluoroalkyl anions in nucleophilic fluoroalkylation reactions, it is at least helpful to understand many nucleophilic fluoroalkylation reactions. The results (as presented in the next section) indicate that both understanding NFE and applying the strategies to tackle NFE are highly beneficial to predict and design new efficient nucleophilic fluoroalkylation reactions.

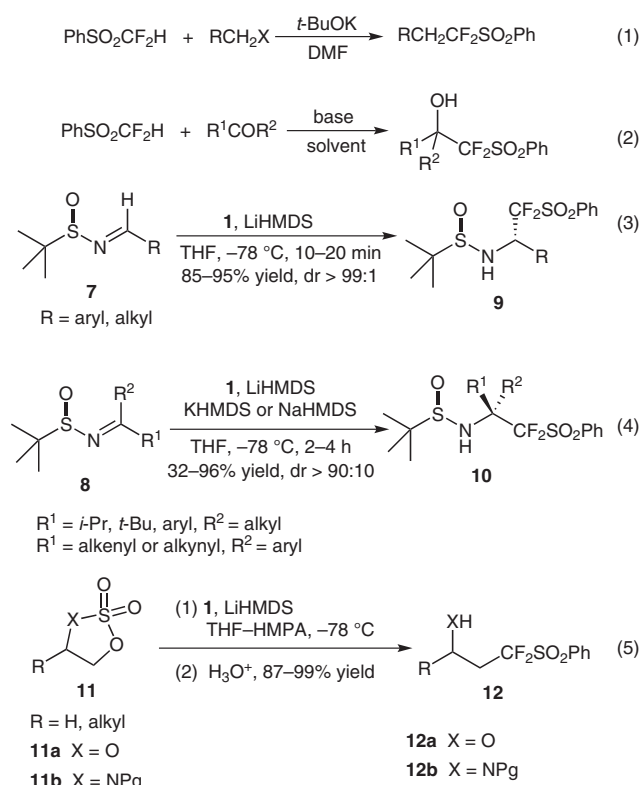
3 Nucleophilic Di- and Monofluoroalkylation Reactions

3.1 Nucleophilic Difluoromethylation with $PhSO_2CF_2H$ and Related Reagents

Due to the low thermal stability of difluoromethyl anion, the α -elimination of LiF from CF_2HLi will be predominant.¹² Given that the repulsion between the electron lone pair occupying the p-orbital of the anionic carbon and the electron lone pairs on the fluorine atoms is the origin of the thermal instability of CF_2H^- , replacing the hydrogen atom with an electron-withdrawing substituent may diminish the repulsion and thus increase the thermal stability of the carbanions. Thus, a new stabilized ' CF_2H^- ' synthon emerged.

In the beginning of our research, the introduction of an electron-withdrawing sulfonyl group to the fluoroalkyl anions had been exploited (strategy 1, as mentioned in Section 2.3). On one hand, the electron delocalization by the sulfonyl group can reduce the electron repulsion between the electron pairs on the carbanionic carbon and those on the fluorine atoms; on the other hand, the sulfonyl group acts as a good auxiliary group that can be readily removed by reductive desulfonylation after desired transformations.

By using difluoromethylsulfone **1** as a nucleophilic difluoromethylating agent, the (phenylsulfonyl)difluoromethyl group can be incorporated into a series of electrophiles such as alkyl halides, aldehydes, ketones, imines, esters, disulfides, cyclic sulfates, and cyclic sulfamidates (Scheme 4).^{5b,20–22} After reductive removal of the sulfonyl group, difluoromethylated alcohols, amines, and alkanes could be prepared (Scheme 5).

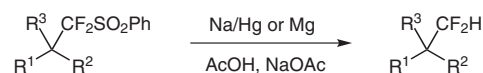


Scheme 4 Nucleophilic difluoromethylation of halides, carbonyls, imines cyclic sulfates, and sulfamidates with PhSO₂CF₂H (**1**)

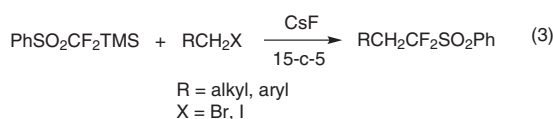
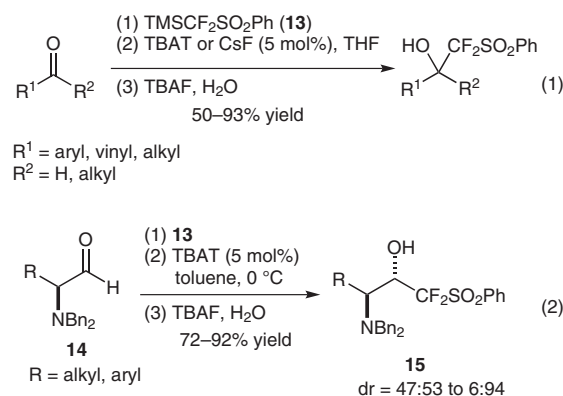
The in situ generated PhSO₂CF₂[−] anion can react with a variety of structurally diverse *N*-*tert*-butylsulfinyl aldimines **7**^{22a} and ketimines **8**^{22b} to give the corresponding chiral sulfinamides **9** and **10** in excellent yields and with very high diastereoselectivity (Scheme 4, eq. 3 and 4). The thermal stability, good nucleophilicity, and the softness of the in situ generated (phenylsulfonyl)difluoromethyl anion accounts for high efficiency of these reactions. Unlike aldimines and β-acetylenic *N*-*tert*-butylsulfinyl ketimines, the reaction between the anion and β-unsaturated *N*-*tert*-butylsulfinyl ketimines is highly dependent on

the metal counterions. The later preferred potassium base to other metal bases, while the former showed little base preference. It is believed that the kinetically preferred generation of the PhSO₂CF₂[−] anion by KHMDS and nucleophilic addition of the PhSO₂CF₂[−] anion to ketimines over the undesired aza-enolization of ketimines are the key factors for the success of difluoromethylation of simple ketimines. Reductive desulfonylation of the *N*-*tert*-butylsulfinyl sulfinamides using either Na/Hg amalgam or Mg/AcOH/NaOAc followed by acid alcoholysis provided a convenient and facile preparation of various enantiopure secondary and tertiary α-difluoromethyl amines (Scheme 5).²²

However, as mentioned in the discussion of NFE, the reactions between PhSO₂CF₂[−] anion and epoxides (or aziridines) failed to give the β-difluoromethyl alcohols (or amines). We overcome this synthetic limitation by using strategy 3 as mentioned in Section 2.3, that is, using the more electrophilic epoxide and aziridine equivalents, 1,2-cyclic sulfates (**11a**) and sulfamidates (**11b**) (Scheme 4, eq. 5).¹⁵ Nucleophilic (phenylsulfonyl)difluoromethylation of 1,2-cyclic sulfates **11a** and sulfamidates **11b** with in situ generated PhSO₂CF₂[−] anion affords the corresponding β-(phenylsulfonyl)difluoromethylated products **12a** and **12b** in excellent yields, respectively. Upon reductive desulfonylation, compounds **12** can be readily transformed into β-difluoromethylated alcohols and amines.¹⁵



Scheme 5 Preparation of difluoromethylated compounds via reductive desulfonylation



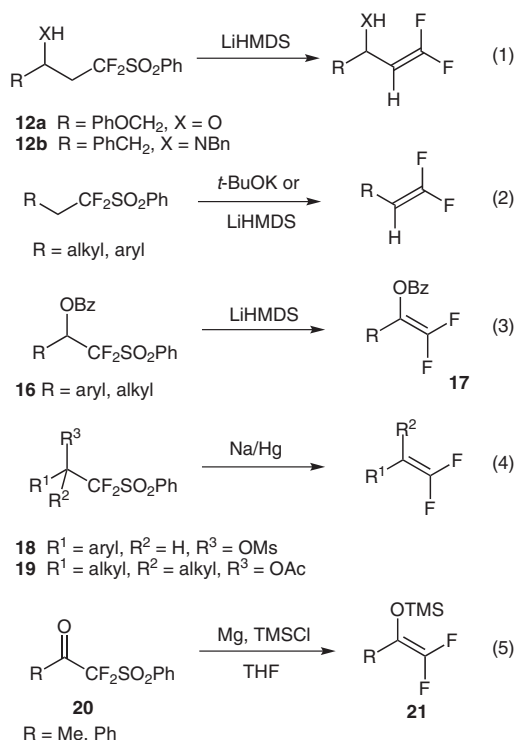
Scheme 6 Nucleophilic difluoromethylation of alkyl halides and carbonyl compounds with TMSCF₂SO₂Ph (**13**)

Due to the mildness of the reaction conditions used for nucleophilic trifluoromethylation with TMSCF₃ reagent, TMSCF₂SO₂Ph (**13**) is expected to possess similar virtue.

TMSCF₂SO₂Ph could be prepared in good yields from PhSO₂CF₂Br by Br/Li exchange.^{23a,b} By using **13** as the reagent via a fluoride-induced (phenylsulfonyl)difluoromethylation protocol, an improved nucleophilic difluoromethylation protocol of carbonyl compounds was achieved (Scheme 6, eq. 1).^{23a} Compared with the PhSO₂CF₂H reagent method, this method avoided the use of excess amount of base and carbonyl compounds and is rather effective with enolizable aldehydes. Diastereoselective synthesis of α -difluoromethyl- β -amino alcohols from α -amino aldehydes **14** can also be achieved by this protocol, otherwise it is difficult to prepare from **1** (Scheme 6, eq. 2).^{23b} Moreover, nucleophilic (phenylsulfonyl)difluoromethylation of both alkyl iodides and bromides was successfully accomplished by using CsF/15-crown-5 as an initiating system in DME, and the amount of 15-crown-5 was found to be critical to the yield of the product (Scheme 6, eq. 3).^{23c}

3.2 Transformations of (Phenylsulfonyl)difluoromethylated Compounds

The phenylsulfonyl group in the (phenylsulfonyl)difluoromethylated products cannot only be replaced by a hydrogen atom via reductive desulfonylation (Scheme 5), but also be elaborated to *gem*-difluoroalkenes and difluoromethylene-containing compounds.



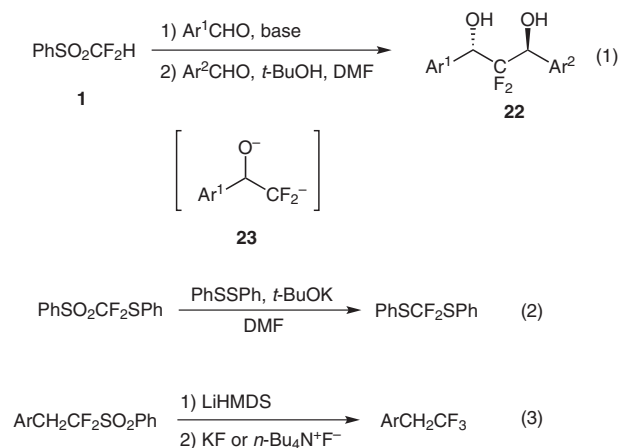
Scheme 7 Transformations of (phenylsulfonyl)difluoromethylated intermediates to *gem*-difluoroalkenes

β -Elimination was the most common pathway for the construction of *gem*-difluoroalkenes from (phenylsulfonyl)difluoromethylated intermediates with an active β -

hydrogen atom. Following this approach, a series of fluorinated alkenes, enolates, allyl alcohols, and amines could be prepared with the assistance of a base (Scheme 7, eq. 1–3).^{15,20,24} When there is a proper leaving group in the β -position, the *gem*-difluoroalkenes can be prepared under reductive conditions (Scheme 7, eq. 4).²⁵ The fluorinated β -ketosulfones **20** prepared by the reaction between carboxylic esters and **1** can also undergo magnesium-mediated reductive desulfonylation in the presence of TMSCl affording the *gem*-difluoro enol silyl ethers **21** (Scheme 7, eq. 5).²⁶

As for the synthesis of difluoromethylene-containing compounds, the chemistry is based on the nucleophilic attack by a nucleophile on the sulfur center of the sulfone (or sulfoxide) to release a fluoroalkyl anion. Thus, potassium *tert*-butoxide-induced difluoromethylation of aromatic aldehydes with **1** affording both symmetrical and unsymmetrical *anti*-2,2-difluoropropane-1,3-diols **22** with high diastereoselectivity (up to 94% de, Scheme 8, eq. 1).²⁷ It is believed that this unusual type of high diastereoselectivity was obtained by means of an intramolecular charge–charge repulsion effect rather than the traditional steric control. Diphenyl disulfide can also work as an electrophile for the trapping of fluoroalkyl anions (Scheme 8, eq. 2).

Furthermore, the phenylsulfonyl group can also be formally substituted by a fluorine atom, via the *gem*-difluoroalkene intermediates formed by β -elimination (Scheme 8, eq. 3).^{22c}

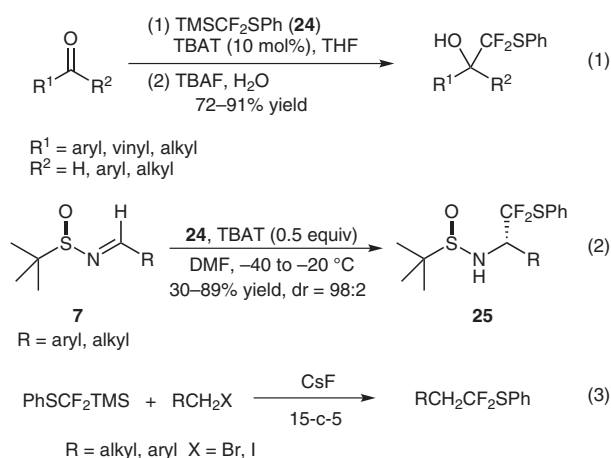


Scheme 8 Transformations of (phenylsulfonyl)difluoromethylated intermediates to *gem*-difluoromethylenated and trifluoromethylated compounds

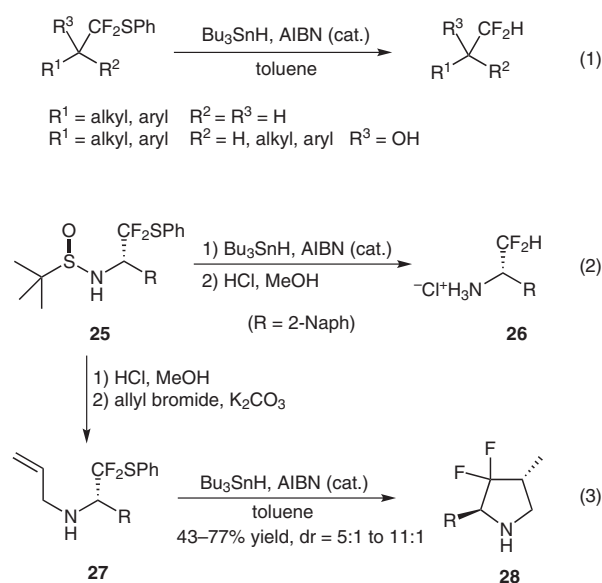
3.3 Nucleophilic Difluoromethylation with TMSCF₂SPh and Related Reagents

The nucleophilic difluoroalkylation of aldehydes and ketones with R₃SiCF₂H⁸ (and TMSCF₂CH₃²⁸) were found to be sluggish, and the asymmetric synthesis of α -fluoroalkyl amines using R₃SiCF₂H and *N*-*tert*-butylsulfinyl imines proved problematic due to the low reactivity of R₃SiCF₂H reagents. This is mainly due to the less polarized Si–CF₂R (R = H or Me) bond.⁸ When the electron-

withdrawing phenylthio group (PhS) was used as an activating group (via the inductive effect), nucleophilic (phenylthio)difluoromethylation of (*R*)-*N*-*tert*-butylsulfanyl imines **7** with TMSCF_2SPh (**24**) under promotion by tetrabutylammonium triphenyldifluorosilicate (TBAT) affords the corresponding products **25** in good yields and with high diastereoselectivity (Scheme 9, eq. 2). The obtained PhSCF_2 -containing sulfonamides **25** cannot only be converted into α -difluoromethyl amines **26** after a radical desulfonation with Bu_3SnH , but also can be further transformed to chiral 2,4-transdisubstituted 3,3-difluoropyrrolidines **28** through an intramolecular radical-cyclization methodology (Scheme 10).^{29a} As a useful reagent, **24** can also react with primary alkyl halides^{29b} and carbonyl compounds^{29c} in a similar way as $\text{TMSCF}_2\text{SO}_2\text{Ph}$ (**13**) does (Scheme 9, eq. 1 and 3). In addition, $\text{TMSCF}_2\text{SePh}$ ³⁰ can also serve as a stable difluoromethylation reagent that is similar to TMSCF_2SPh (**24**).



Scheme 9 Nucleophilic difluoromethylation with TMSCF_2SPh (**24**)



Scheme 10 Transformations of (phenylthio)difluoromethylated compounds

3.4 Nucleophilic Phosphoryldifluoromethylation Reactions

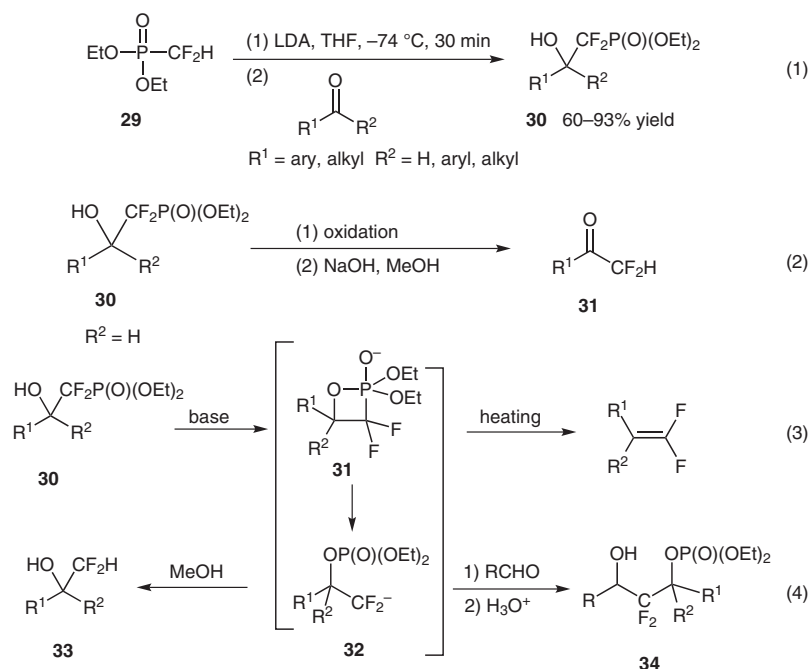
Despite the fact that the phenylsulfonyl group (PhSO_2) can significantly stabilize the fluorinated carbanions, the $\text{PhSO}_2\text{CF}_2^-$ anion is still not stable enough to be pre-generated and stored. As a result, the nucleophilic (phenylsulfonyl)difluoromethylation requires an in situ generation of the $\text{PhSO}_2\text{CF}_2^-$ anion in the presence of an electrophilic reaction partner. However, the thermal stability of the fluorinated carbanion could be improved by attaching an electron-withdrawing group (such as the phosphoryl group) that possesses low leaving ability. For instance, $(\text{EtO})_2\text{P(O)CF}_2^-$ anion can be pre-generated at -78 °C, and thus facilitates the fluoroalkylation of base-sensitive electrophiles. For a long time, $(\text{EtO})_2\text{P(O)CF}_2^-$ anion was most often used as the building block for the synthesis of biologically important fluorinated phosphoric acid, while the further transformation via the cleavage of P-CF_2 bond is very limited. In 1982, Obayashi and co-workers disclosed that a lithium phosphoryl-difluoromethyl carbinolate could undergo Wadsworth–Emmons reaction to give *gem*-difluoroalkenes by heating its THF solution, and this reaction was found to be generally applicable to various ketones and aldehydes (Scheme 11, eq. 3).³¹

In 1996, Piettre et al. reported a three-step synthesis of difluoromethyl ketones **31** from aldehydes, via difluoromethylation–oxidative dephosphorylation strategy (a combination of eq. 1 and 2 in Scheme 11).³² Very recently, Prakash and co-workers showed that the P-CF_2 bond in 1,1-difluoro-2-hydroxyphosphonates **30** could be cleaved via a four-membered ring intermediate **31**.³³ In a protic solvent, the difluoromethyl anion was quenched by proton to give the difluoromethyl alcohol **33**, while in a nonprotic solvent, the difluoromethyl anion could react with a second electrophile, such as benzaldehyde, to afford **34** as a 1:1 mixture of isomers (Scheme 11, eq. 4).³³ $\text{TMSCF}_2\text{P(O)(RO)}_2$ (**35**) can also be used for the synthesis of 2,2-difluoro-1,3-diols with an isomeric ratio of 1:1 initiated by a catalytic amount of CsF or TBAT.³⁴

3.5 Nucleophilic Monofluoromethylation with $\text{PhSO}_2\text{CH}_2\text{F}$ Reagent

Compared with nucleophilic difluoromethylation, the nucleophilic monofluoromethylation is relatively easier due to the decreasing number of fluorine atoms (and therefore the decreased electron repulsion between the electron pairs) substituted on the fluorinated carbanion center. During our study on the reactivity difference of mono- and difluoromethyl anions in nucleophilic fluoroalkylation reactions,¹⁴ we found that $\text{PhSO}_2\text{CHF}^-$ anion [generated from $\text{PhSO}_2\text{CH}_2\text{F}$ (**36**)] possesses higher thermal stability than $\text{PhSO}_2\text{CF}_2^-$ anion and is suitable for pre-generation. Previously, **36** was used for the synthesis of monofluorinated alkenes by nucleophilic monofluoromethylation of carbonyls.³⁵

For active electrophiles, such as aldimines **7** and **38**, nucleophilic monofluoromethylation with the in situ gener-

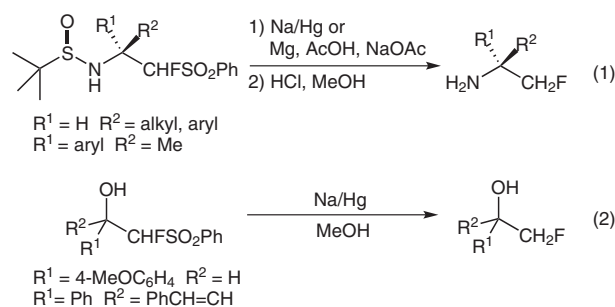


Scheme 11 Nucleophilic difluoromethylation with $(\text{RO})_2\text{P}(\text{O})\text{CF}_2\text{H}$ reagent (**29**)

ated $\text{PhSO}_2\text{CHF}^-$ anion can readily take place to afford the intermediates **37** and **39** in good yields (Scheme 12, eq. 1 and 2).³⁶ The nucleophilic fluoroalkylation of ketimines is relatively difficult due to the low electrophilicity of ketimines (compared to aldimines) and low nucleophilicity of fluorinated carbanions (compared to nonfluorinated carbanions). However, a pre-generation of $\text{PhSO}_2\text{CHF}^-$ anion facilitated this monofluoromethylation reaction, and α,α -dibranched monofluoromethyl amines could be prepared with high diastereoselectivity starting from ketimines **8** (Scheme 12, eq. 3 and Scheme 13, eq. 1).³⁷

According to the stereochemical outcome of these diastereoselective (phenylsulfonyl)monofluoromethylation and (phenylsulfonyl)difluoromethylation of chiral imines, the stereocontrol modes were believed to be different for ald-

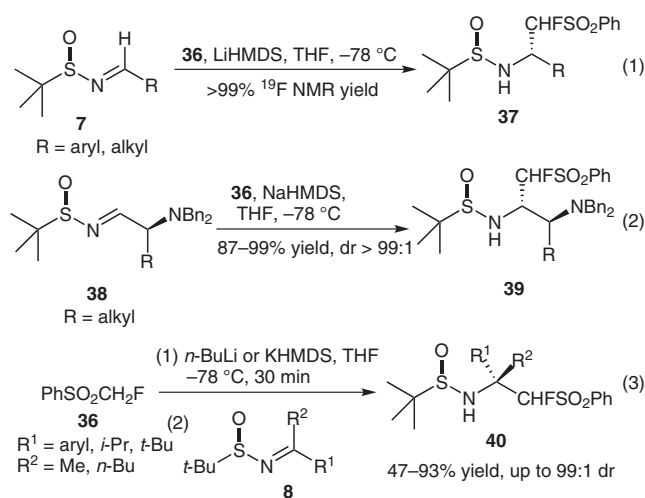
imines and ketimines: a nonchelation-controlled mode dominates in the reactions with aldimines, while a chelation-controlled cyclic six-membered transition state is preferred for the reactions with ketimines.^{22,36,37}



Scheme 13 Preparation of monofluoromethylated compounds via reductive desulfonylations

3.6 Nucleophilic Monofluoromethylation with α -Functionalized Fluoro(phenylsulfonyl)-methanes

As we discussed in Section 2.3, attaching one or two electron-withdrawing groups on the fluorinated carbanion can enhance both the thermal stability (strategy 1) and softness (strategy 2) of the carbanion species. For instance, fluorobis(phenylsulfonyl)methyl anion derived from fluorobis(phenylsulfonyl)methane (**41**) is a stabilized anion with good thermal stability and increased softness.¹⁴ Very recently, α -fluorobis(phenylsulfonyl)methide with a tetrabutylammonium counterion has been prepared and fully characterized by Prakash and co-workers,³⁸ which represents the first isolation of a persistent monofluoroalkylated carbanion. The critical role of electron-withdrawing

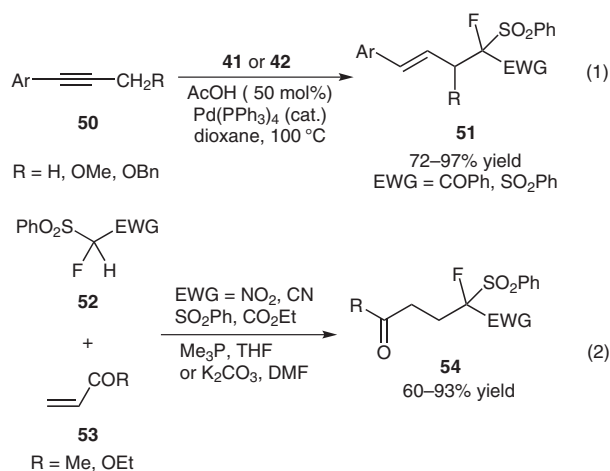


Scheme 12 Nucleophilic monofluoromethylation with $\text{PhSO}_2\text{CFH}_2$ reagent (**36**)

groups in modulating the properties of bis(phenylsulfonyl)methide anions has been verified by theoretical calculations and X-ray crystallographic studies of the α -fluorobis(phenylsulfonyl)methide salt. It is also revealed that the highly electronegative α -fluoro substituent results in a pyramidalization structure of the fluorocarbanion. Because of their unique properties of these bifunctionalized fluorocarbanions, they are widely used in nucleophilic monofluoromethylation reactions under very mild conditions.

Arynes and alkynes are two categories of compounds that are highly useful in organic synthesis. However, the nucleophilic fluoroalkylation of arynes and alkynes with fluorinated carbanions are generally difficult due to their unmatched hard–soft nature. In general, arynes and alkynes are soft electrophiles, and the polyfluorinated carbanions belong to hard nucleophiles. However, by using the ‘softened’ fluorinated carbanions that were derived from functionalized fluoromethanes **41** and **42**, we have recently achieved the nucleophilic fluoroalkylation of arynes and some activated alkynes (Scheme 14).¹⁸ Both CsF and CsOH were used as base to promote the generation of the nucleophilic fluorocarbanions. During the reaction between fluoromethane **42** and arynes **44** or activated alkynes **45**, an intramolecular tandem-reaction process leads to the formation of acyl-fluoroalkylated arenes **47** or α -acyl- β -fluoroalkylated α,β -enones **49**.

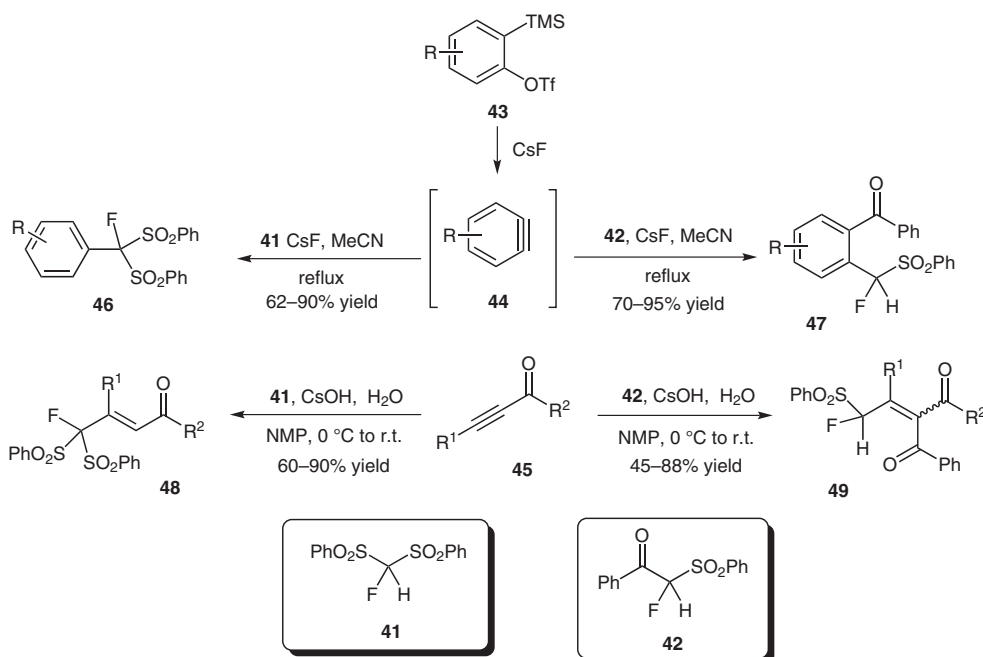
Under acidic conditions, palladium-catalyzed fluoroalkylation of arylpropynes with α -substituted fluoro(phenylsulfonyl)methanes (such as **41** and **42**) in the presence of acetic acid via isomerization of propynes **50** to allenes can afford *E*-allylated monofluoromethyl compounds **51** with high regio- and stereoselectivity (Scheme 15, eq. 1).³⁹



Scheme 15 Nucleophilic monofluoromethylation with various functionalized fluoro(phenylsulfonyl)methanes

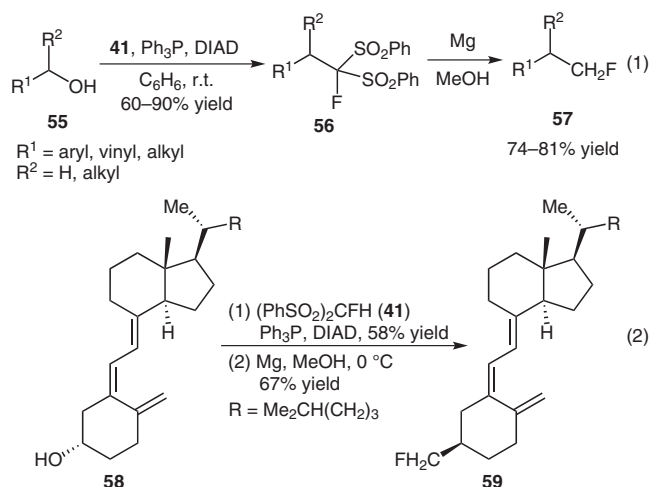
Prakash and co-workers reported the synthetic applications of α -substituted fluoro(phenylsulfonyl)methanes **52** in 1,4-addition to a variety of Michael acceptors under nearly neutral conditions (Scheme 15, eq. 2).⁴⁰ With PMe_3 as a Lewis base catalyst, **52** reacted with methyl vinyl ketone (or ethyl acrylate) **53** to furnish the corresponding products **54** in moderate to excellent yields. The reaction can also be carried out in $\text{K}_2\text{CO}_3/\text{DMF}$ system, and it was found to be applicable for various α,β -unsaturated compounds such as ketones, esters, nitriles, and sulfones.⁴⁰

The successful use of **41** in Mitsunobu reaction reported by Prakash and co-workers⁴¹ is another impressive example for the mediation of NFE. The reaction was performed under mild conditions and was amenable to primary, secondary, allylic, benzylic, and alicyclic alcohols (Scheme 16, eq. 1). Excellent enantiospecificity was ob-



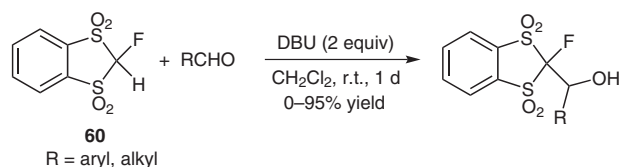
Scheme 14 Nucleophilic monofluoroalkylation of arynes and activated alkynes

served for chiral alcohols. The versatile synthetic utility of that method was manifested in the synthesis of monofluoromethylated vitamin D₃ (**59**) and the monofluoromethyl adduct of glucopyranose (Scheme 16, eq. 2).⁴¹



Scheme 16 Mitsunobu reactions with (PhSO₂)₂CHF (**41**)

Although PhSO₂CH₂F (**36**) has been used to prepare monofluoromethyl carbinols from carbonyl compounds,^{18,42} it is less favorable for an organocatalytic process. To address this problem, a cyclic monofluorinated disulfonyl methane **60** was prepared to realize the nucleophilic monofluoromethylation of aldehydes under mild conditions, which provided an opportunity for the organocatalyzed asymmetric synthesis of monofluoromethyl carbinols (Scheme 17).⁴³



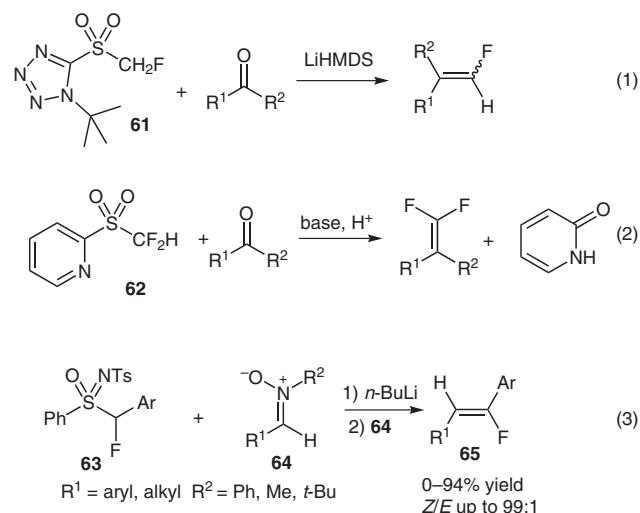
Scheme 17 Nucleophilic monofluoroalkylation of aldehydes with cyclic monofluorinated disulfonylmethane **60**

The above-mentioned synthetically useful phenylsulfonyl-containing fluoromethylation reagents can be prepared either by electrophilic fluorination of their nonfluorinated counterparts or by modification of monofluoromethyl phenyl sulfone with electrophiles, such as sulfonyl fluorides, carboxylic esters, sulfinic esters, and phosphoryl chlorides.^{26,44} From most of the α -functionalized fluoro(phenylsulfonyl)methyl-containing intermediates one sulfonyl group⁴⁵ can be removed at least, either by reduction or β -elimination to afford the monofluoroalkanes, monofluoroalkenes, or monofluoromethylated molecules.

3.7 Synthesis of Fluorinated Alkenes with Fluorinated Sulfoximines and Heteroaryl Sulfones

The rearrangement initiated by nucleophilic attack of the activating group with an intramolecular nucleophile is an important pathway for the elaboration of fluoroalkylated intermediates. Recently, the synthesis of fluoroolefins from fluorinated heteroaryl sulfones via Julia–Kocienski olefination has been extensively reviewed by Zajc and Kumar.⁴⁶ In this part, we will only discuss some of our own results in the context of the discussion on tackling the NFE.

In this Account, phenylsulfonyl is the most frequently mentioned removable activation group due to its versatility. By carefully modification of the aryl group, some heteroarylsulfonyl-substituted fluoromethyl reagents for a particular purpose are developed by us. The Julia–Kocienski olefination of carbonyls with 1-*tert*-butyl-1*H*-tetrazol-5-yl fluoromethylsulfone [TBTSO₂CH₂F (**61**)]⁴⁷ and difluoromethyl 2-pyridyl sulfone [PySO₂CHF₂ (**62**)]⁴⁸ can provide monofluorinated and *gem*-difluorinated alkenes, respectively (Scheme 18, eq. 1 and 2).



Scheme 18 Synthesis of fluorinated alkenes with fluorinated sulfoximines and heteroaryl sulfones

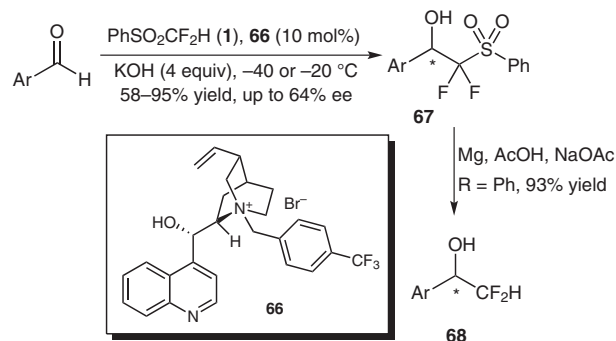
When one oxygen in the sulfonyl group is changed by NTs, the so-obtained sulfoximinyl group not only retains the strong electron-withdrawing ability to stabilize the carbanion, but also displays better leaving-group ability for further transformations. Although both tri- and difluoromethylated sulfoximine derivatives have been used as electrophilic fluoromethylation reagents,⁵⁰ the use of fluorinated sulfoximines as nucleophiles is rare. Previously, Finch and co-workers⁴⁹ reported that monofluorinated sulfoximines could react with carbonyl compounds to yield hydroxy adducts, which can be converted into fluoroalkenes (albeit with poor Z/E selectivity) by reduction with aluminum amalgam. In 2009, we reported an unusual reaction between α -fluoro-*N*-tolyl-*S*-phenylsulfoximines **63** and nitrones **64** (Scheme 18, eq. 3),⁵⁰ which turns out to be a novel stereoselective method for the preparation of

monofluoroalkenes **65** in excellent *Z/E* stereoselectivity. This chemistry can be considered as an extension of the above-mentioned strategy 3 for the mediation of NFE by altering the electrophile reactivity.

3.8 Catalytic Asymmetric Fluoroalkylation Reactions

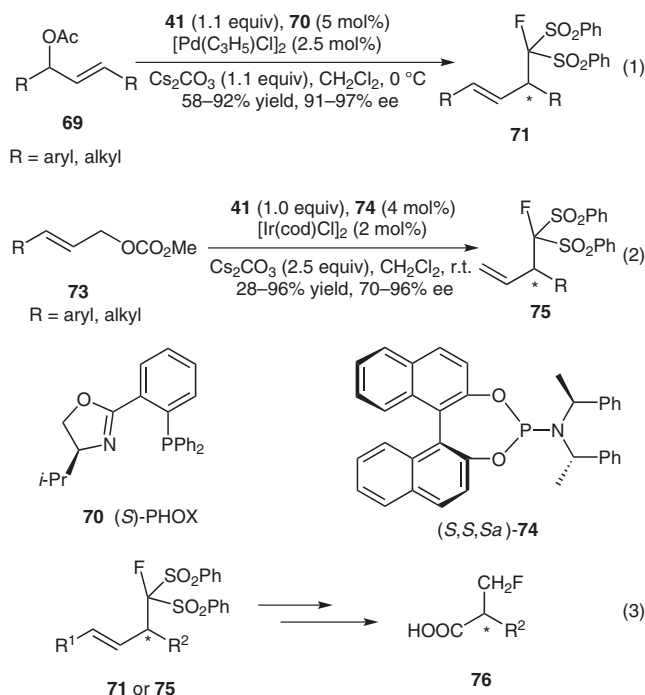
Although nucleophilic additions of $\text{PhSO}_2\text{CF}_2^-$ or $\text{PhSO}_2\text{CFH}^-$ anion to a number of electrophiles can proceed well, the corresponding enantioselective reactions with these anions are generally very difficult. By using $\text{PhSO}_2\text{CF}_2\text{H}$ (**1**) as a difluoromethylation reagent, we have also carried out chiral quaternary ammonium salts catalyzed enantioselective difluoromethylation of aromatic aldehydes (Scheme 19).⁵¹ With KOH as a base and cinchonium **66** as a phase-transfer catalyst, the reaction can proceed smoothly to give (phenylsulfonyl)difluoromethyl-substituted alcohols **67** with moderate enantioselectivity. We found that the enantioselectivity is substrate-dependent: the aldehydes with halogen substituent resulted in better enantioselectivity than those with methyl and methoxyl substituents. Among the halogenated benzaldehydes that were tested, the reaction with 2-chlorobenzaldehyde showed an enantiomeric excess up to 64%.⁵¹

In contrast, since bifunctionalized fluorocarbanions possess significantly higher thermal stability, they have been successfully applied in many enantioselective nucleophilic monofluoromethylations. For example, Shibata and co-workers⁵² have shown a palladium-catalyzed enantioselective fluorobis(phenylsulfonyl)methylation of allyl acetates **69** with $(\text{PhSO}_2)_2\text{CHF}$ (**41**) in the presence of a catalytic amount of $[\{\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}\}_2]$ and chiral phosphorous ligand (*S*)-PHOX (**70**, Scheme 20, eq. 1) or (*R,R*)-DPPBA (**72**). Zhao and You⁵³ realized a highly regio- and enantioselective allylation of $(\text{PhSO}_2)_2\text{CHF}$ (**41**) catalyzed by $[\text{Ir}(\text{cod})\text{Cl}]_2$ /phosphoramidite (*S,S,Sa*)-**74**, affording fluorobis(phenylsulfonyl)methylated compounds bearing a terminal alkene **75** in high enantioselectivity (Scheme 20, eq. 2).



Scheme 19 Enantioselective nucleophilic difluoroalkylation with reagent **1**

The products (**71** or **75**) were readily converted into chiral monofluorinated compounds **76**, such as ibuprofen, by reductive desulfonylation and oxidation reactions.



Scheme 20 Enantioselective allylic monofluoromethylation

Asymmetric Michael addition represents one of the most extensively studied reactions for the construction of chiral centers. The activation of the C–H bonds by two electron-withdrawing groups greatly facilitates the organocatalyzed reactions. In 2008, Shibata and co-workers⁵⁴ firstly reported the enantioselective conjugate addition of $(\text{PhSO}_2)_2\text{CHF}$ (**41**) to α,β -unsaturated ketones **81** with quinidinium salts **77** bearing a sterical-demanding benzyl substituent as the phase-transfer catalyst (Scheme 21, eq. 1).⁵⁴ In 2009, Kim and co-workers⁵⁵ realized the similar reaction with 9-amino-9-deoxyepiquinine **80** as catalyst (Figure 1). In 2009, Moyano and Rios,⁵⁶ Córdova,⁵⁷ and Wang⁵⁸ independently reported the enantioselective conjugate addition of **41** to α,β -unsaturated aldehydes **86** with

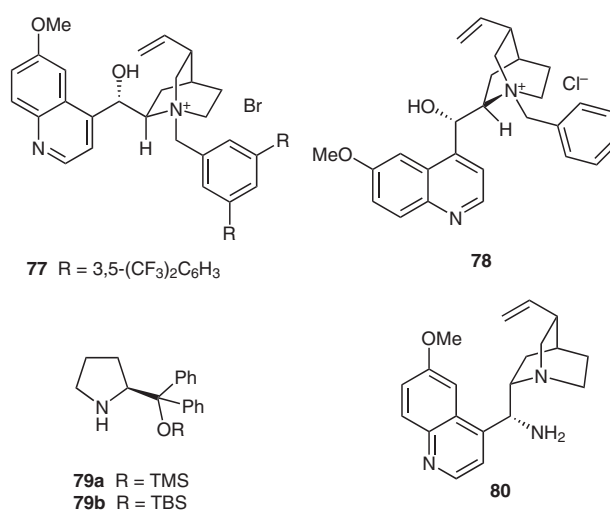
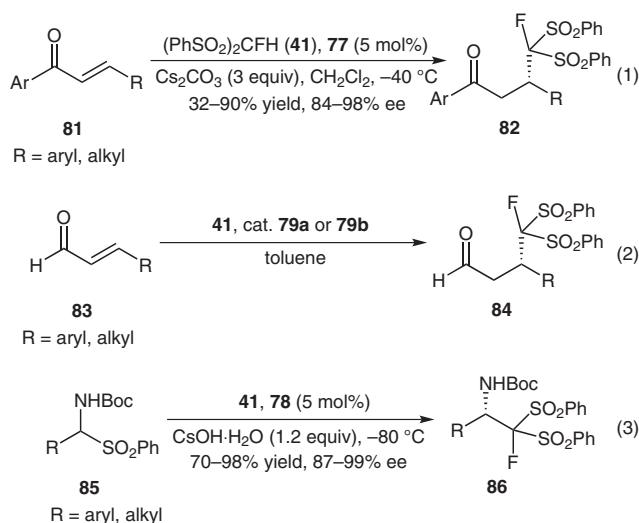


Figure 1 Structures of organocatalysts used for asymmetric monofluoroalkylations

chiral diarylprolinol silyl ethers **79a** or **79b** under varying conditions (Scheme 21, eq. 2). The conjugate addition adducts **82** and **84** are useful for the synthesis of chiral monofluoromethylated molecules after desulfonylation.^{54–58}

With $(\text{PhSO}_2)_2\text{CFH}$ (**41**) as a monofluoromethylation reagent, Shibata and co-workers⁵⁹ also described an enantioselective fluorobis(phenylsulfonyl)methylation of in situ generated aldimines (from α -amido sulfones **85**) under the combination of Mannich-type conditions. By using CsOH as a base and quinidinium **78** as the phase-transfer catalyst, the reaction could proceed smoothly at -80°C to give α -fluorobis(phenylsulfonyl)methylated amines **86** with excellent enantioselectivity (Scheme 21, eq. 3). The α -fluorobis(phenylsulfonyl)methylated amines **86** can be converted into α -monofluoromethyl amines by reductive desulfonylation.⁵⁹



Scheme 21 Organocatalyzed asymmetric monofluoroalkylations

Besides $(\text{PhSO}_2)_2\text{CFH}$, some other bifunctionalized nucleophiles, such as 1-fluoro-1-nitro(phenylsulfonyl)methane, fluoromalonate, α -fluoro- β -keto esters, and their derivatives, have also been used in the asymmetric reactions⁶⁰ and some of the tetrasubstituted intermediates can remove one carbonyl group via deacylation or decarboxylation under basic conditions.^{60c}

4 Concluding Remarks

In this Account, we have shown some recent advances in the field of nucleophilic fluoroalkylation chemistry, particularly in nucleophilic difluoromethylations, difluoromethylenations, and monofluoromethylations. Based on our own experience in this field, we noticed that the fluorine substitution on a carbanion center possesses a negative effect in many nucleophilic fluoroalkylation reactions that involve the transfer of fluorinated carbanions to electrophiles. We have discussed two factors contributing to the negative fluorine effect (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 atom(s) (such as hard/soft nature of the fluorinated carbanions). Several examples of recently developed nucleophilic fluoroalkylation reactions, including the state-of-the-art enantioselective nucleophilic mono- and difluoromethylations, as given in Section 3 of this article, suggest that the electron-withdrawing group(s) (such as phenylsulfonyl group) can remarkably tune the reactivity of fluorinated carbanions. Furthermore, enhancing the reactivity of the electrophiles can also facilitate the desired nucleophilic fluoroalkylation reactions. We fully realize that a full understanding of the unusual reactivity of fluorinated carbanions (the fluorine substitution is on the carbanionic carbon) needs more investigations and insights. Therefore, our discussions in terms of negative fluorine effect in this article only represent a simplified, yet useful (as we hope) model for predicting, designing, and explaining many nucleophilic fluoroalkylation reactions.

Acknowledgment

Support of our work by the National Natural Science Foundation of China (20772144, 20825209, 20832008) and the Chinese Academy of Sciences is gratefully acknowledged.

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