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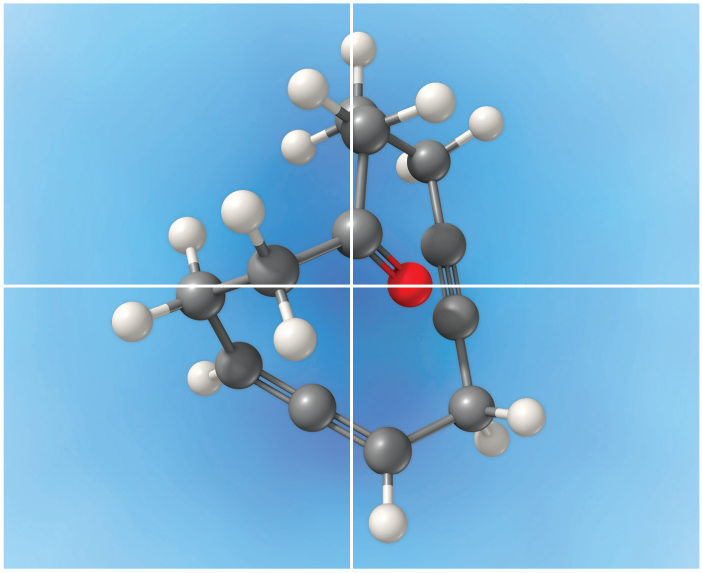

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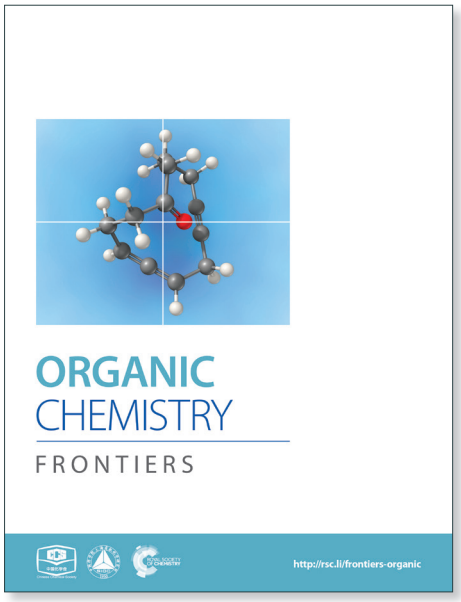

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Selective Monofluorination of Active Methylene Compounds: The Important Role of $ZnCl_2$ in Inhibiting Overfluorination

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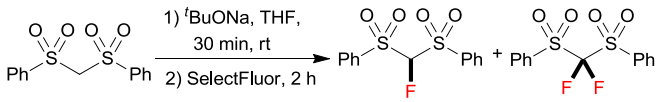
In the presence of zinc chloride ($ZnCl_2$), active methylene compounds can be selectively monofluorinated at room temperature, and the undesired overfluorination (*gem*-difluorination) can be significantly diminished. The mechanistic study shows that $ZnCl_2$ plays an important role in selective monofluorination through its interaction with Brønsted base to control the deprotonation of the starting methylene compounds over the corresponding monofluorinated products.

Owing to their structural diversity and peculiar reactivity, active methylene compounds have found many applications in organic synthesis such as Michael addition, aldol and Knoevenagel reactions.[1] On the other hand, compounds bearing a monofluoromethylene group (–CHF–) are important candidates in isostere-based drug design,[2] and these compounds can be usually prepared by an electrophilic C–H monofluorination of active methylene compounds. However, this reaction often suffers from overfluorination,[1b,3] resulting in a mixture of mono- and difluorinated products. In many cases, the similar polarity of the mono- and difluorinated products leads to the difficulty in their separation (purification).[3b] The general solution to this problem is that equal equivalents of base and fluorination reagent (based on that of the active methylene compounds) are incorporated at low temperature, but the efficiency of fluorination is often unsatisfactory.[4] Other methods[3a,5] include the conversion of active methylenes to the corresponding enol ethers, and the latter species are selectively monofluorinated; however, this protocol is not amenable to methylene-containing sulfones. Fluorine-containing sulfones prove to be of great value in organic synthesis,[6] especially in selective fluoroalkylation reactions.[7] To the best of our knowledge, however, practical methods for the preparation of monofluorinated sulfones via selective fluorination of non-fluorinated sulfones are rare.[8] In this communication, we wish to report a $ZnCl_2$-mediated selective monofluorination of active methylene compounds using an electrophilic fluorination reagent at room temperature.

Table 1 Survey of reaction conditions



1a **2a** **3a**

entry	^{t}BuONa (equiv)[a]	$ZnCl_2$ (equiv)[a]	**2a** (%)[b]	**3a** (%)[b]
1	1.0	-	73	2
2	1.2	-	71	3
3	1.5	-	61	19
4	1.8	-	60	22
5	1.8	1.0	79	3
6	1.8	1.5	57	-
7	1.8	1.8	45	-
8	2.2	1.5	91	7
9	2.2	1.8	79	-
10	2.5	2.2	94	3
11	**2.5**	**2.5**	**91**	**1**

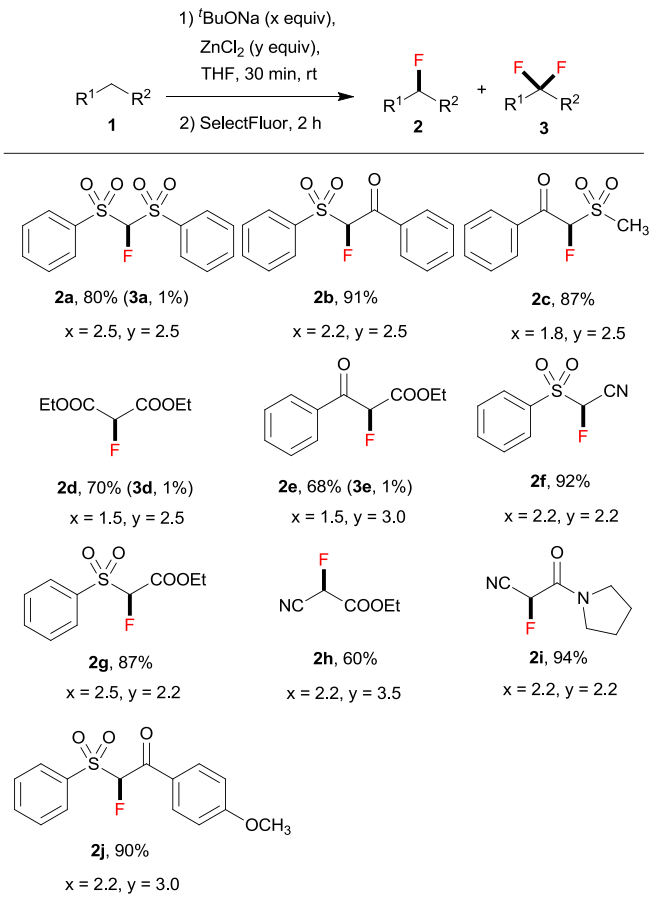
[a]The equivalent is relative to that of **1a**. [b]Determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCF_3$ as an internal standard.

At the onset of our investigation, we focused on the monofluorination of bis(phenylsulfonyl)methane (**1a**), since selective monofluorination of **1a** can lead to a highly useful monofluoromethylation reagent **2a**.[3b,9] Previously, efforts have been made by the Hu[9a] and Shibata[9b] groups through electrophilic fluorination to synthesize **2a**; however, in both cases the formation of difluorinated by-product **3a** was observed.[9a,10] After a brief screening, we found that the employment of a bulky base was beneficial to minimize difluorination. Therefore, we chose sodium *tert*-butoxide (1.0 equiv) as a base to react with **1a** in THF at room temperature, and then 2.0 equiv of SelectFluor was added. It turned out that a good yield of monofluorinated **2a** was obtained, with only a small amount of difluorinated by-product **3a** being observed by ^{19}F NMR (Table 1, entry 1). However, when we increased the

equivalents of base to improve the conversion of starting material **1a**, the tendency of overfluorination was unfortunately increased (Table 1, entries 2-4).

We presumed that the van der Waals radius of fluorine resembles with that of hydrogen, leading to the difficulty in preventing overfluorination. Inspired by the monoiodination of methylene-containing sulfones reported by Imamoto,[11] we supposed that it could be possible to prepare the corresponding organozinc reagent[12] after deprontonation of active methylene compounds. Given the fact that the basicity of organozinc reagent is relatively weak, over-deprontonation should be significantly inhibited. To test our hypothesis, 1.0 equiv of anhydrous $ZnCl_2$ was added in the reaction mixture. We were satisfied to find that monofluorinated product **2a** was formed in 79% yield, with the difluorinated by-product **3a** being formed in 3% yield (Table 1, entry 5). After further tuning the molar ratio between ^{t}BuONa and $ZnCl_2$ (entries 6-11), we found that an optimal yield (91%) of **2a** was obtained when 2.5 equiv of ^{t}BuONa and 2.5 equiv of $ZnCl_2$ were employed (Table 1, entry 11).

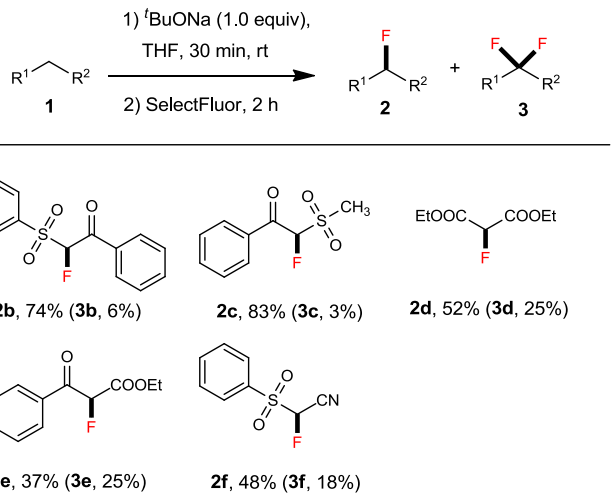
Table 2 Electrophilic monofluorination of active methylene compounds **1** (R^1, R^2 = EWG)[a-e]



[a] In all cases, the equivalents of ^{t}BuONa (x) and $ZnCl_2$ (y) are based on that of the corresponding starting material **1**. [b]The yield of **2** refers to the isolated yield. [c]Unless otherwise mentioned, difluorinated products **3** are not observed by ^{19}F NMR; when **3** was formed, the yield of **3** are determined by ^{19}F NMR. [d]The range of pKa values of C-H bonds among these methylene compounds **1** is between 11.4 and 17.2 in DMSO. [e] EWG = electron-withdrawing group.

Thereafter, we continued to examine the substrate scope of this new protocol of $ZnCl_2$-mediated monofluorination. Initailly, we applied the optimized reaction conditions (as described in Table 1, entry 11) to other active methylene compounds such as **1b**, **1c**, and **1d**; however, we quickly realized that the reaction is very sensitive to different substrates, and further optimizations are needed for different active methylene substrates.[13] It is obvious that a significant change in the C–H acidity of **1** caused by different substituents results in a great influence in the degree of deprotonation of methylene compounds, and therefore, the alteration of the basicity of the reaction mixture could be crucial to the selectivity of deprotonation. We found that when substituents R^1 and R^2 on the methylene compound **1** are more electron-withdrawing, a decrease of the amount of ^{t}BuONa and/or an increase of that of $ZnCl_2$ could improve the selectivity of monofluorination.[14] It should be mentioned that, by tuning the ratio between ^{t}BuONa and $ZnCl_2$, selective monofluorination was accomplished with a variety of structurally diverse active methylene compounds (Table 2). This $ZnCl_2$-mediated new method was found to be also amenbale to other active methylene compounds without sulfonyl groups (see **2d**, **2e**, **2h** and **2i**). To verify the important role of $ZnCl_2$ in selective monofluorination of active methylene compounds, we chose some methylene-containing substrates (**1b**- **1f**) to be fluorinated in the absence of $ZnCl_2$: 1.0 equiv sodium *tert*-butoxide was added to react with **1** in THF at room temperature, and then 2.0 equiv of SelectFluor was added. In all cases, difluorinated by-products were observed by ^{19}F NMR analysis. Moreover, for substrates **1d**, **1e** and **1f**, these reactions suffered from overfluorination severely (Table 3).

Table 3 Electrophilic fluorination of active methylene compounds **1** in the absence of $ZnCl_2$ (R^1, R^2 = EWG)[a,b]

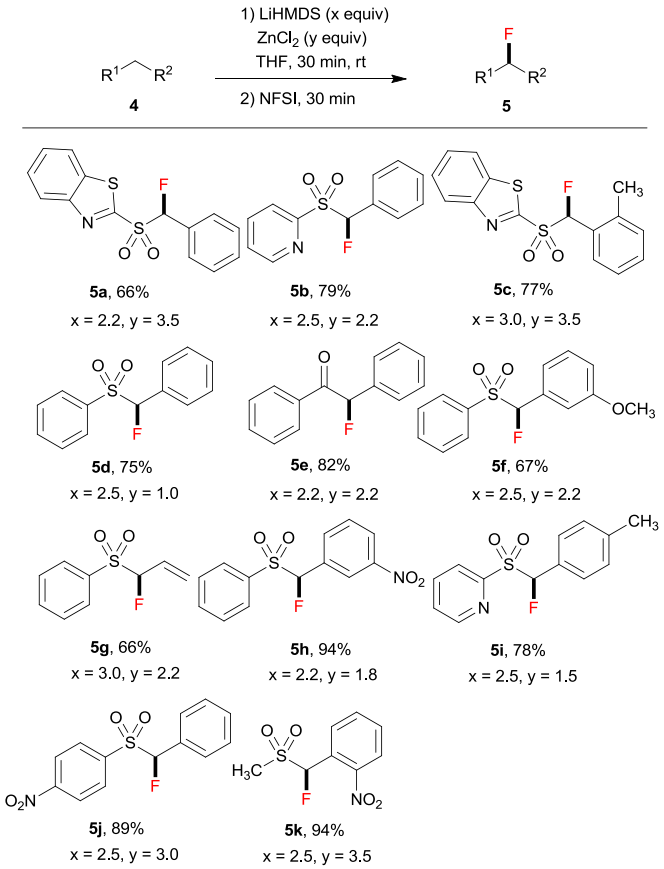


[a]The equivalent of NaO^{t}Bu is based on that of the corresponding starting material **1**. [b]The yield of **2** and **3** are determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCF_3$ as an internal standard.

Inspired by the achievement of selective monofluorination with active methylene compounds **1**, we extended the substrate scope of this reaction to relatively inactive methylene compounds **4** (see Table 4). Fluorinated benzothiazolyl sulfones have been reported as

general synthons for fluoro-Julia-Kocienski olefinations, and the resulting monofluoroalkene moiety can be used as a nonhydrolyzable mimetic of amide in peptidomimetic unit of protease inhibitors.[15] We envisaged that, for relatively inactive methylene compounds with less acidic $-CH_2-$ unit, a stronger base than *t*BuONa should be used. Therefore, lithium hexamethyldisilazide (LiHMDS) was chosen as a base for the reaction, and the amounts of base and $ZnCl_2$ were further optimized for each substrate **4** (for details of optimization, see SI). As shown in Table 4, a variety of relatively inactive methylene compounds can be selectively fluorinated to give the corresponding products **5**; in all cases, no difluorinated by-products were observed.

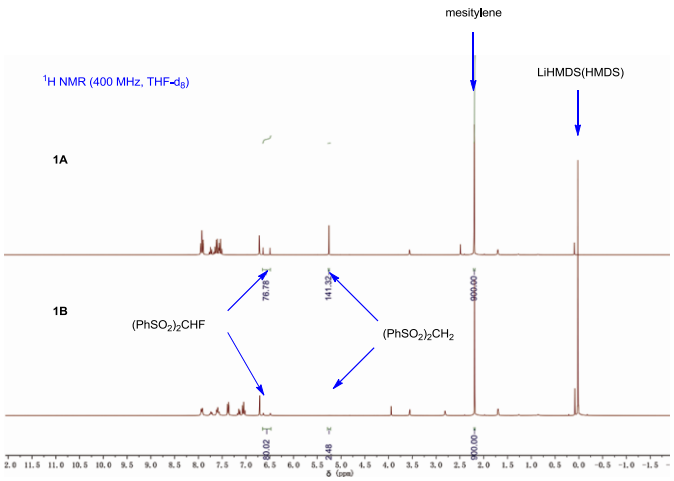
Table 4 Electrophilic monofluorination of active methylene compounds 4 (R^1 = EWG, R^2 = phenyl, alkenyl)[a-d]



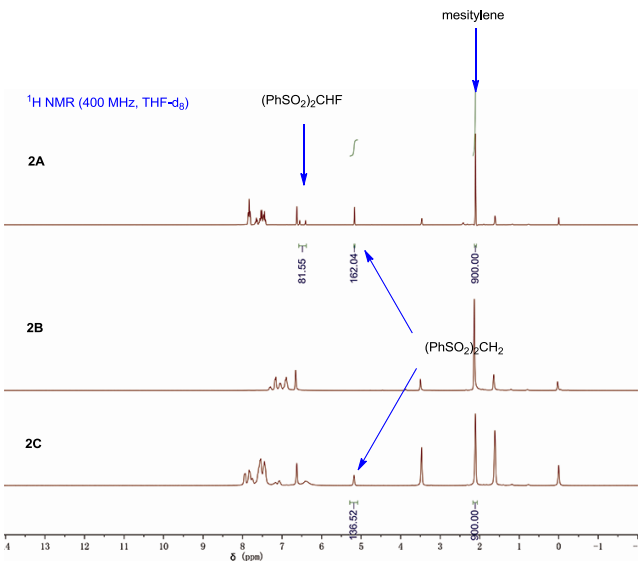
[a] In all cases, the equivlents of LiHMDS (x) and $ZnCl_2$ (y) are based on that of starting materials **4**. [b] The yield of **5** refers to the isolated yield. [c]In all cases, the difluorinated by-products are not observed. [d]The range of pKa values of C-H bonds among these methylene compounds is between 17.7 and 23.4 in DMSO.

To gain more insight into this $ZnCl_2$-mediated selective monofluorination, we carried out some experiments. First of all, we compared the tendency of deprontonation and fluorination between methylene compounds and the corresponding monofluorinated ones using $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ as model compounds. Equal equivalent of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ were mixed in THF-D_8 in the presence of substoichiometric amount of LiHMDS, and the mixture was characterized by ^1H NMR (1A, 1B, for details, see SI). It was found that $(PhSO_2)_2CH_2$ was more easily deprotonated than $(PhSO_2)_2CHF$, which was consistent with the theoretical calculation reported by Prakash and Olah.[16] Secondly, we mixed equal equivalent of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-D_8 in the presence of excess amount of NaH, and thereafter, the reaction was quenched by a substoichiometric amount of *N*-fluorobisphenylsulfonimide (NFSI) (2A-2F, for details, see SI). It was found that $(PhSO_2)_2CHF$ showed higher tendency for fluorination. According to these experimental results, the key to acquire the most monofluorinated product and inhibit the difluorination is to maximize the deprotonation of methylene compound $(PhSO_2)_2CH_2$ and minimize the further deprotonation of monofluorinated intermediate $(PhSO_2)_2CHF$. Thirdly, we added $(PhSO_2)_2CH_2$ into THF-D_8 under the optimized conditions (2.5 equiv of ^{t}BuONa and 2.5 equiv of $ZnCl_2$) (3A, 3B, for details, see SI). Unexpectedly, $(PhSO_2)_2CH_2$ was almost intact (i.e., the deprontonation hardly occurred), which was indicated by ^1H NMR.

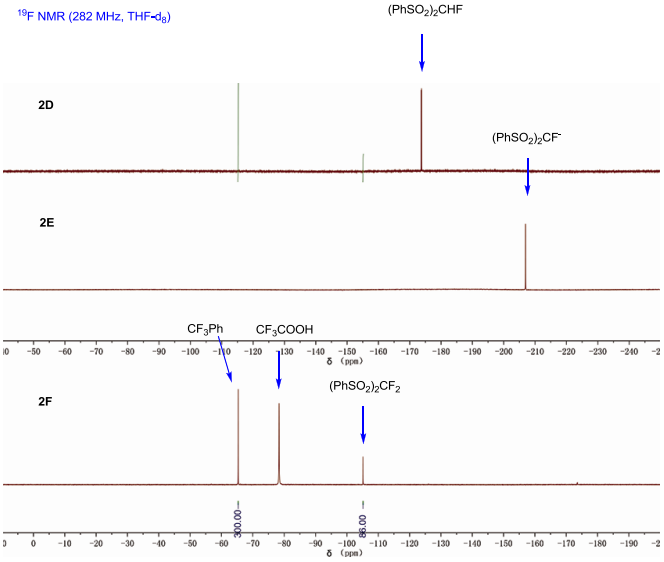
Figure 1 Mechastic study through ^1H NMR experiments



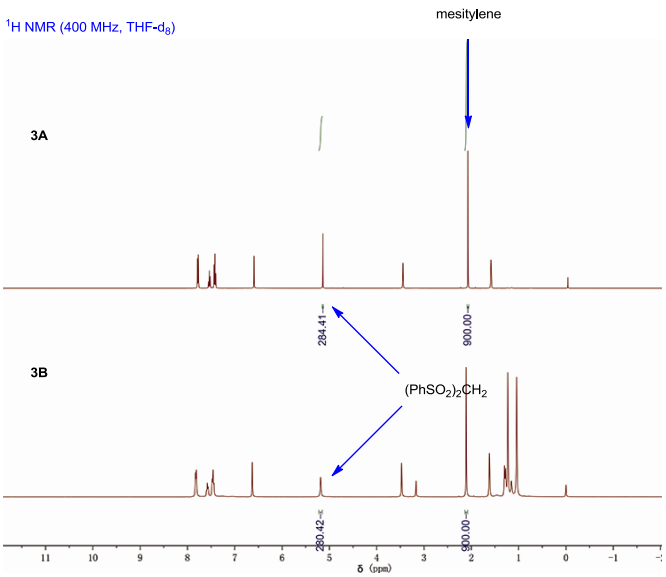
(1A) Mixing equal equivalent of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8; (1B) Adding substoichiometric amount of LiHMDS into the mixture.



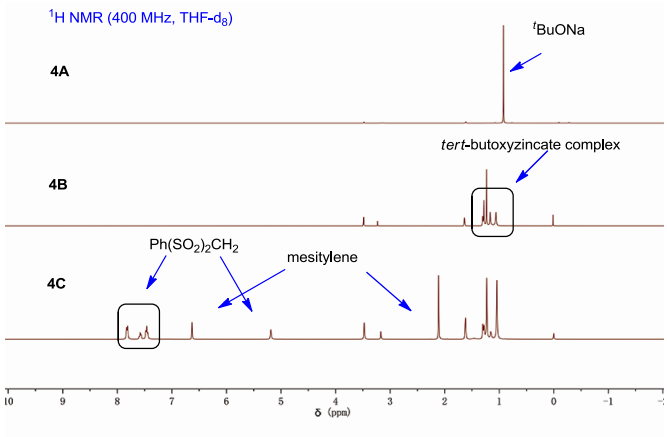
(2A) Mixing equal equivalent of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8; (2B) Adding excess amount of NaH into the mixture; (2C) Adding substoichiometric amount of NFSI into the mixture, and then quenching it by CF_3COOH.



(2D) Mixing equal equivalent of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8; (2E) Adding excess amount of NaH into the mixture; (2F) Adding substoichiometric amount of NFSI into the mixture, and then quenching it by CF_3COOH.



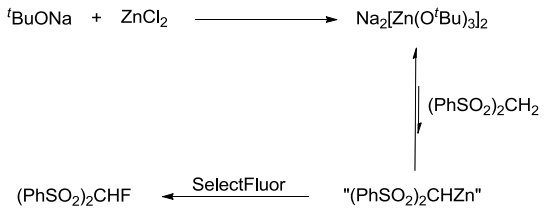
(3A) Mixing $(PhSO_2)_2CH_2$ and $ZnCl_2$ in THF-d_8; (3B) Adding ^{t}BuONa (2.5 equiv) into the mixture of $(PhSO_2)_2CH_2$ (1.0 equiv) and $ZnCl_2$ (2.5 equiv).



(4A) Only ^{t}BuONa dissolved in THF-d_8; (4B) The mixture of ^{t}BuONa (1.0 equiv) and $ZnCl_2$ (1.0 equiv) in THF-d_8; (4C) Adding $(PhSO_2)_2CH_2$ (1.0 equiv) into the mixture of ^{t}BuONa (2.5 equiv) and $ZnCl_2$ (2.5 equiv).

As reported previously,[17] mixing ^{t}BuONa with $ZnCl_2$ could generate *tert*-butoxyzincate complex $Na_2[Zn(O^tBu)_3]_2$, whose basicity was too weak to deprontonate $(PhSO_2)_2CH_2$. Indeed, we observed a new species by ^{1}H NMR spectrocopy when ^{t}BuONa and $ZnCl_2$ was mixed (Figure 1, 4B).

Scheme 1 The equilibria in the process of fluorination



Based on the aforementioned results, the selective monofluorination reaction is explained as depicted in Scheme 1. A trace amount of "$(PhSO_2)_2CHZn$" is generated in an equilibrium when $(PhSO_2)_2CH_2$ is added into the mixture of ^{t}BuONa and $ZnCl_2$ (through *in situ* formation of $Na_2[Zn(O^tBu)_3]_2$). Subsequently, SelectFluor is added into this mixture. "$(PhSO_2)_2CHZn$" is therefore fluorinated, which shifts the equilibrium to the side of "$(PhSO_2)_2CHZn$" (Scheme 1). Furthermore, for the reactions with different methylene substrates, ^{t}BuONa and $ZnCl_2$ should exist in proper ratios to prevent over-deprotonation and therefore over-fluorination. It is obvious that the deprotonation of $(PhSO_2)_2CHF$ by $Na_2[Zn(O^tBu)_3]_2$) is almost negligible. In the cases of relatively inactive methylene compounds (as shown in Table 4), we also presume that the reaction proceeds through a similar pathway in the presence of LiHMDS and $ZnCl_2$.[18]

Conclusions

In conclusion, we have developed a highly selective and efficient monofluorination of methylene compounds with inhibition of

undesired difluorination products. $ZnCl_2$ plays an important role in selective monofluorination through its interaction with Brønsted base to control the deprotonation of the starting methylene compounds rather than the monofluorinated products. Given the mild reaction conditions and ready availability of the reagents, this method promises to find important applications in the synthesis of monofluoromethylene-containing compounds.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures amd the characterization data of new compounds. See DOI: 10.1039/c000000x/

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