Journal of Fluorine Chemistry 130 (2009) 1130–1139

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylations

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ARTICLE INFO

Article history:
Received 17 May 2009
Received in revised form 26 May 2009
Accepted 27 May 2009
Available online 6 June 2009

Keywords:
(Phenylsulfonyl)difluoromethylation
Nucleophilic
Radical
Electrophilic
Fluoroalkylation

ABSTRACT

Selective incorporation of a fluoroalkyl moiety to modulate the properties of an organic molecule has become a frequently used strategy in life science- and materials science-related applications. In this context, selective introduction of a (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) into organic molecules has attracted much attention, since the $PhSO_2CF_2$ group can be regarded as a "chemical chameleon" that can be readily transformed into difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) functionalities. This article overviews the recent development of (phenylsulfonyl)difluoromethylation reactions from 2003, including the nucleophilic (phenylsulfonyl)difluoromethylations with $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$ and $PhSO_2CF_2Br$ reagents, free radical (phenylsulfonyl)difluoromethylations with $PhSO_2CF_2I$ reagent, and electrophilic (phenylsulfonyl)difluoromethylations with a hypervalent iodine(III)-CF_2SO_2Ph reagent.

1. Introduction

Since the selective incorporation of fluorinated moieties into organic molecules can often bring about unique physical, chemical, and biological properties, a variety of synthetic methods have been developed for this purpose [1–10]. In this context, selective (phenylsulfonyl)difluoromethylation reactions (the transfer of a $PhSO_2CF_2$ group into organic substrates) has been systematically studied in recent years [11]. In retrospect, difluoromethyl phenyl sulfone (**1**, $PhSO_2CF_2H$) was prepared by Hine and Porter during their study of difluorocarbene chemistry in 1960 [12]. However, the synthetic utility of compound **1** as a nucleophilic (phenylsulfonyl)difluoromethylation reagent was not recognized at that time, although Hine and Porter realized that the (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$) was formed by deprotonation of **1** with a base such as sodium methoxide [12]. In 1972, Edwards and co-workers claimed in a patent that $PhSO_2CF_2^-$ anion (derived from compound **1** and potassium *tert*-butoxide in diglyme/Et_2O at −78 °C) was able to undergo 1,4-addition to a cyclic α,β-unsaturated ketone, but the chemical yield was not reported [13,14]. In 1989, Stahly reported that the nucleophilic (phenylsulfonyl)difluoromethylation of some aldehydes in a two phase system (50% aqueous NaOH/CH_2Cl_2/Aliquat 336) gave corresponding $PhSO_2CF_2$-containing carbinols in good yields [15]. In 1992, McCarthy et al. succeeded in the nucleophilic (phenylsulfonyl)difluoromethylation of a cyclic ketone, and they transformed the resulting carbinol product into a 1,1-difluoro alkene [16]. Although McCarthy's protocol was later applied by Boger and Jenkins in their synthesis of fluorocyclopropane analogs of the Duocarmycins [17], this method was proved unsuccessful in the synthesis of 3′-difluoromethylene-3′-deoxythymidine and its derivatives [18].

By 2003, the synthetic potential of (phenylsulfonyl)difluoromethylation reactions had been largely overlooked, as evidenced by only four research articles of this subject being available in the literature [15–18]. Since 2003, the situation has been changed, and a variety of (phenylsulfonyl)difluoromethylation reagents and reactions have been systematically developed by Prakash, Olah, Hu and their co-workers [11]. A major part of these (phenylsulfonyl)difluoromethylations is based on nucleophilic reactions with reagents such as $PhSO_2CF_2H$ (**1**), $PhSO_2CF_2Br$ (**2**), and $PhSO_2CF_2SiMe_3$ (**3**). The free radical (phenylsulfonyl)difluoromethylation has also been achieved by using $PhSO_2CF_2I$ reagent (**4**). More recently, the electrophilic (phenylsulfonyl)difluoromethylation reactions with a hypervalent iodine(III)-CF_2SO_2Ph reagent (**5**) were also developed by us. It has now been realized that the importance of the (phenylsulfonyl)difluoromethylation lies in three aspects: (a) the "chemical chameleon" [52] character of the phenylsulfonyl group enables the transformation of the (phenylsulfonyl)difluoromethyl group into other highly useful fluorinated functionalities such as difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) groups (Scheme 1); (b) the phenylsulfonyl group can not only remarkably increase the thermal stability of the fluorinated carbanion ($PhSO_2CF_2^-$), but also enhance the carbanion's nucleophilicity toward many electrophiles; (c) the nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylation reagents (such as compounds **1**–**5**) can

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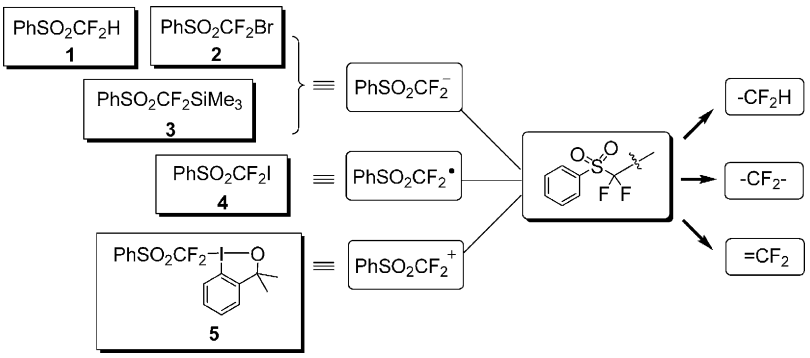
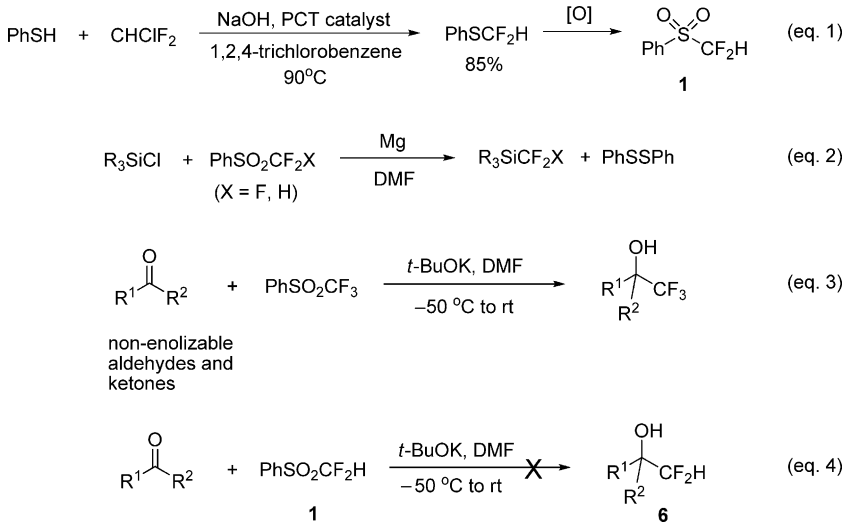
doi:10.1016/j.jfluchem.2009.05.016



Scheme 1.



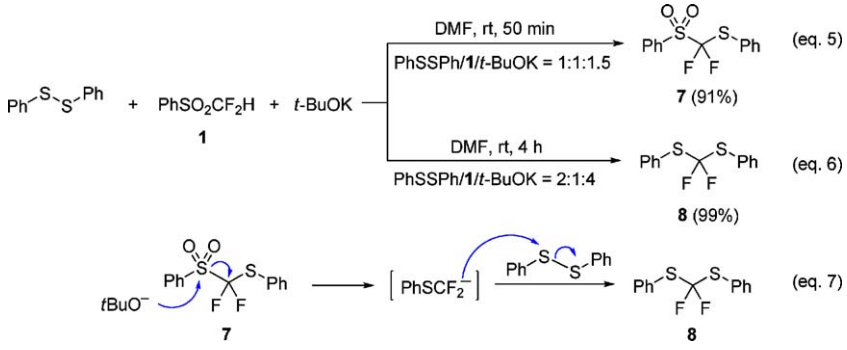
Scheme 2.

be easily obtained. This article overviews the development of nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylation reactions as well as their synthetic applications in organic synthesis since 2003.

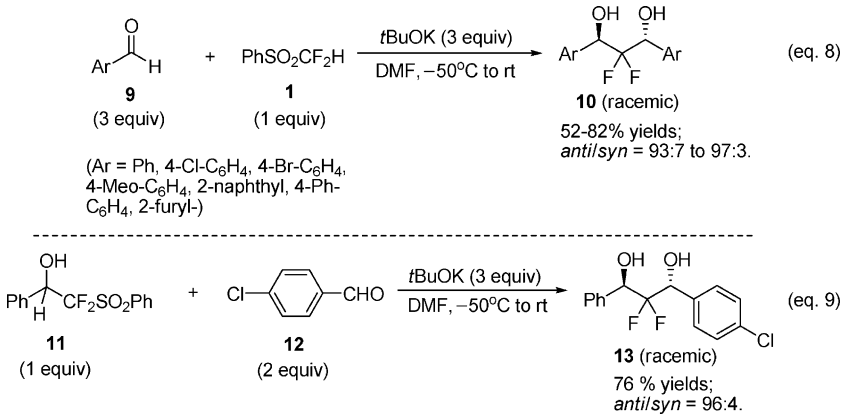
2. Nucleophilic (phenylsulfonyl)difluoromethylation reactions

2.1. Using $PhSO_2CF_2H$ reagent (1)

Difluoromethyl phenyl sulfone (**1**) is the most frequently used nucleophilic (phenylsulfonyl)difluoromethylation reagent, partially owing to its simple preparative procedure. Currently, reagent **1** is commonly prepared via the reaction between PhSH and $CHClF_2$ in the presence of a base, followed by oxidation (Scheme 2, Eq. (1)) [12,19,20]. In 2003, following a serendipitous discovery of the magnesium metal-mediated reductive tri- and difluoromethylation of chlorosilanes (Eq. (2)) [11,19] and potassium *tert*-butoxide-mediated trifluoromethylation (Eq. (3)) with fluorinated sulfones [21], we were interested in the similar type of nucleophilic difluoromethylation reactions with difluoromethyl phenyl sulfone (**1**) (Eq. (4)). The expected difluoromethyl carbinol products (**6**) were not obtained. We quickly realized from Stahly's previous work [15] that the base (such as *t*-BuOK) would first deprotonate the rather acidic reagent **1** to give $PhSO_2CF_2^-$ anion, which undergoes nucleophilic addition to carbonyl compounds to afford $PhSO_2CF_2$-containing carbinols. Considering that diphenyl



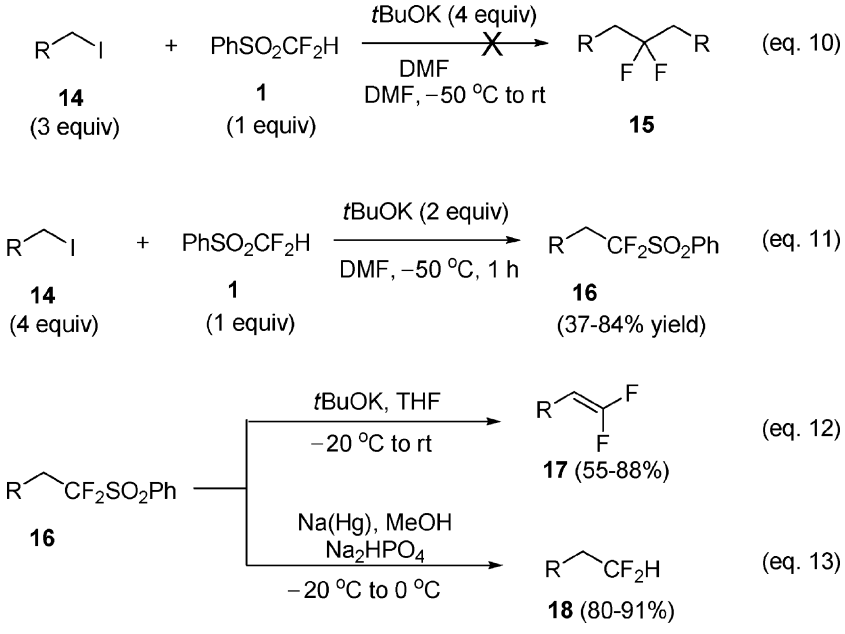
Scheme 3.



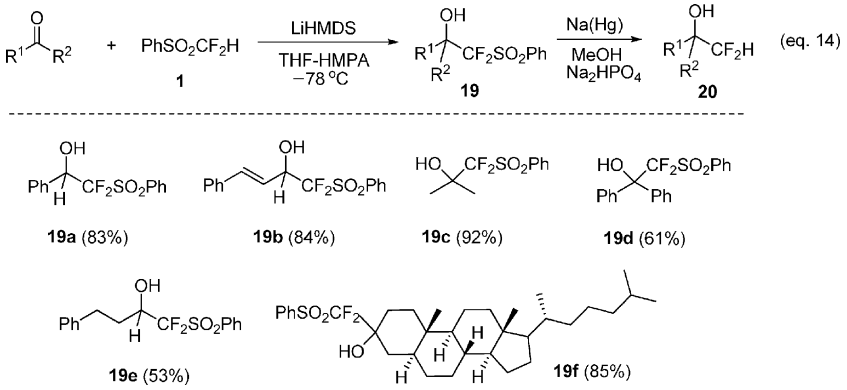
Scheme 4.

disulfide (PhSSPh) is not sensitive to potassium *tert*-butoxide, we chose PhSSPh as a model substrate to react with **1**/*t*-BuOK in DMF at room temperature [22]. The results were very intriguing (Scheme 3): (a) as expected, the (phenylsulfonyl)difluoromethylated product **7** (via the nucleophilic reaction between $PhSO_2CF_2^-$ and PhSSPh) was obtained in 91% yield within 50 min when the reactant ratio was PhSSPh/**1**/*t*-BuOK = 1:1:1.5 (Eq. (5)); (b) when the electrophile (PhSSPh) and the base (*t*-BuOK) were added in excess amount, an unexpected product **8** was formed in excellent yield (Eq. (6)), which was possibly formed via a *t*-BuOK-mediated S–C cleavage of intermediate **7** (Eq. (7)) [22]. These results suggest that the reactivity of deprotonation and S–C bond cleavage are different for compound **1**, and these two steps can be controlled selectively [22]. In this process, *t*-BuOK acts both as a base and as a good nucleophile. However, Stahly [15] and McCarthy [16] did not observe the S–C cleavage in their previous studies, implying that the bases they used (NaOH and LiHMDS) were not able to cleave the S–C bond. After we realized that reagent **1** can act as a difluoromethylene dianion equivalent ("CF_2^{2-}") via selective deprotonation and S–C cleavage, we applied it in the one-pot synthesis of 2,2-difluorinated 1,3-diols (Scheme 4, Eq. (8)) [22]. It was found that the $PhSO_2CF_2H$ (**1**)/*t*-BuOK/DMF system was able to couple two molecules of aryl aldehydes to give 2,2-difluoro-1,3-diols (**10**) in 52–82% chemical yields and with high *anti*/*syn* ratio (93:7 to 97:3). This observed high diastereoselectivity (*anti*/*syn* ratio) is possibly attributed to the charge–charge repulsion effect during the second addition step [22]. This method was also applicable to the synthesis of unsymmetrical *anti*-2,2-difluoropropane-1,3-diols (Scheme 4, Eq. (9)) [22].

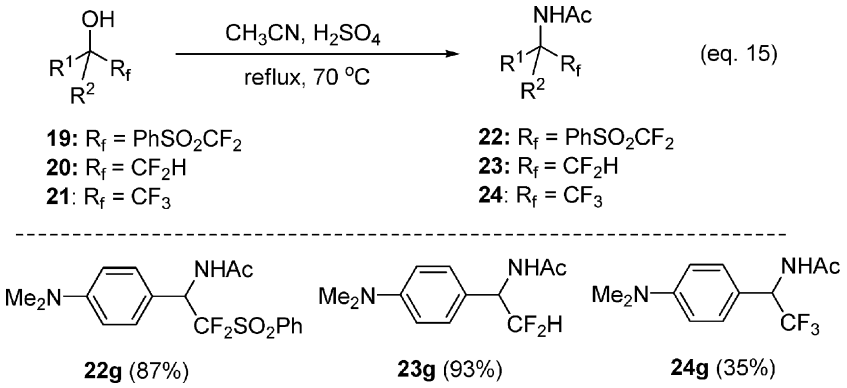
Encouraged by the one-pot synthesis of *anti*-2,2-difluoropropane-1,3-diols from aryl aldehydes and **1**, we applied the same protocol to convert primary iodides to dialkylated difluoromethane products **15** (Eq. (10)). This reaction proved to be unsuccessful, and we observed that S_N2 products **16** and 1,1-difluoro alkenes **17** were formed in the reaction mixture. After optimization of the reaction conditions, we found that the nucleophilic (phenylsulfonyl)difluoromethylation of primary alkyl iodides with $PhSO_2CF_2^-$ anion (in situ generated from **1** and *t*-BuOK) could smoothly proceed to afford the $PhSO_2CF_2$-containing alkanes **16** in satisfactory yields (Scheme 5, Eq. (11)) [23]. Products **16** are highly useful precursors, which can either be subjected to base-mediated dehydrosulfonylation to give 1,1-difluoro alkenes **17** in 55–88% yields (Eq. (12)) [23], or be subjected to reductive desulfonylation to afford CF_2H-containing alkanes **18** in 80–91% yields (Eq. (13)) [24]. Therefore, in addition to its synthetic power as a difluoromethylene dianion equivalent ("CF_2^{2-}") (Scheme 4),



Scheme 5.



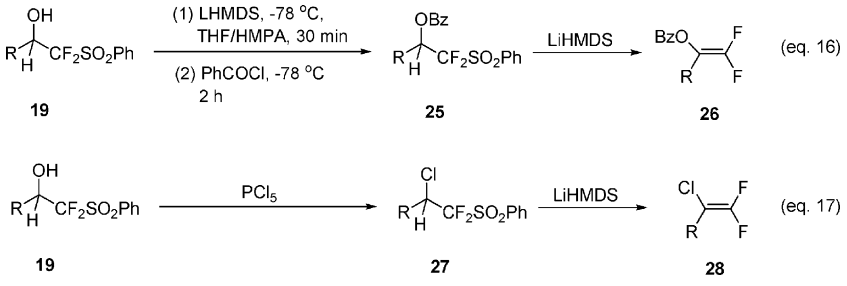
Scheme 6.



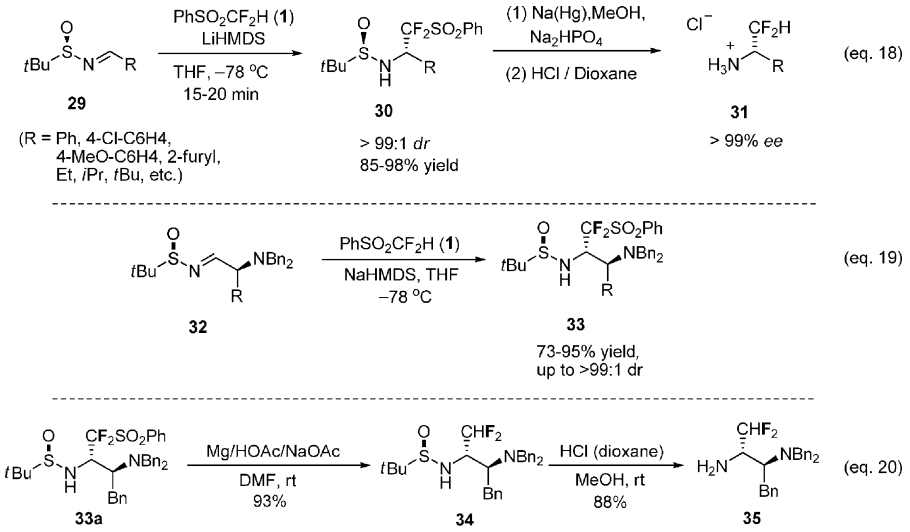
Scheme 7.

reagent **1** can also be regarded as both difluoromethylidene equivalent ("$=CF_2$") and difluoromethyl anion equivalent ("CF_2H^-"). It should be noted that one-pot conversion of alkyl iodides (**14**) to 1,1-difluoro alkenes (**17**) by using $PhSO_2CF_2H$ (**1**) and *t*-BuOK was also possible, but the isolation of alkenes **17** from unreacted **14** was problematic due to their similar polarity.

Based on our success in the synthesis of CF_2H-containing compounds from simple alkyl iodides using **1** as a nucleophilic difluoromethylation reagent (Eq. (13)) [24], we became interested in applying **1** as a robust CF_2H-transferring agent to a broad range of aldehydes and ketones. Although the Ruppert–Prakash reagent (Me_3SiCF_3) has been extensively used as a powerful nucleophilic trifluoromethylation reagent [25–27], its analogous R_3SiCF_2H was not effective in difluoromethylation (especially in the cases of ketones) [28,29]. The $Me_3SiCF_2SiMe_3$ reagent was also unable to efficiently react with ketones [30]. We also realized that Stahly's (phenylsulfonyl)difluoromethylation procedure with **1** [15] could not work with ketones and many enolizable aldehydes. McCarthy's (phenylsulfonyl)difluoromethylation protocol in the organic solvent was only demonstrated in limited examples of cyclic ketones [16–18,31]. Therefore, we embarked on a systematic study on the potential of using reagent **1** as a nucleophilic difluoromethylation (CF_2H-transferring) reagent for aldehydes and ketones through a (phenylsulfonyl)difluoromethylation-reductive desulfonylation protocol (Scheme 6, Eq. (14)) [32]. This two-step difluoromethylation method was found to be amenable to a variety of structurally diverse aldehydes and ketones. It is remarkable that even enolizable ketones can be efficiently (phenylsulfonyl)difluoromethylated by **1**/LiHMDs/HMPA system to give the $PhSO_2CF_2$-containing carbinols (such as **19c** in Scheme 6) in high yields. The limitation of this method was that, the product yields for enolizable aldehydes and sterically hindered ketones) were somewhat lower (such as **19d** and **19e** in Scheme 6) [32]. The $PhSO_2CF_2$- and CF_2H-containing alcohols **19** and **20** were used by us in the preparation of fluorinated amides via Ritter reaction (Scheme 7, Eq. (15)) [33]. Since the Ritter reaction is believed to proceed via a carbocation intermediate, an electron-withdrawing group in the substrate usually decreases the product yield. Therefore, the result in Scheme 7 indicates that the order of electron-withdrawing ability of the three fluorinated groups decreases in the following order: $CF_3 > PhSO_2CF_2 > CF_2H$ [33]. We also used (phenylsulfonyl)difluoromethyl alcohols **19** in the



Scheme 8.



Scheme 9.

preparation of 2,2-difluoro enol esters **26** (Scheme 8, Eq. (16)) and 1-chloro-2,2-difluoro alkenes **28** (Eq. (17)) [34].

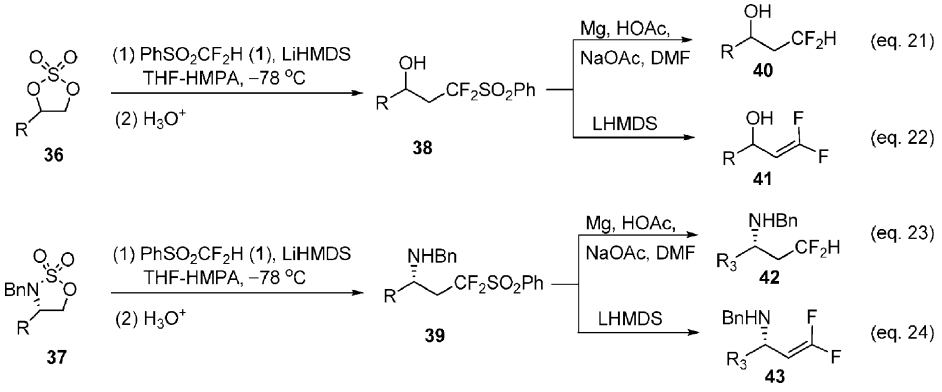
In 2005, we successfully applied reagent **1** in the stereoselective synthesis of enantiopure α-difluoromethyl amines by using Ellman's (*R*)-*N*-*tert*-butylsulfinyl aldimines (**29**) [35]. The reaction was compatible with different substituents in the substrates and afforded the (phenylsulfonyl)difluoromethylated amines **30** in excellent yields and with excellent diastereoselectivity (Scheme 9, Eq. (18)). The sense of the diastereoselective induction was depicted by a non-chelation-controlled transition state model [35]. After removal of the protective groups, enantiopure α-difluoromethyl amines (in salt form) **31** were obtained (Eq. (18)) [35]. The same strategy was also used by us in the stereoselective synthesis of difluoromethylated vicinal ethylenediamines (Scheme 9, Eqs. (19) and (20)) [36].

Although difluoromethyl phenyl sulfone (**1**) is an excellent nucleophilic fluoroalkylation reagent (via $PhSO_2CF_2^-$ anion), its reaction with epoxides (or aziridines) has remained a challenging task [37]. Inspired by Dolbier's work on nucleophilic trifluoromethylation of 1,2-cyclic sulfates [38], we have successfully carried out an efficient nucleophilic fluoroalkylation of cyclic sulfates **36** and sulfamidates **37** with $PhSO_2CF_2H$ (**1**)/LiHMDS/HMPA system (Scheme 10) [39]. These regioselective reactions afforded corresponding β-(phenylsulfonyl)-difluoromethylated products **38** and **39** in excellent yields. Upon selective desulfonylation, compounds **38** and **39** were readily transformed into β-difluoromethylated and β-difluoromethylenated alcohols (**40** and **41**) and amines (**42** and **43**), which are highly useful building blocks for many applications in life science and materials science (Scheme 10) [39].

Since (phenylsulfonyl)difluoromethyl carbanion ($PhSO_2CF_2^-$) belongs to hard nucleophiles, its reaction with α,β-unsaturated ketones (α,β-enones) generally proceeds in a 1,2-addition mode [32,40]. However, recently we found that both solvent and the structure of α,β-enones (**44**) can influence the 1,2-/1,4-addition ratio (Table 1) [40]. When the reactions were carried out in THF-HMPA solvent system, 1,2-addition products (**45**) were obtained as the predominant products; however, when THF alone was applied as solvent, in some cases the 1,4-addition products (**46d–f**) could be formed in significant amount (Table 1). The structure of α,β-enones **44** also affects the regioselectivity of the reaction; for example, for the enones with an electron-donating methoxyl group (**44d–f**), the tendency of 1,4-addition was increased (Table 1, entries 4–6) [40].

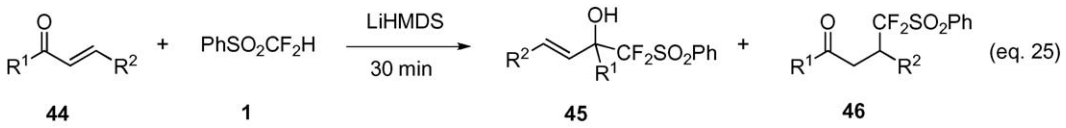
With a chiral quaternary ammonium salt as a catalyst and KOH as a base, we have also attempted the enantioselective nucleophilic difluoromethylation of aromatic aldehydes with $PhSO_2CF_2H$ (**1**) reagent (Scheme 11) [41]. The enantioselectivity was found to be substrate-dependent and for 2-chlorinated benzaldehyde an ee up to 64% was obtained [41].

Difluoromethyl phenyl sulfone (**1**) can also be used to react with elemental iodine and *N*-chlorosuccinimide (NCS) to give iododifluoromethyl phenyl sulfone (**4**) and chlorodifluoromethyl phenyl sulfone (**49**) in good yields, respectively (Scheme 12, Eqs. (27) and



Scheme 10.

Table 1
Nucleophilic (phenylsulfonyl)difluoromethylation of α,β-enones [40]



44 1 45 46

.

Entry[a]	Enone	Products	Overall yield (in THF) (%)[b,c]	Overall yield (in THF-HMPA) (%)[c,d]
1	R^1 C_6H_5, R^2 C_6H_5 (**44a**)	**45a**	97	90
2	R^1 C_6H_5, R^2 4-ClC_6H_4 (**44b**)	**45b**	91	95
3	R^1 4-BrC_6H_4, R^2 C_6H_5 (**44c**)	**45c**	93	93
4	R^1 C_6H_5, R^2 4-$MeOC_6H_4$ (**44d**)	**45d**, **46d**	97 (68:32)	90 (>99:1)
5	R^1 4-$MeOC_6H_4$, R^2 C_6H_5 (**44e**)	**45e**, **46e**	95 (73:27)	98 (>99:1)
6	R^1 4-$MeOC_6H_4$, R^2 4-$MeOC_6H_4$ (**44f**)	**45f**, **46f**	90 (68:32)	93 (>99:1)

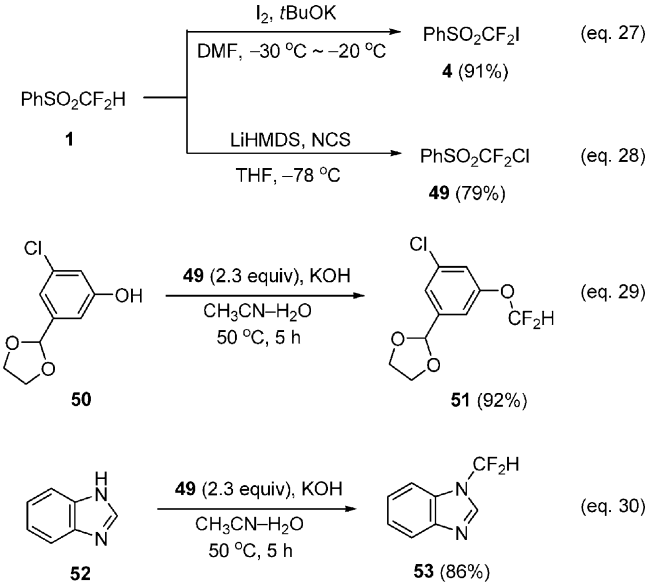
[a] Molar ratio **44**/**1**/LiHMDS 1.0:1.2:1.2.
[b] The reaction was performed at −98 °C.
[c] The overall yield of the isolated products. The number in parentheses refers to the ratio of **45**:**46**, which was determined by ^{19}F NMR analysis of the isolated product mixture.
[d] The reaction was performed at −78 °C.

(28)) [24,42]. Compound **4** has been successfully applied by us in free radical (phenylsulfonyl)difluoromethylation reactions (see Section 3). Chlorodifluoromethyl phenyl sulfone (**49**) is a robust difluorocarbene reagent for *O*- and *N*-difluoromethylations (Scheme 12, Eqs. (29) and (30)) [42]. More recently, we also developed an efficient method for the synthesis of (phenylsulfonyl)difluoromethyl ketones (**55**) by nucleophilic (phenylsulfonyl)-difluoromethylation of esters with reagent **1** (Scheme 13) [43]. The yields were generally excellent, and this preparative method has been scaled up to 10–20 mmol scale with reproducible product yields [43].

2.2. Using $PhSO_2CF_2SiMe_3$ reagent (3)

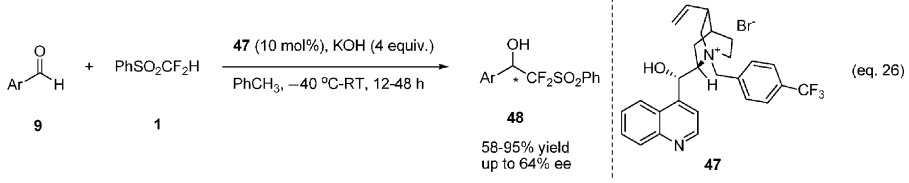
As an alternative nucleophilic (phenylsulfonyl)difluoromethylation reagent to $PhSO_2CF_2H$ (**1**), we also developed [(phenylsulfonyl)difluoromethyl]trimethylsilane ($PhSO_2CF_2SiMe_3$, **3**) reagent. Compound **3** was first prepared in 2003 via mCPBA-mediated oxidation of $PhSCF_2SiMe_3$ in 51% yield [19]. In 2005, we improved the synthesis of **3** (with 78% isolated yield) by the reaction of $PhSO_2CF_2Br$ (1 equiv.), *n*-BuLi (1.8 equiv.), and Me_3SiCl (1.5 equiv.) in THF at −78 °C [43]. In 2008, we further optimized the reaction conditions and found that when the reactant ratio was changed to $PhSO_2CF_2Br$/*n*-BuLi/Me_3SiCl = 1.0:1.1:1.5 and a subsequent acid-quenching procedure was used, an excellent yield of **3** (87–98%) could be obtained (Scheme 14, Eq. (32)) [44,43].

Compound **3** was successfully applied in the fluoride-initiated nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes and ketones (Eq. (33)). Tetrabutylammonium triphenyldifluorosilicate (TBAT) and CsF are the two commonly used fluoride initiator, and the use of CsF is preferred in the reactions with sterically hindered ketones [43]. Unlike $PhSO_2CF_2H$ (**1**), reagent **3** does not need a strong base (such as LiHMDS) to facilitate the (phenylsulfonyl)difluoromethylation. Therefore, $PhSO_2CF_2SiMe_3$ reagent (**3**) has showed some advantages over $PhSO_2CF_2H$ in the reactions

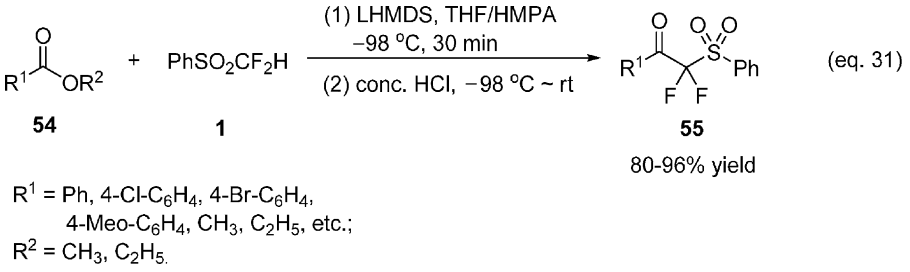


Scheme 12.

with base-sensitive substrates such as enolizable aldehydes (Scheme 14) [43]. For example, in the (phenylsulfonyl)difluoromethylation of α-amino aldehyde **56**, we found that $PhSO_2CF_2H$ (**1**)/LiHMDS reagent was not effective and only 46–52% product yields were obtained [44]. When we used the $PhSO_2CF_2SiMe_3$ (**3**) reagent and TBAT as a fluoride initiator (5 mol%), the amino alcohol product **57** can be obtained in 92% isolated yields with a *syn*/*anti* ratio of 11:89 (Scheme 15, Eq. (35)). The *anti*-α-(phenylsulfonyl)-difluoromethyl-β-amino alcohol (*anti*-**57**) was further transformed to chiral difluoromethylated oxazolidinone **60** (Eq. (36)) [44]. The advantageous use of reagent **3** over reagent **1** has also



Scheme 11.



Scheme 13.

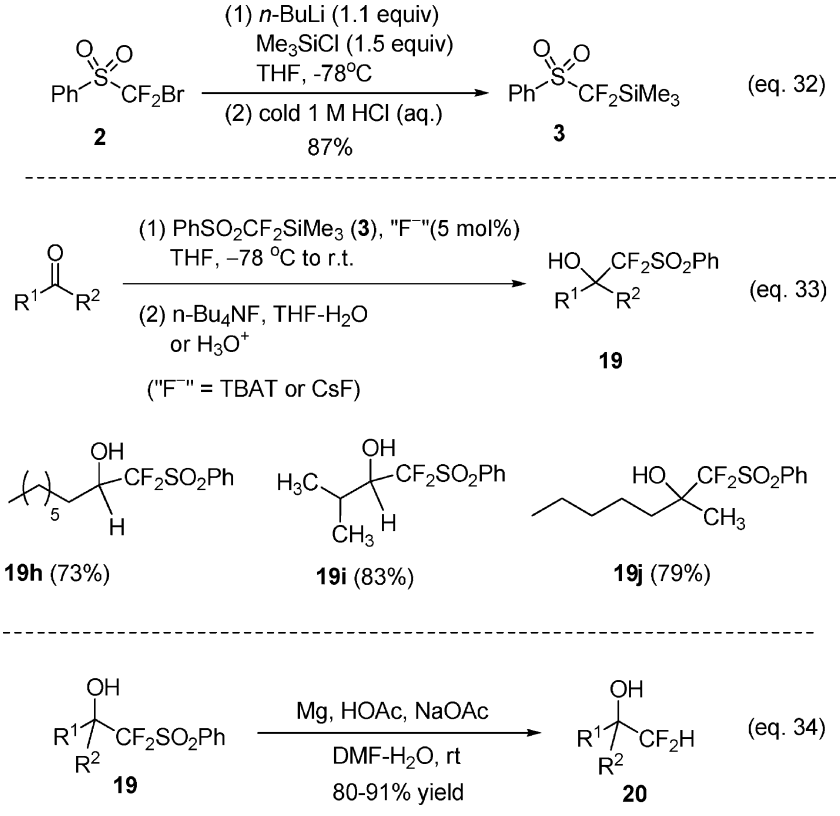
been demonstrated by us in the preparation of a hypervalent iodine(III)-CF_2SO_2Ph compound [45]. Furthermore, we attempted the use of reagent **3** in the enantioselective nulceophilic (phenylsulfonyl)difluoromethylation of aromatic aldehydes, but the enantioselectivity was only moderate [41].

2.3. Using $PhSO_2CF_2Br$ reagent (2)

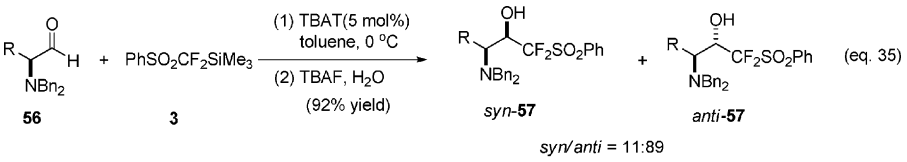
Bromodifluoromethyl phenyl sulfone ($PhSO_2CF_2Br$, **2**) was first reported by Burton and Wiemers [46], but the reports on its synthetic utility are rare [19,47]. Inspired by Dolbier's work that tetrakis(dimethylamino)ethylene (TDAE) can act as an efficient reducing agent to generate substituted difluoromethylated carbanions from halo-difluoromethyl precursors [48], Prakash et al. have used $PhSO_2CF_2Br$/TDAE combination as a nucleophilic (phenylsulfonyl)difluoromethylation reagent (Scheme 16) [47]. The reactions were shown to be efficient with both aryl and alkyl aldehydes, but not applicable to ketones. The obtained products **19** were able to be transformed to difluoromethyl alcohols **20** and 1,1-difluoro alkenes **17** (Scheme 16) [47].

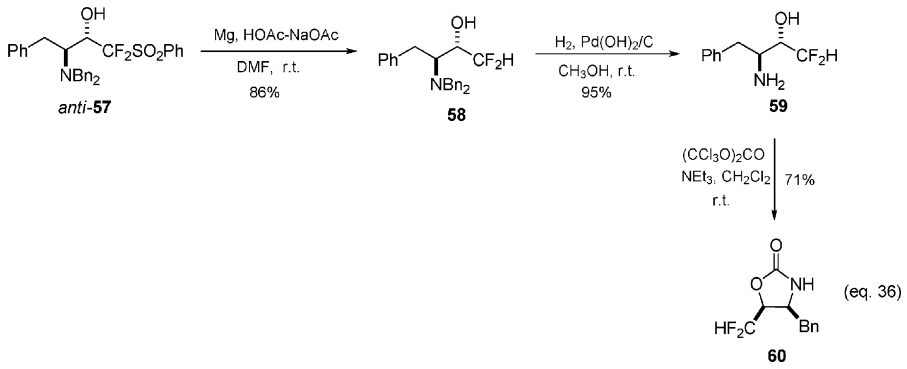
3. Radical (phenylsulfonyl)difluoromethylation reactions

In 2007, we reported the first free radical (phenylsulfonyl)difluoromethylation reaction with alkenes by using iododifluoromethyl phenyl sulfone (**4**) [49]. Compound **4** can be easily prepared in excellent yield from $PhSO_2CF_2H$ (**1**) and elemental iodine in the presence of *t*-BuOK in DMF (Scheme 12, Eq. (27)) [24]. After trying several radical initiators, we found that copper powder (Cu^0), $Pd(PPh_3)_4$, and $Na_2S_2O_4$ were not suitable for the reaction, which is surprisingly different from other known free radical polyfluoroalkylation reactions [49]. It turned out that Et_3B/air was an efficient initiating system for the generation of (phenylsulfonyl)difluoromethyl radical ($PhSO_2CF_2^{\bullet}$) at low temperature (−30 °C). Therefore, by using this Et_3B/air-initiated radical (phenylsulfonyl)difluoromethylation with reagent **4**, a variety of structurally diverse terminal alkenes (**61**) were transformed to regioselective products **62** in 56–78% yields (Scheme 17) [49]. The reaction was shown to be compatible with different functionalities such as carbonyl, ester, carboxylic acid, ether, and hydroxyl groups. This synthetic methodology was also used in the one-pot regioselective preparation of

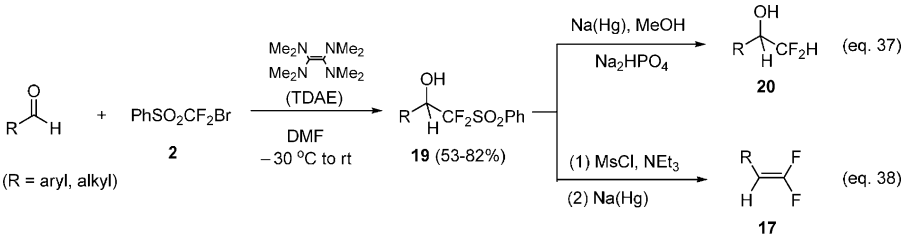


Scheme 14.

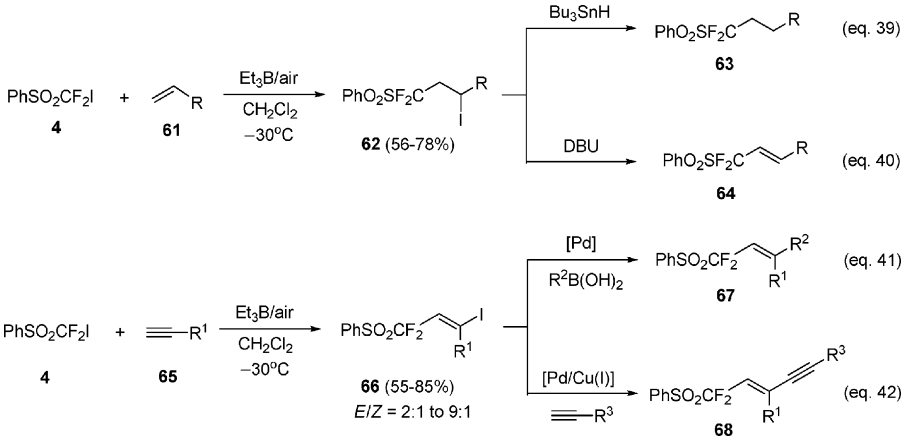




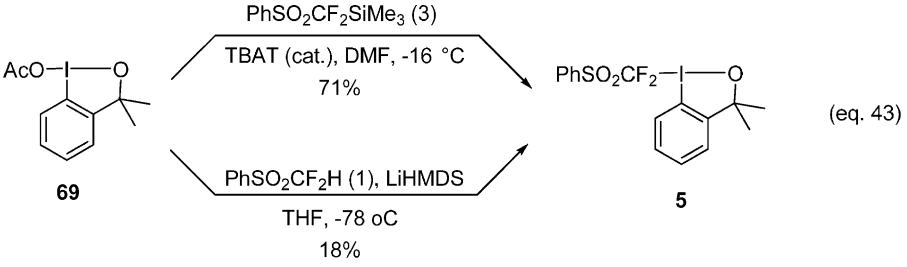
Scheme 15.



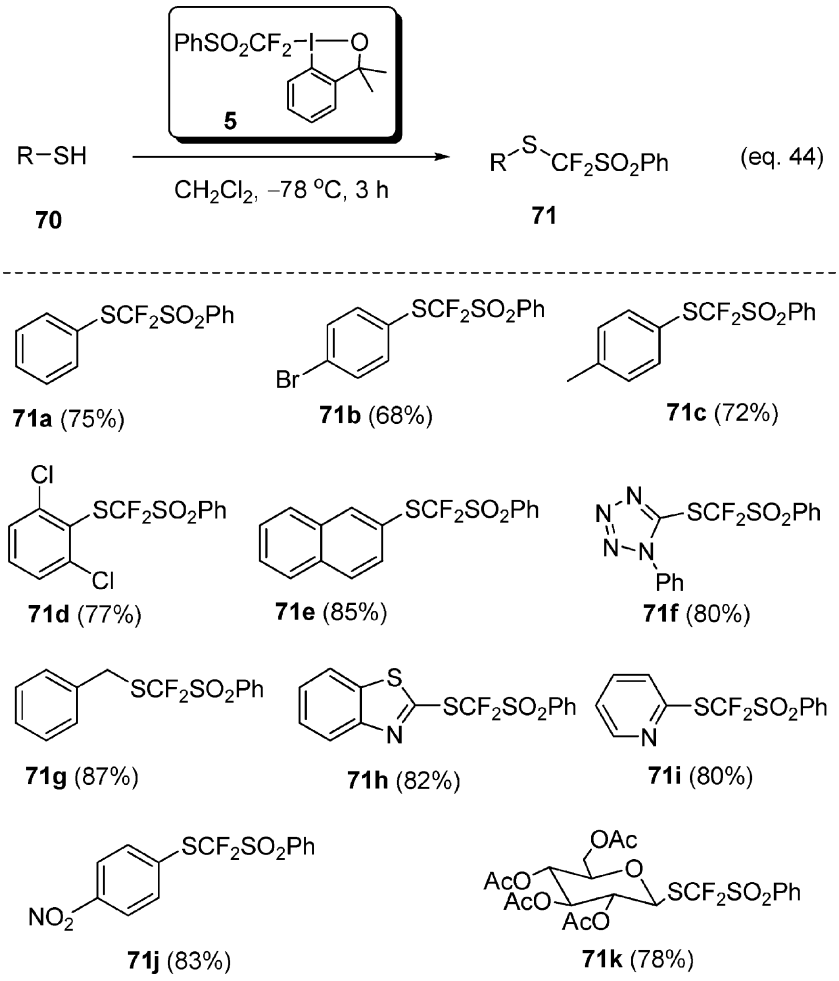
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

$PhSO_2CF_2$-substituted alkanes (**63**) and in the regio- and stereoselective preparation of $PhSO_2CF_2$-substituted alkenes (**64**) with high *E*/*Z* ratio (up to 100:1) (Scheme 17, Eqs. (39) and (40)) [49]. More recently, we extended this useful synthetic method in the radical (phenylsulfonyl)difluoromethylation of terminal alkynes (Scheme 17, Eqs. (41) and (42)) [50]. It turned out that by using Et_3B/air as radical initiator, $PhSO_2CF_2I$ (**4**) was able to add to a variety of terminal alkynes (**65**) to afford the corresponding products **66** in good yields and with moderate to good E/Z stereoselectivity. The obtained products **66** could be further utilized to undergo Suzuki or Sonogashira coupling reactions to give products **67** and **68** in good yields, respectively (Scheme 17, Eqs. (41) and (42)) [50].

4. Electrophilic (phenylsulfonyl)difluoromethylation reactions

Inspired by the electrophilic trifluoromethylation work of Togni and co-workers [51], we developed the electrophilic (phenylsulfonyl)difluoromethylation reaction with a hypervalent iodine(III)-CF_2SO_2Ph reagent (**5**) [45]. The preparation of reagent **5** from precursor **69** were tried using both $PhSO_2CF_2SiMe_3$ (**3**) and $PhSO_2CF_2H$ (**1**), and the product yields were 71 and 18%, respectively (Scheme 18) [45]. Reagent **5** is a relatively stable compound, which can be easily purified by silica gel column chromatography. The electrophilic (phenylsulfonyl)difluoromethylation reagent **5** can efficiently transfer the $PhSO_2CF_2$ moiety to a diverse range of sulfur-nucleophiles under mild reaction conditions (Scheme 19) [45].

5. Conclusions

This article overviews the nucleophilic, free radical, and electrophilic (phenylsulfonyl)difluoromethylations with reagents such as $PhSO_2CF_2H$ (**1**), $PhSO_2CF_2Br$ (**2**), $PhSO_2CF_2SiMe_3$ (**3**), $PhSO_2CF_2I$ (**4**), and the hypervalent iodine(III)-CF_2SO_2Ph during the past 6–7 years. Nucleophilic (phenylsulfonyl)difluoromethylation has been most extensively studied in this category (especially with $PhSO_2CF_2H$ reagent), while both free radical and electrophilic (phenylsulfonyl)difluoromethylations have also been recently emerged. These reagents and reactions have showed their power in the synthesis of many difluoromethyl-, difluoromethylene-, and difluoromethylidene-containing organic molecules. However, several issues in this (phenylsulfonyl)difluoromethylation chemistry need to be addressed, including (a) how to achieve enantioselective (phenylsulfonyl)-difluoromethylation in a practically useful level, (b) how to remove the phenylsulfonyl group in a more efficient and environmentally friendly way [53], (c) is it possible to discover new "chemical chameleon" [52] type of reactivity with $PhSO_2CF_2$-containng compounds, (d) is it possible to use the easily accessible $PhSO_2CF_2$ group itself as a routine and useful substituent in materials science- and life science-related applications. There is no doubt that further exploration of this interesting chemistry will provide new possibilities for the application of $PhSO_2CF_2$-containing compounds in many important fields.

Acknowledgements

The author gratefully acknowledges all of his co-workers whose names appeared in the cited references. Financial support by the National Natural Science Foundation of China (20502029, 20772144, 20825209, 20832008), Shanghai Rising-Star Program (06QA14063), and the Chinese Academy of Sciences (Hundred-Talents Program and Knowledge Innovation Program) are gratefully acknowledged.

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