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ARTICLES

Selective Fluoroalkylations with Fluorinated Sulfones, Sulfoxides, and Sulfides†

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ABSTRACT

Efficient fluoroalkylations have been proven to be a highly useful strategy for the synthesis of bioactive fluorine-containing compounds and other materials. The design and use of a single category of reagents for multiple synthetic goals are much more attractive to preparative organic chemists. In this Account, we show how we have succeeded in the nucleophilic trifluoromethylation, difluoromethylation, difluoromethylenation, (phenylsulfonyl)difluoromethylation, (phenylthio)difluoromethylation, and monofluoromethylation as well as radical (phenylsulfonyl)difluoromethylation and electrophilic difluoromethylation by using fluorinated sulfones, sulfoxides, sulfides, or fluorinated sulfonium salts. The chemistry not only provides practically powerful synthetic methods, but the molecular design concept that we have developed may also be adopted to tackle other related chemical problems.

Introduction

Fluorine, because of its small size (r_v = 1.35 Å) and high electronegativity, has become an ubiquitous element in our modern life ranging from materials, to medicines, to agrochemicals.[1] The selective introduction of the fluorine (or fluorine-bearing building blocks) into organic molecules and polymers can dramatically alter their physical, chemical, and biological properties. As a result, extensive studies have been carried out in seeking new synthetic fluorination methodologies during the past 30 years.[2–5] Nucleophilic fluoroalkylation, such as nucleophilic tri-, di-, and monofluoromethylation and perfluoroalkylation, is one of the most important and fast-growing fields in organofluorine chemistry.[6] Perfluoroalkylation of aromatics is readily achieved with a variety of methods, most notably using perfluoroalkylcopper (R_fCu) reagents pioneered by Burton.[5] Nucleophilic introduction of perfluoroalkyl groups (R_f) into carbonyl compounds has been known for a long time through the organometallic reagents of zinc, calcium, manganese, magnesium, silver, and lithium; however, these procedures are seldom applicable to trifluoromethylation due to the instability of trifluoromethyl anion.[3,5,7] The first efficient nucleophilic trifluoromethylation was reported by Prakash, Olah, and co-workers in 1989 using (trifluoromethyl)trimethylsilane ($TMSCF_3$),[8] and the chemistry has been extended to other nucleophilic perfluoroalkylations with various substrates including carbonyl compounds, sulfur-based electrophiles, azirines, imines, organohalides, organotin compounds, and others.[6,9–13] Thereafter, several other nucleophilic trifluoromethylation methods have appeared in the past decade, using various reagents such as potassium trifluoroacetate,[14,15] trifluoromethane,[16–21] hemiaminals of trifluoroacetaldehyde,[22] trifluoromethyl iodide,[23] CF_3^-/*N*-formylmorpholine adduct,[24] piperazino hemiaminal of trifluoroacetaldehyde,[25,26] trifluoromethylacetophenone–*N,N*-dimethyltrimethylsilylamine adduct,[27] trifluoroacetic acid derivatives,[28,29] trifluoromethanesulfinic acid derivatives,[30] trifluoroacetophenone,[31] and trifluoroacetamides from amino alcohols.[32] However, unlike $TMSCF_3$, most of these reagents do not work effectively with enolizable carbonyl compounds. Therefore, $TMSCF_3$ (now known as "Ruppert–Prakash reagent"[1b,8,13,42]) is currently the most widely used nucleophilic trifluoromethylating agent for various synthetic applications.

Compared to the well-known nucleophilic trifluoromethylation reactions, much less has been studied on nucleophilc di- and monofluoromethylations, although the latter two functionalities can play critical roles in the bioactivity of fluoroorganics. The difluoromethyl group (CF_2H) acts as a lipophilic isostere of the carbinol group (CH_2OH)[33–35] as well as a hydrogen donor through hydrogen bonding.[36] Monofluoromethyl-substituted compounds carry enhanced effects in biological systems; for

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Jinbo Hu was born in Zhejiang, China (1973). He completed his B.S. (1994) and M.S. degrees (1997) at Hangzhou University and Chinese Academy of Sciences (CAS), respectively. He did his Ph.D. work during 1997−2002 at the University of Southern California (USC) with Professors G. K. S. Prakash and G. A. Olah. After his postdoctoral work at USC with Professors Prakash and Olah, he accepted the Research Professorship at Shanghai Institute of Organic Chemistry (SIOC), CAS in early 2005. The same year he received the Faculty Excellence Award by Air Products Inc. His main research interests are in selective fluorination methodologies and fluorinated materials.

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† Dedicated to Professor George A. Olah on the occasion of his 80th birthday.

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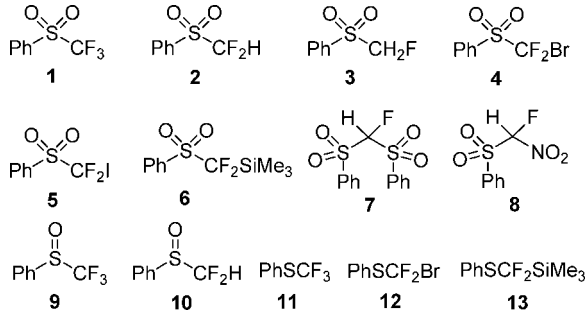


FIGURE 1. Sulfur-based fluoroalkylating reagents.

example, monofluoroacetic acid is a lethal inhibitor for the mammal's Kreb cycle.[37] Although nucleophilic trifluoromethylation of carbonyl compounds with $TMSCF_3$ are well-developed and widely used,[6,10,11] its analogous nucleophilic difluoromethylation with R_3SiCF_2H is more challenging regarding the generality and efficacy. This is mainly due to the fact that Si–CF_2H bond is less polarized than the Si–CF_3 bond, suggesting that the cleavage of former bond is much more difficult.[38] Furthermore, CF_2H anion is relatively less stable than the corresponding CF_3 anion. Fuchikami and co-workers have attempted the fluoride-induced difluoromethylation of carbonyl compounds with difluoromethylsilane derivatives in DMF and found that the reaction required high temperature (100 °C) and gave poor yields with ketones.[38] Fluoride-induced difluoromethylation of carbonyl compounds with $Me_3SiCF_2SiMe_3$ has been reported by Prakash et al.;[40] however, this method could not be applied to ketones. Burton and co-workers have reported the nucleophilic difluoromethylation by using difluoromethylcadmium and other related organometallic reagents, but these reagents work only with activated organic halides.[41] Therefore, there is still lack of a general and efficient nucleophilic difluoromethylation method applicable to both enolizable and nonenolizable aldehydes and ketones, imines, simple alkyl halides, and others. Moreover, few examples of nucleophilic pathways of introducing difluoromethylene and difluoromethylidene building blocks into organic molecules are reported.

During the past several years, we have discovered that fluorinated organosulfur compounds, including tri-, di-, and monofluorinated sulfones, sulfoxides, and sulfides, can be used as new efficient fluoroalkylation reagents (Figure 1). Although some of these fluorinated organosulfur compounds are known for several decades, their potential as powerful nucleophilic fluoroalkylating agents has been rarely realized. In this Account, we present our systematic study of fluoroalkylation chemistry using fluorinated sulfones, sulfoxides, and sulfides, particularly focusing on nucleophilic trifluoromethylation, difluoromethylation, difluoromethylenation, difluoromethylidenation, and monofluoromethylation. Our recent findings in electrophilic and radical fluoroalkylation using some of these sulfur-based fluoroalkylating agents are also presented.

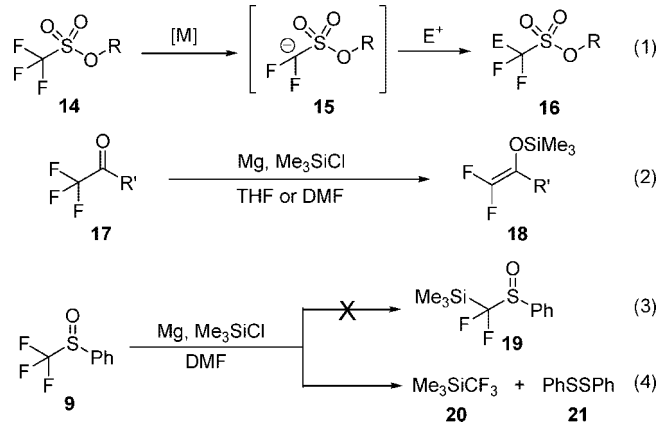
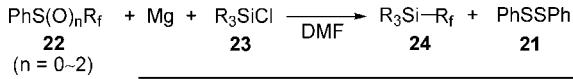


FIGURE 2. Mg-mediated C–F bond cleavage versus F_3C–S bond cleavage.

Mg/Me_3SiCl-Mediated Reductive Tri- and Difluoromethylation Using Tri- and Difluoromethyl Sulfones, Sulfoxides, and Sulfides: A Serendipitous Discovery

Initially, our inspiration to develop new synthons based on fluorinated organosulfur compounds originated from a serendipitous discovery. In a superacid-related research program, we were interested in developing new functionalized difluoromethanesulfonic acid derivatives **16** through C–F bond activation of triflic acid derivatives **14** (Figure 2, eq 1). After many unsuccessful experiments, we encountered a newly published article by Uneyama and coworkers[43] on the Mg^0-mediated reductive defluorination of trifluoromethyl ketones **17** to give 2,2-difluoro enol silyl ethers **18** (Figure 2, eq 2). Inspired by their results, we envisioned that trifluoromethyl phenyl sulfoxide **9** could also undergo reductive C–F bond cleavage by action of Mg/Me_3SiCl reagent to give silylated difluoromethyl sulfoxide **19** (Figure 2, eq 3). To our surprise and delight, the reaction between **9**, Mg, and Me_3SiCl in DMF at 0 °C to RT gave (trifluoromethyl)trimethylsilane **20** and diphenyl disulfide **21** as products with quantitative conversion (Figure 2, eq 4).[44] The sharp contrast between Uneyama's C–F bond cleavage chemistry (Figure 2, eq 2) and our observed F_3C–S bond cleavage chemistry (Figure 2, eq 4) immediately stimulated our curiosity about the chemistry of fluorinated sulfoxides, sulfones, and sulfides, which were scarcely known at the time.

Further study of this unusual reductive fluoroalkylation chemistry revealed that, besides trifluoromethyl phenyl sulfoxide, the analogous trifluoromethyl sulfone and sulfide were also able to undergo similar F_3C–S bond cleavage to yield Me_3SiCF_3 as the product (Figure 3). In addition, tri- and difluoromethyl phenyl sulfone (or sulfoxide) and other trialkylsilyl chlorides **23** can be used under similar reaction conditions to prepare structurally diverse (fluoroalkyl)trialkylsilane **24** (Figure 3), possibly via a single-electron transfer (SET) process from magnesium metal to organosulfur compounds.[44] It is interesting that $PhSO_2CF_2Br$, $PhSO_2CF_2SiMe_3$, or $(PhSO_2)_2CF_2$ was able to react with Mg/Me_3SiCl in DMF to give $Me_3SiCF_2CF_2SiMe_3$



22	23(R_3Si)	24	yield (%)
$PhSO_2CF_3$	Me_3Si	Me_3SiCF_3	83
$PhSOCF_3$	Me_3Si	Me_3SiCF_3	81
$PhSCF_3$	Me_3Si	Me_3SiCF_3	45
$PhSO_2CF_3$	Et_3Si	Et_3SiCF_3	95
$PhSO_2CF_3$	Me_2(*t*Bu)Si	Me_2(*t*Bu)$SiCF_3$	57
$PhSO_2CF_3$	$(Me_3Si)_3Si$	$(Me_3Si)_3SiCF_3$	62
$PhSO_2CF_2H$	Me_3Si	Me_3SiCF_2H	76
$PhSO_2CF_2H$	Et_3Si	Et_3SiCF_2H	51
$PhSO_2CF_2Br$	Me_3Si	$(Me_3SiCF_2)_2$	55

FIGURE 3. Mg-mediated reductive tri- and difluoromethylation.[44]

as the major product.[44] $PhSO_2CH_2CF_3$ reacted with Mg/Me_3SiCl in DMF at RT for 15 min to give 1,1-difluoroethylene with quantitative conversion, possibly through a $CF_3CH_2^-$ intermediate.[44] However, under similar reaction conditions only 20% of $PhSOCH_2CF_3$ were converted to 1,1-difluoroethylene even during a period of 8 h, and $PhSCH_2CF_3$ did not show any reactivity with Mg/Me_3SiCl at all. These experimental data indicate that the reactivity order in Mg/Me_3SiCl/DMF condition is sulfone > sulfoxide > sulfide.[44] Furthermore, since trifluoromethyl phenyl sulfone **1** and sulfoxide **9** can be readily prepared from CF_3H and PhSSPh,[45] and in our above-mentioned reductive fluoroalkylation process PhSSPh is produced as a byproduct, the presently developed method provides a novel and useful pathway (via PhSSPh) for the production of Me_3SiCF_3 from nonozone depleting trifluoromethane and chlorotrimethylsilane.[44]

The Mg^0-mediated reductive fluoroalkylation reaction was also used in the preparation of (1,1-difluoroethyl)trimethylsilane **26** (from 1,1-difluoroethyl phenyl sulfone **25**), which can act as a novel nucleophilic 1,1-difluoroethylating reagent (Figure 4).[46]

Nucleophilic Trifluoromethylation of Carbonyl Compounds with Trifluoromethyl Phenyl Sulfone and Sulfoxide

The above-mentioned Mg^0-mediated reductive trifluoromethylation chemistry works well with chlorotrialkylsilanes; however, it cannot be applied to other electrophiles such as carbonyl compounds. We anticipated that by using a nucleophilic base such as an alkoxide or a hydroxide this problem could be solved. In the presence of a nucleophilic base, F_3C–S in trifluoromethyl phenyl sulfone **1** or sulfoxide **9** is readily cleaved to generate the trifluoromethyl anion (CF_3^-) that immediately undergoes addition to carbonyl compounds (Figure 5, eq 1).[47]

The experimental results show that potassium *tert*-butoxide (*t*BuOK), sodium methoxide (CH_3ONa), and potassium hydroxide (KOH) can be used as active nucleophiles, and the use of *tert*-butoxide gave the best result (Figure 5, eq 2). Both DMF and dimethyl sulfoxide (DMSO) are suitable solvents for the reaction.[47] This indicates that the formation of CF_3^-/DMF adduct is not a necessary intermediate for this new type of nucleophilic trifluoromethylation. From a mechanistic point of view, however, it can be reasonably postulated that the actual trifluoromethylating intermediate is **28** (or **29**) (Figure 5, eq 1). The developed methodology allows the preparation of trifluoromethylated products in high yields in the case of nonenolizable aldehydes and ketones (Figure 5, eq 2). However, with enolizable aldehydes and ketones, only low yield (10–30%) of trifluoromethylated products were observed due to competing and facile aldol reactions. Trifluoromethyl phenyl sulfoxide (**9**) is equally effective as **1**, and similar trifluoromethylations were observed with aldehydes and ketones.[47] Furthermore, this novel trifluoromethylation method also works with diphenyl disulfide to give $PhSCF_3$ in good yield (Figure 5, eq 3). The protocol is also applicable to other systems. For instance, methyl benzoate can be trifluoromethylated to generate 2,2,2-trifluoroacetophenone in 30% yield at –50 to –20 °C. CF_3Cu has been in situ generated with **1**/*t*BuOK and copper iodide (CuI), which upon reaction with iodobenzene at 80 °C for 20 h give α,α,α-trifluorotoluene in 26% yield by an oxidative addition–reductive elimination pathway.[47]

We found that, unlike trifluoromethyl phenyl sulfone **1** and sulfoxide **9**, $PhSCF_3$ (**11**) was inert to *t*BuOK and thus unable to act as a trifluoromethylating agent under similar reaction conditions. On the other hand, Yokoyama and Mochida found that with the action of Et_3GeNa compound **11** was able to trifluoromethylate aldehydes, imines, and esters in high yields.[48]

Nucleophilic (Phenylsulfonyl)difluoromethylation, Difluoromethylation, and Difluoromethylenation with $PhSO_2CF_2H$ Reagent

On the basis of the above-mentioned alkoxide-induced trifluoromethylation chemistry, we assumed that a similar type of S–C bond cleavage could occur with difluoromethyl phenyl sulfone **2**. Studies with difluoromethyl phenyl sulfone ($PhSO_2CF_2H$, **2**) [39,49] were first reported by Hine and co-workersa in 1960 as a difluorocarbene precursor. In 1989, Stahly found that the reaction between **2** and excess amount of aldehydes in the presence of aqueous NaOH and a phase-transfer catalyst gave the (phenylsulfonyl)difluoromethyl carbinols in good yields.[39] However, in Stahly's study, he did not observe any S–C bond cleavage under the aqueous NaOH conditions (at room temperature for 4 h). Obviously, aqueous NaOH is not nucleophilic enough to activate the S–C bond scission in this reaction. It also indicates that with hydroxide or alkoxide the deprotonation on difluoromethyl sulfone **2** is much faster than the S–C bond cleavage. By use of a proper alkoxide such as *t*BuOK working both as a base and a nucleophile, sulfone **2** could react stepwise with two electrophiles (E^+ and E'^+) to give new difluoromethylene-containing products **35** (Figure 6).[50] Thus, difluoromethyl phenyl sulfone **2** can be regarded as a selective difluoromethylene dianion ("$^-CF_2^-$") synthon **36**. Indeed, we found that sulfone **2** readily reacted with PhSSPh (2 equiv)

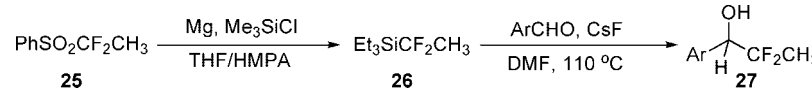


FIGURE 4. Mg-mediated preparation of (1,1-difluoroethyl)triethylsilane **26**.[44]

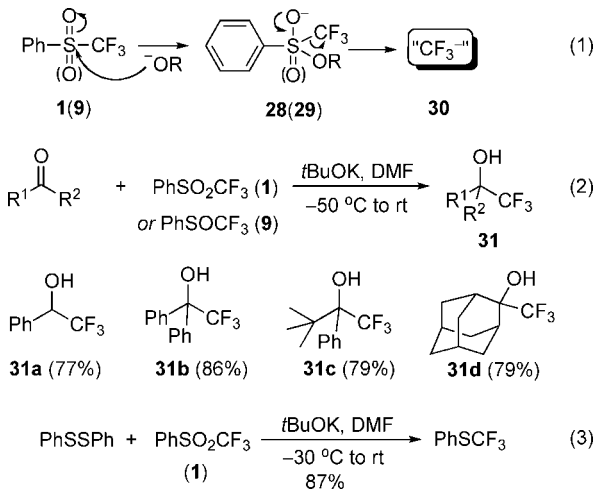


FIGURE 5. Alkoxide- and hydroxide-induced nucleophilic trifluoromethylation with **1** (or **9**).[47]

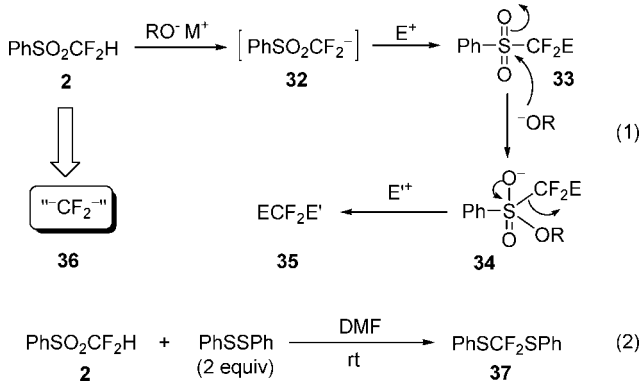


FIGURE 6. Use of $PhSO_2CF_2H$ as a difluoromethylene dianion equivalent.[50]

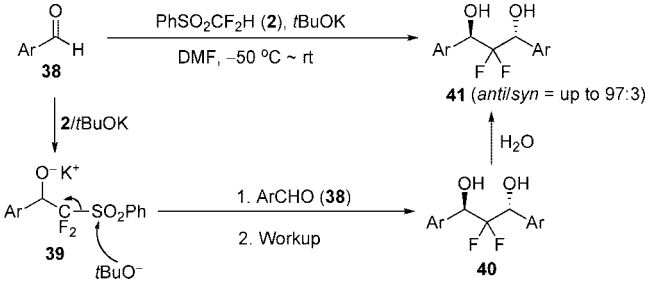


FIGURE 7. Diastereoselective synthesis of *anti*-2,2-difluoropropan-1,3-diols **41**.[50]

in the presence of *t*BuOK (4 equiv) to give disubstituted product $PhSCF_2SPh$ (**37**) in high yield.[50] Similarly, the $PhSO_2CF_2H$/*t*BuOK system was also able to couple two molecules of aryl aldehydes to give 2,2-difluorinated *anti*-1,3-diols with high diastereoselectivity (*anti*/*syn* up to 97:3), and the observed high diastereoselectivity can be attributed to the charge–charge repulsion effect during the second addition (Figure 7).[50]

The (phenylsulfonyl)difluoromethyl anion species **32** (generated from **2** and *t*BuOK or LHMDS) can efficiently undergo nucleophilic (phenylsulfonyl)difluoromethylation with a variety of electrophiles such as simple alkyl halides,[51,52] aldehydes and ketones,[53] imines,[33,54] and cyclic sulfates and sulfamidates[55] to give corresponding substitution or addition products in good to excellent yields (Figure 8). Since the (phenylsulfonyl)difluoromethyl group can be further transformed into difluoromethyl (CF_2H) and difluoromethylidene ($=CF_2$) functionalities via reductive desulfonylation or base-mediated dehydrosulfonylation, sulfone **2** has become a robust fluoroalkylating reagent for the preparation of a variety of difluoromethylated and difluoromethylenated products **48–57** (Figure 8). The reactions with homochiral *N*-*tert*-butanesulfinimines were found to be in a non-chelation-controlled diastereoselective mode, and the corresponding α-difluoromethylated amine salts **53** were obtained with excellent optical purity (Figure 8, eq 7).[33] We also found that similar diastereoselective nucleophilic difluoromethylation of α-amino-*N*-*tert*-butanesulfinimines with **2** afforded chiral α-difluoromethylated ethylenediamines in good yields and with excellent stereoselectivity (*dr* up to 99:1).[54] The reactions between **2** and homochiral cyclic sulfamidates in the presence of lithium hexamethyldisilazide (LHMDS) produced β-difluoromethylated and β-difluoromethylenated amines **56** and **57** (Figure 8, eqs 10 and 11).[55]

The carbinols **51** and **43** were found to be useful precursors for the preparation of fluoroalkylated amides **58** and **59** via Ritter reaction (Figure 9, eqs 1 and 2).[56] 1-Aryl-2,2-difluoro-2-phenylsulfonylethanols **43** are also useful compounds to prepare 2,2-difluoroenol esters **60** and α-chloro-β,β-difluorostyrene derivatives **61** (Figure 9, eq 3 and 4).[57]

Nucleophilic (Phenylsulfonyl)difluoromethylation, Difluoromethylation, and Difluoromethylenation with $Me_3SiCF_2SO_2Ph$ or $PhSO_2CF_2Br$ Reagent

As an alternative nucleophilic (phenylsulfonyl)difluoromethylating agent, [(phenylsulfonyl)difluoromethyl]trimethylsilane ($Me_3SiCF_2SO_2Ph$, **6**) was developed by us in the fluoride-induced $PhSO_2CF_2$ group transfer reactions (Figure 10, eqs 1 and 2).[58] Since fluoride derived from either tetrabutylammonium triphenyldifluorosilicate (TBAT) or CsF is a relatively weaker base than LHMDS and *t*BuOK, the nucleophilic (phenylsulfonyl)difluoromethylation method with **6** can be more efficient (compared to the method using **2**) with base-sensitive substrates such as enolizable aldehydes.[58] We also developed the Mg/HOAc/NaOAc system as a reductive desulfonylation reagent, which has advantages over traditional Na(Hg) amalgam reagent (Figure 10, eq 2).[58]

Furthermore, nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes can also be accomplished by the

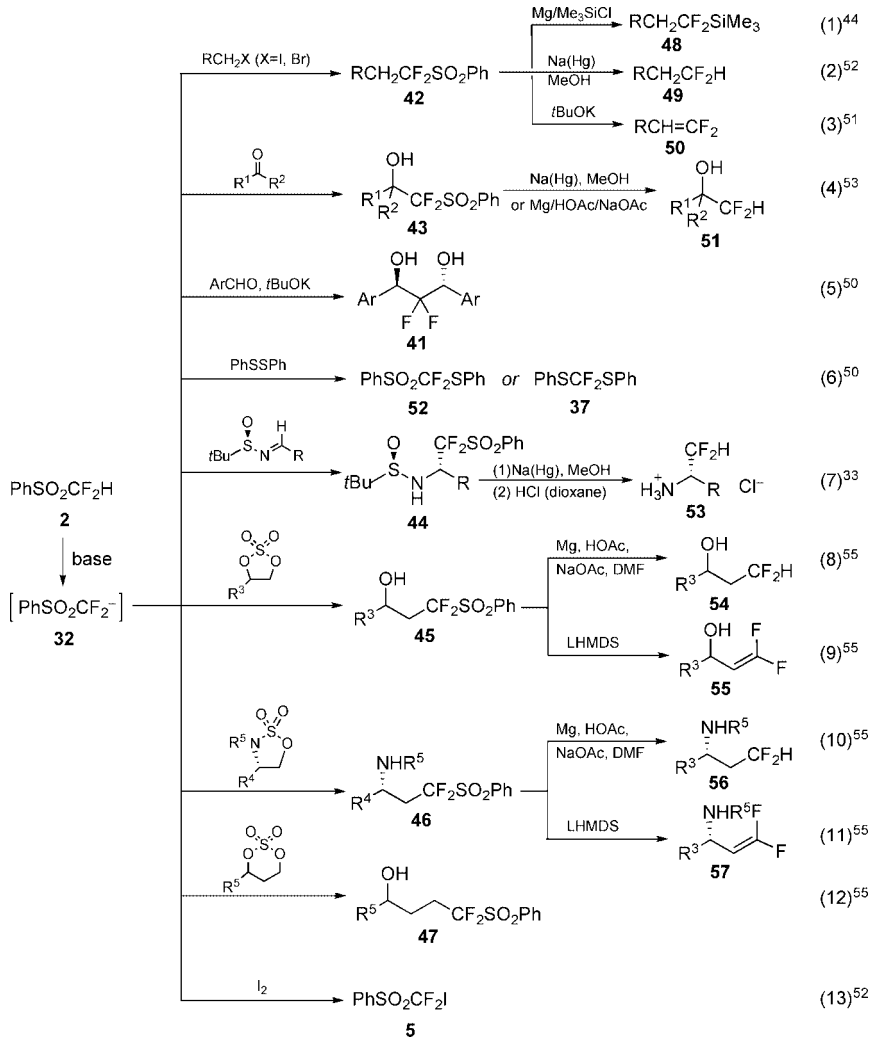


FIGURE 8. Nucleophilic (phenylsulfonyl)difluoromethylation of different electrophiles.

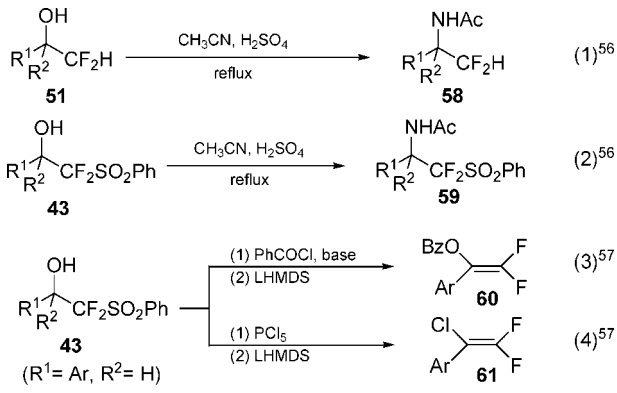


FIGURE 9. Synthetic applications of (phenylsulfonyl)difluoromethylated and difluoromethylated carbinols **43** and **51**.

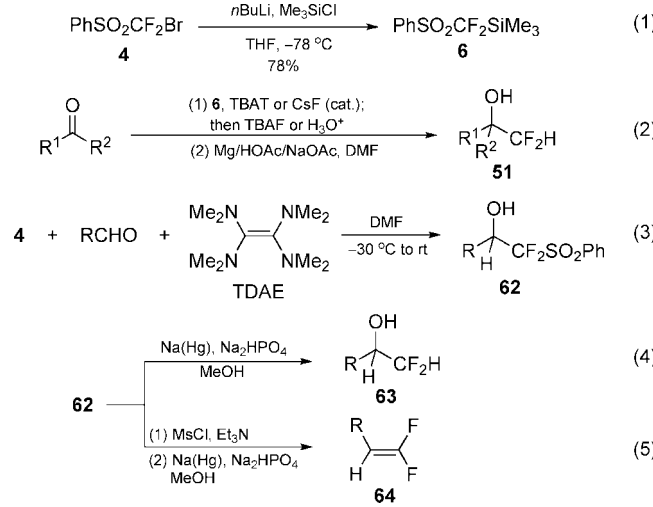


FIGURE 10. Nucleophilic (phenylsulfonyl)difluoromethylation with reagents **4** and **6**.

use of bromodifluoromethyl phenyl sulfone (**4**) in the presence of stoichiometric amount of single-electron-transfer agent tetrakis(dimethylamino)ethylene (TDAE) (Figure 10, eq 3).[59] The obtained (phenylsulfonyl)difluoromethylated carbinols **62** can be further transformed into difluoromethylated carbinols **63** and 1,1-difluoroalkenes **64** under reductive desulfonylation or Julia olefination conditions (Figure 10, eqs 4 and 5).[59]

Nucleophilic (Phenylsulfinyl)difluoromethylation with $PhSOCF_2H$ Reagent

Nucleophilic (phenylsulfinyl)difluoromethylation of both enolizable and nonenolizable aldehydes and ketones has also been achieved by using difluoromethyl phenyl sul-

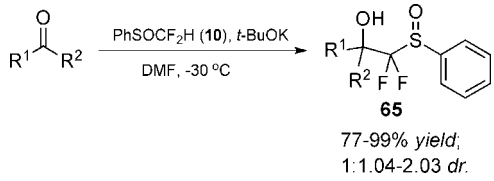


FIGURE 11. Nucleophilic (phenylsulfinyl)difluoromethylation with **10**.

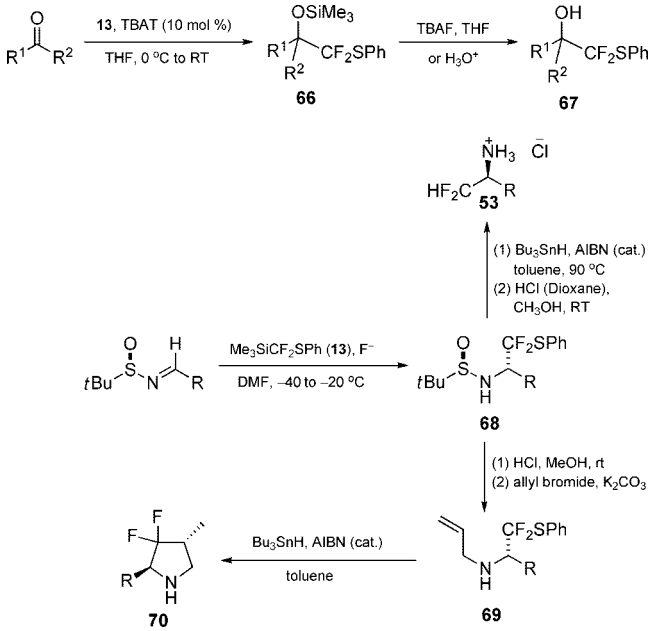


FIGURE 12. (Phenylthio)difluoromethylation, difluoromethylation, and difluoromethylenation with reagent **13**.

foxide ($PhSOCF_2H$, **10**) as the fluoroalkylating agent. Although the chemical yields of the reactions are good to excellent, the observed diastereoselectivity is poor (dr = 1:1.04−2.03) (Figure 11).[60] The present synthetic methodology provides a convenient alternative for the direct preparation of α-(phenylsulfinyl)difluoromethylated carbinols that were previously synthesized via a two-step procedure.[61]

Nucleophilic (Phenylthio)difluoromethylation, Difluoromethylation, and Difluoromethylenation with Me_3SiCF_2SPh Reagent

[Difluoro(phenylthio)methyl]trimethylsilane (Me_3SiCF_2SPh, **13**) was prepared for the first time by us as a stable liquid (in 86% yield) under the Barbier reaction conditions.[44] Fluoride-induced nucleophilic (phenylthio)difluoromethylation reaction with **13** can efficiently transfer the "$PhSCF_2$" group into both enolizable and nonenolizable aldehydes and ketones to give corresponding (phenylthio)difluoromethylated alcohols **67** in good to excellent yields (Figure 12).[62] More recently, we successfully developed a new synthetic application of Me_3SiCF_2SPh as a difluoromethylene radical anion synthon ($^{\bullet}CF_2^-$), based on the selective ionic cleavage of its F_2C–Si bond and radical cleavage of its F_2C–S bond (Figure 12). Nucleophilic (phenylthio)difluoromethylation of (*R*)-*N*-*tert*-butanesulfinimines with **13** affords the corresponding products

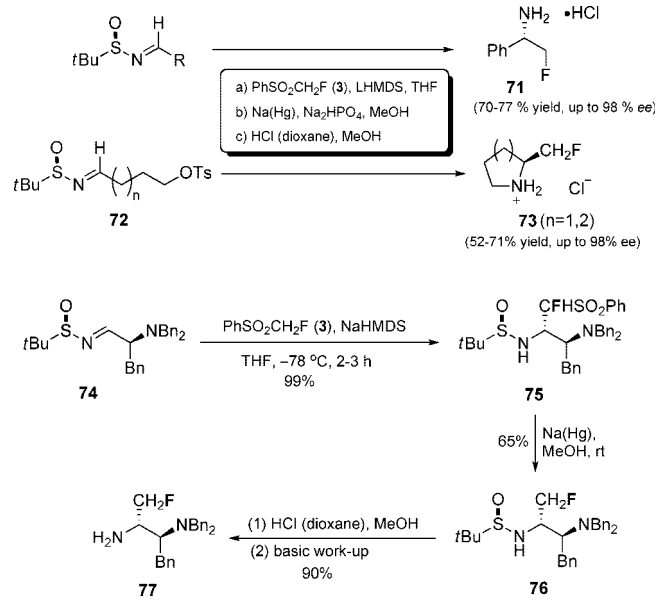


FIGURE 13. Stereoselective monofluoromethylation with reagent **3**.[64]

68 in good yields and with high diastereoselectivity ($dr \geq$ 98:2). The obtained $PhSCF_2$-containing sulfinamides **68** can be further transformed into chiral 3,3-difluoro-2,4-*trans*-disubstituted pyrrolidines **70** via an intramolecular radical cyclization methodology.[63] Furthermore, compounds **68** can be further conveniently transformed into chiral difluoromethylated amines (in the salt form) **53** under radical conditions (Figure 12).[63] Thus, reagent **13** can be regarded as a multifunctional "$PhSCF_2^-$", "HCF_2^-", and "$^{\bullet}CF_2^-$" equivalents.

Nucleophilic Monofluoromethylation with $PhSO_2CH_2F$ or $(PhSO_2)_2CHF$ Reagent

For a long time, nucleophilic monofluoromethylation (the transfer of the "CH_2F" group to carbon electrophiles) has not been studied. In 2006, we reported the first highly stereoselective monofluoromethylation of (*R*)-*N*-*tert*-butanesulfinimines using fluoromethyl phenyl sulfone ($PhSO_2CH_2F$, **3**) as a novel nucleophilic monofluoromethylating reagent (Figure 13).[64] The reaction has been shown to be highly stereoselective and convenient for the synthesis of enantiomerically pure α-monofluoromethyl amines **71**. The same methodology can also be used to synthesize homochiral α-monofluoromethylated cyclic secondary amines **73** by using tosylate (OTs)-bearing (*R*)-(*tert*-butanesulfinyl)imine precursors **72** (Figure 13).[64] The diastereoselective monofluoromethylation of α-amino *N*-*tert*-butanesulfinimine **74** with reagent **3** can afford homochiral α-monofluoromethylated ethylenediamine **77** in good yield (Figure 13).[54]

In 2006, we reported a previously unknown compound, fluorobis(phenylsulfonyl)fluoromethane [$(PhSO_2)_2CHF$, 7] as an excellent monofluoroalkylating reagent.[65] We found that the bis(phenylsulfonyl)fluoromethyl anion [$(PhSO_2)_2CHF^-$] generated from 7 was able to readily undergo nucleophilic ring-opening reactions with simple epoxides and aziridines, which are generally inert to

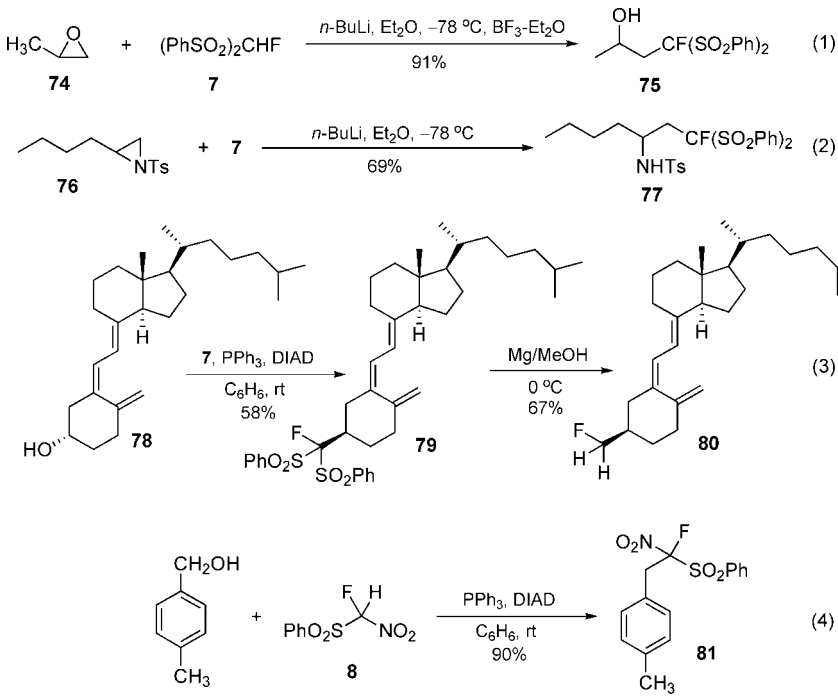


FIGURE 14. Nucleophilic monofluoromethylation with reagents **8** and **14**.

normal fluorinated carbanions (Figure 14, eqs 1 and 2).[65] Around the same time, Shibata and co-workers independently reported that reagent **7** could also be applied in the enantioselective monofluoromethylation reactions.[66] More recently, we successfully applied reagent **7** in the stereospecific monofluoromethylation of primary and secondary alcohols via a Mitsunobu reaction, and excellent enantiospecificity was observed for chiral alcohols (Figure 14, eq 3).[67] The reaction is also found to be applicable to other monofluoro systems with the appropriate pK_a value, and we have found that fluorobis(phenylsulfonyl)nitromethane **8** also smoothly underwent the desired Mitsunobu reaction under similar reaction conditions, giving the adduct **81** in high yields (Figure 14, eq 4).[67]

"Negative Fluorine Effect" in Nucleophilic Fluoroalkylation Chemistry

It has been well-recognized that most primary and secondary fluorinated carbanions are kinetically unstable species.[68] The lifetimes, reactivity, and synthetic utility of fluorinated carbanions are influenced by many factors, and as a result, the chemistry of fluorinated carbanions is much different from their nonfluorinated counterparts. Although there is a recent argument that "fluorine is more effective than the heavier halogens" in "α-stabilization of carbanions",[69] we found that the thermal stability and nucleophilicity of the fluorinated carbanions were indeed weaker than the chlorinated carbanions.[65] The unusual difficulty of the ring-opening reaction between an epoxide and a fluorine-bearing carbanion, although not fully understood, presumably can be attributed to the intrinsic property of the fluorine-bearing carbanion (R_f^-), i.e., its low thermal stability (caused by its high tendency to undergo α-elimination of a fluoride ion due to the electron

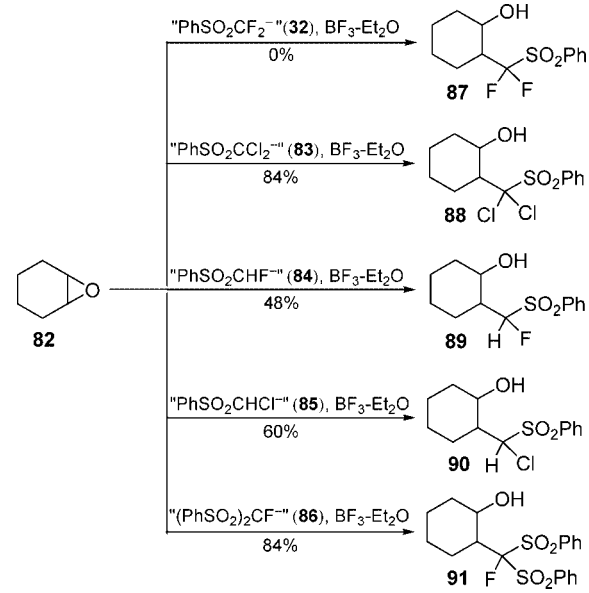


FIGURE 15. "Negative fluorine effect" in nucleophilic fluoroalkylation of epoxide.[65]

repulsion between the electron pairs on the small fluorine atom(s) and the electron lone pair occupying the p-orbital of the carbanionic center) as well as its weak nucleophilicity toward epoxides.[65]

During our recent study on nucleophilic fluoroalkylation of epoxides with fluorinated sulfones, the "negative fluorine effect" (that is, the fluorine substitution on carbanion center will significantly decrease carbanion's nucleophilicity toward electrophiles) was probed by a reactivity comparison between carbanions $PhSO_2CF_2^-$ (**32**) and $PhSO_2CCl_2^-$ (**83**) and between carbanions $PhSO_2CHF^-$ (**84**) and $PhSO_2CHCl^-$ (**85**) (nucleophilicity order **83** > **32**; **85** > **84**). The introduction of phenylsulfonyl group(s)

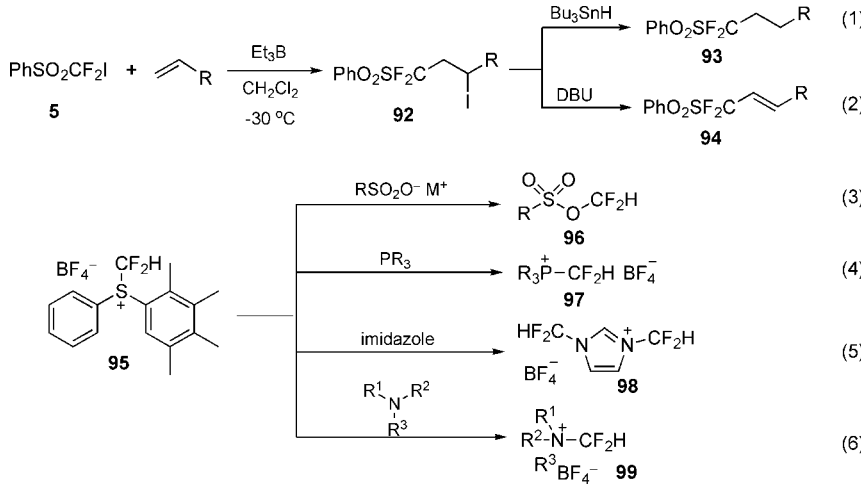


FIGURE 16. Radical and electrophilic fluoroalkylation.

was found to be an effective way to attenuate the "negative fluorine effect", with the nucleophilicty order $[(PhSO_2)_2CF^-]$ (**86**) > $PhSO_2CHF^-$ (**84**) ≫ $PhSO_2CF_2^-$ (**32**) (Figure 15).[65]

Radical and Electrophilic Fluoroalkylation with Sulfur-Based Fluoroalkylating Reagents

Because of the easy homolytic cleavage of the R_f–S bond under radical conditions, fluorinated organosulfur compounds are potential useful reagents for radical fluoroalkylation. Reutrakul and co-workers have applied bromodifluoromethyl phenyl sulfide **12** as a (phenylthio) difluoromethyl radical as well as difluoromethylene diradical synthon.[70] Besides our above-mentioned radical cyclization reaction with Me_3SiCF_2SPh reagent **13** (Figure 12),[63] very recently, we discovered a triethylborane-promoted radical (phenylsulfonyl)difluoromethylation methodology by using iododifluoromethyl phenyl sulfone **5** as a "$PhSO_2CF_2^{\bullet}$" precursor (Figure 16, eqs 1 and 2).[71] This radical (phenylsulfonyl)difluoromethylation is a good complement to the well-studied nucleophilic (phenylsulfonyl)difluoromethylation.

Trifluoromethyl sulfonium salts are well-known to be powerful electrophilic trifluoromethylating agents, which are successfully used for the trifluoromethylation of a wide range of substrates differing in reactivity.[72] Recently, we have reported that *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate can be used as an effective electrophilic difluoromethylating agent for the selective introduction of a "CF_2H" group into a variety of nucleophiles, such as sulfonic acids, tertiary amines, imidazole derivatives, and phosphines (Figure 16, eqs 3−6).[35]

Concluding Remarks

We have shown a variety of nucleophilic, radical, and electrophilic fluoroalkylation chemistry with fluorinated organosulfur compounds, through which trifluoromethyl-, difluoromethyl-, (phenylsulfonyl)difluoromethyl-, (phenylthio)difluoromethyl-, difluoromethylene-, difluoromethylidene-, and monofluoromethyl-containing compounds can be readily prepared. The sulfur-based functionalities not only act as auxiliary groups that alter the polarity and softness of the reagents but also by themselves are excellent functional groups for various transformations (so-called "chemical chameleon"). These molecular design concepts can be further extended to other synthetic problems in organofluorine chemistry.

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