ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2014, **1**, 625

Selective monofluorination of active methylene compounds: the important role of $ZnCl_2$ in inhibiting overfluorination†

Fanzhou Jiang, Yanchuan Zhao and Jinbo Hu*

Received 25th March 2014,
Accepted 25th April 2014

DOI: 10.1039/c4qo00090k

rsc.li/frontiers-organic

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 a 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 the Michael addition and 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 difficulty in their separation (purification).[3b] The general solution to this problem is that equal equivalents of a base and fluorination reagent (based on that of the active methylene compounds) are incorporated at low temperatures, 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 proved 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.

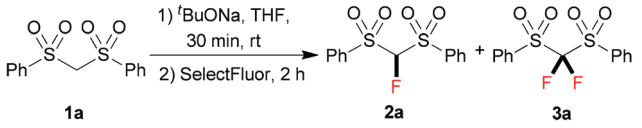
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China. E-mail: jinbohu@sioc.ac.cn; Fax: +86 21-64166128

† Electronic supplementary information (ESI) available: Experimental procedures and the characterization data of new compounds. See DOI: 10.1039/c4qo00090k

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 the 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 the monofluorinated **2a** was obtained, with only a small amount of the difluorinated by-product **3a** being observed by ^{19}F NMR (Table 1, entry 1). However, when we increased the equivalents of the base to improve the conversion of the starting material **1a**, the tendency of overfluorination unfortunately increased (Table 1, entries 2–4).

We presumed that the van der Waals radius of fluorine resembles 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 deprotonation of active methylene compounds. Given the fact that the basicity of the organozinc reagent is relatively weak, over-deprotonation should be significantly inhibited. To test our hypothesis, 1.0 equiv. of anhydrous $ZnCl_2$ was added to the reaction mixture. We were satisfied to find that the 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 ^tBuONa and $ZnCl_2$ (entries 6–11), we found that an optimal yield (91%) of **2a** was obtained when 2.5 equiv. of ^tBuONa and 2.5 equiv. of $ZnCl_2$ were employed (Table 1, entry 11).

Table 1 Survey of reaction conditions



1a 2a 3a

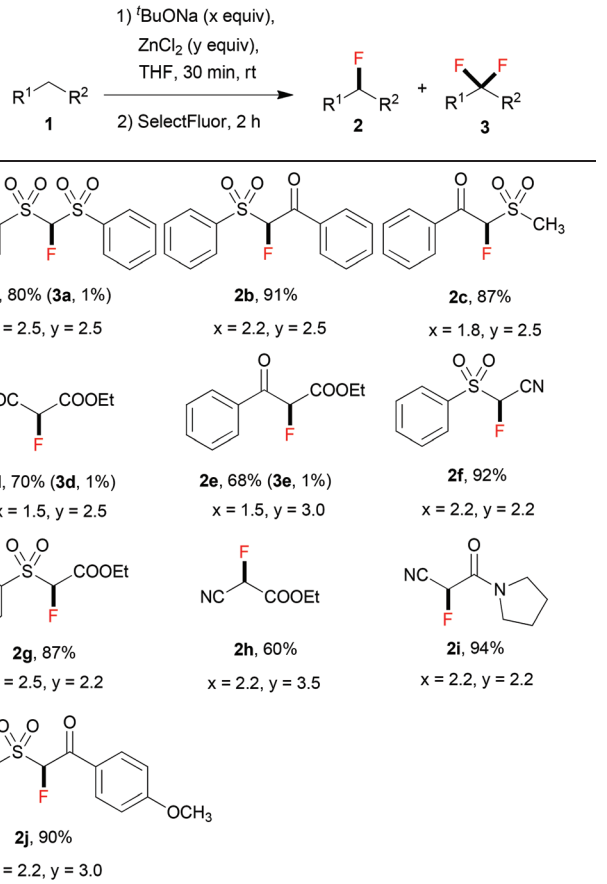
Entry	^{t}BuONa (equiv.)[a]	$ZnCl_2$ (equiv.)[a]	**2a** (%)[b]	**2a** (%)[b]
1	1.0	—	73	2
2	1.2	—	71	3
3	1.5	—	61	19
4	1.8	—	60	22
5	1.8	1.0	79	3
6	1.8	1.5	57	—
7	1.8	1.8	45	—
8	2.2	1.5	91	7
9	2.2	1.8	79	—
10	2.5	2.2	94	3
11	**2.5**	**2.5**	**91**	**1**

[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.

Thereafter, we continued to examine the substrate scope of this new protocol of $ZnCl_2$-mediated monofluorination. Initially, 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 also found to be amenable 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).

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 the fluoro-Julia–

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

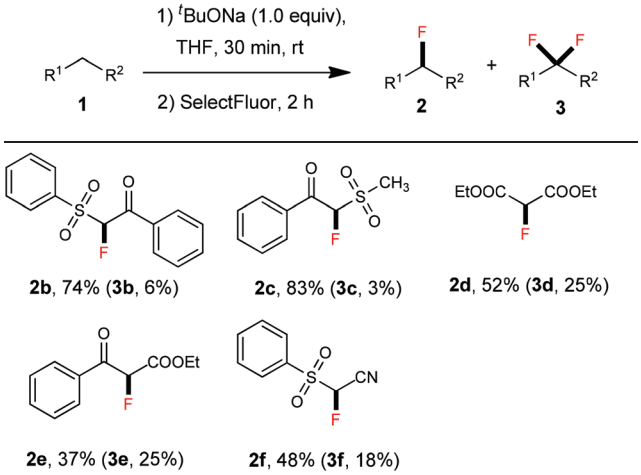


[a] In all cases, the equivalents of ^{t}BuONa (x) and $ZnCl_2$ (y) are based on that of the corresponding starting material **1**. [b] The yield of **2** refers to the isolated yield. [c] Unless otherwise mentioned, difluorinated products **3** were not observed by ^{19}F NMR; when **3** was formed,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

Kocienski olefinations, and the resulting monofluoroalkene moiety can be used as a non-hydrolyzable mimetic of amide in the peptidomimetic unit of protease inhibitors.[15] We envisaged that, for relatively inactive methylene compounds with the 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 ESI†). 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.

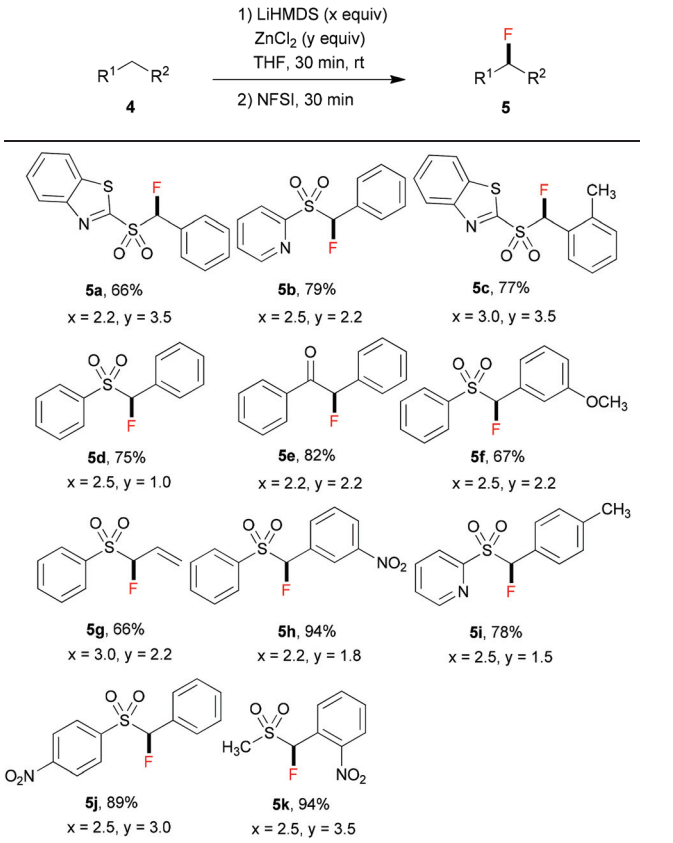
To gain more insight into this $ZnCl_2$-mediated selective monofluorination, we carried out some experiments. First of all, we compared the tendency of deprotonation and fluorination between methylene compounds and the corresponding monofluorinated ones using $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ as model compounds. Equal equivalents of $(PhSO_2)_2CH_2$ and

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

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



[a] In all cases, the equivalents 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 pK_a values of C–H bonds among these methylene compounds is between 17.7 and 23.4 in DMSO.

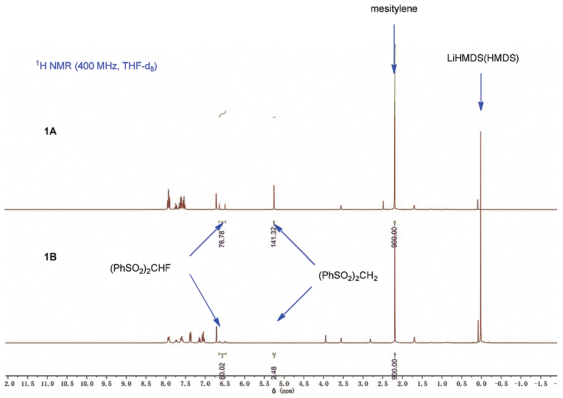
$(PhSO_2)_2CHF$ were mixed in THF-d_8 in the presence of a substoichiometric amount of LiHMDS, and the mixture was characterized by ^{1}H NMR (1A, 1B, for details, see ESI†). It was found that $(PhSO_2)_2CH_2$ was more easily deprotonated than $(PhSO_2)_2CHF$, which was consistent with the theoretical calculation reported by Prakash and Olah.[16] Secondly, we mixed equal equivalents of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8 in the presence of an excess amount of NaH, and thereafter, the reaction was quenched with a substoichiometric amount of *N*-fluorobisphenylsulfonimide (NFSI) (2A–2F, for details, see ESI†). 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 the methylene compound $(PhSO_2)_2CH_2$ and minimize the further deprotonation of the monofluorinated intermediate $(PhSO_2)_2CHF$. Thirdly, we added $(PhSO_2)_2CH_2$ to 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 ESI†). Unexpectedly, $(PhSO_2)_2CH_2$ was almost intact (*i.e.*, the deprotonation hardly occurred), which was indicated by ^{1}H NMR.

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

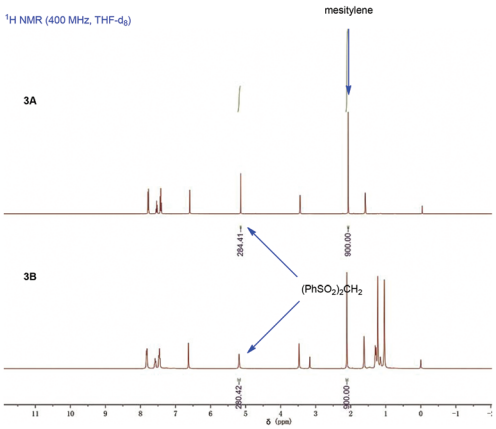
Based on the aforementioned results, the selective monofluorination reaction is explained as depicted in Scheme 1. A trace amount of "$(PhSO_2)_2CHZn$" is generated in an equilibrium when $(PhSO_2)_2CH_2$ is added to the mixture of ^{t}BuONa and $ZnCl_2$ (through *in situ* formation of $Na_2[Zn(O^tBu)_3]_2$). Subsequently, SelectFluor is added to 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 overfluorination. 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

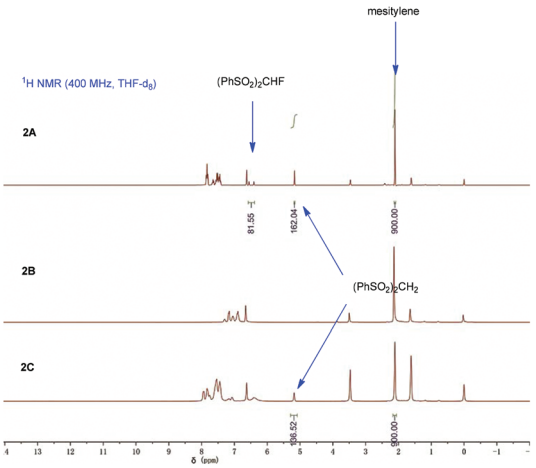
In conclusion, we have developed a highly selective and efficient monofluorination of methylene compounds with inhibition of undesired difluorination products. $ZnCl_2$ plays an important role in selective monofluorination through its interaction with a Brønsted base to control the deprotonation of the starting methylene compounds rather than the monofluorinated products. Given the mild reaction conditions and the ready availability of the reagents, this method has promis-



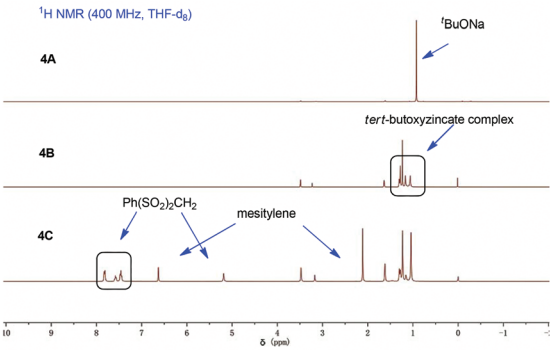
(1A) Mixing equal equivalents of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8. (1B) Adding a substoichiometric amount of LiHMDS to the mixture.



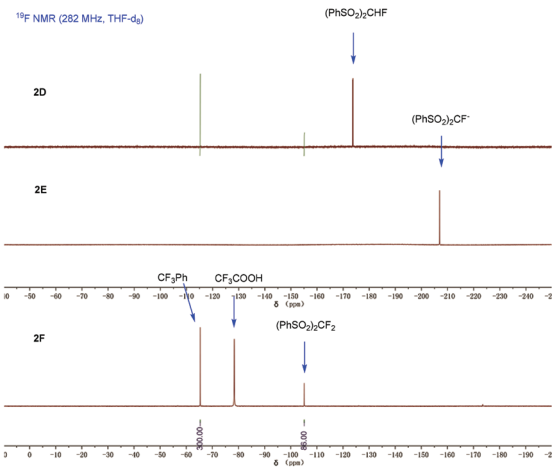
(3A) Mixing $(PhSO_2)_2CH_2$ and $ZnCl_2$ in THF-d_8. (3B) Adding ^{t}BuONa (2.5 equiv) to the mixture of $(PhSO_2)_2CH_2$ (1.0 equiv) and $ZnCl_2$ (2.5 equiv).



(2A) Mixing equal equivalents of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8. (2B) Adding an excess amount of NaH to the mixture. (2C) Adding a substoichiometric amount of NFSI to the mixture, and then quenching it with CF_3COOH.

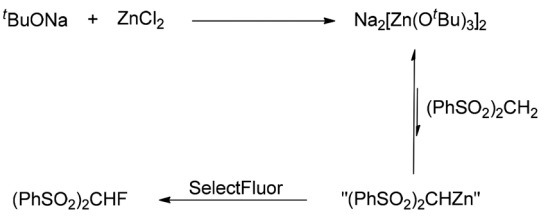


(4A) Only ^{t}BuONa dissolved in THF-d_8. (4B) The mixture of ^{t}BuONa (1.0 equiv) and $ZnCl_2$ (1.0 equiv) in THF-d_8. (4C) Adding $(PhSO_2)_2CH_2$ (1.0 equiv) to the mixture of ^{t}BuONa (2.5 equiv) and $ZnCl_2$ (2.5 equiv).



(2D) Mixing equal equivalents of $(PhSO_2)_2CH_2$ and $(PhSO_2)_2CHF$ in THF-d_8. (2E) Adding an excess amount of NaH to the mixture. (2F) Adding a substoichiometric amount of NFSI to the mixture, and then quenching it with CF_3COOH.

Fig. 1 Mechanistic study through ^{1}H NMR experiments.



Scheme 1 The equilibrium in the process of fluorination.

ing important applications in the synthesis of monofluoromethylene-containing compounds.

Acknowledgements

Support of our work by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (21372246 and 20825209), the Shanghai QMX program (13QH1402400), and the Chinese Academy of Sciences is gratefully acknowledged.

Notes and references

1 (*a*) A. Massa, *Curr. Org. Chem.*, 2012, **16**, 2159; (*b*) C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, *J. Am. Chem. Soc.*, 1958, **80**, 6533; (*c*) R. Connor, C. L. Fleming and T. Clayton, *J. Am. Chem. Soc.*, 1936, **58**, 1386.

2 (*a*) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (*b*) G. K. S. Prakash, X. Zhao, S. Chacko, F. Wang, H. Vaghoo and G. A. Olah, *Beilstein J. Org. Chem.*, 2008, 4; (*c*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3.

3 (*a*) R. D. Chambers and J. Hutchinson, *J. Fluorine Chem.*, 1998, **92**, 45; (*b*) C. Ni, L. Zhang and J. Hu, *J. Org. Chem.*, 2009, **74**, 3767; (*c*) H. Loghmani-Khouzani, M. R. Poorheravi, M. M. M. Sadeghi, L. Caggiano and R. F. W. Jackson, *Tetrahedron*, 2008, **64**, 7419; (*d*) W. M. Peng and J. M. Shreeve, *Tetrahedron Lett.*, 2005, **46**, 4905; (*e*) K. Radwan-Olszewska, F. Palacios and P. Kafarski, *J. Org. Chem.*, 2011, **76**, 1170; (*f*) F. A. Davis, W. Han and C. K. Murphy, *J. Org. Chem.*, 1995, **60**, 4730.

4 (*a*) G. Verniest, E. Van Hende, R. Surmont and N. De Kimpe, *Org. Lett.*, 2006, **8**, 4767; (*b*) M. S. Marma, L. A. Khawli, V. Harutunian, B. A. Kashemirov and C. E. McKenna, *J. Fluorine Chem.*, 2005, **126**, 1467.

5 Selective examples are as follows: (*a*) F. A. Davis, W. Han and C. K. Murphy, *J. Org. Chem.*, 1995, **60**, 4730; (*b*) E. Fuglseth, T. H. K. Thvedt, M. F. Moll and B. H. Hoff, *Tetrahedron*, 2008, **64**, 7318; (*c*) T. Kitamura, S. Kuriki, M. H. Morshed and Y. Hori, *Org. Lett.*, 2011, **13**, 2392; (*d*) G. Stavber, M. Zupan and S. Stavber, *Tetrahedron Lett.*, 2007, **48**, 2671; (*e*) J. C. Xiao and J. M. Shreeve, *J. Fluorine Chem.*, 2005, **126**, 473.

6 (*a*) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2010, **49**, 2668; (*b*) D. C. Meadows and J. Gervay-Hague, *Med. Res. Rev.*, 2006, **26**, 793; (*c*) A. El-Awa, M. N. Noshi, X. M. du Jourdin and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2315.

7 (*a*) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921. Selective examples are as follows: (*b*) Y. Zhao, B. Gao and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 5790; (*c*) X. Shen, W. Zhang, C. Ni, Y. Gu and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 16999; (*d*) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2012, **51**, 6966; (*e*) C. Ni, J. Liu, L. Zhang and J. Hu, *Angew. Chem., Int. Ed.*, 2007, **46**, 786; (*f*) Y. Zhao, W. Huang, L. Zhu and J. Hu, *Org. Lett.*, 2010, **12**, 1444.

8 I. Vints, J. Gatenyo and S. Rozen, *J. Fluorine Chem.*, 2013, **146**, 66.

9 Selective examples are as follows: (*a*) C. Ni, Y. Li and J. Hu, *J. Org. Chem.*, 2006, **71**, 6829; (*b*) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura and T. Toru, *Angew. Chem., Int. Ed.*, 2006, **45**, 4973; (*c*) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; (*d*) X. Shen, L. Zhang, Y. Zhao, L. Zhu, G. Li and J. Hu, *Angew. Chem., Int. Ed.*, 2011, **50**, 2588; (*e*) G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew and G. A. Olah, *Angew. Chem., Int. Ed.*, 2007, **46**, 4933; (*f*) A.-N. Alba, X. Companyo, A. Moyano and R. Rios, *Chem. – Eur. J.*, 2009, **15**, 7035.

10 We repeated the experimental procedure of monofluorination of $(PhSO_2)_2CH_2$ demonstrated by Shibata, and found that $(PhSO_2)_2CHF$ (64%) and $(PhSO_2)_2CF_2$ (14%) were formed (determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard).

11 T. Imamoto and H. Koto, *Synthesis*, 1985, 982.

12 (*a*) P. Knochel and P. Jones, *Organozinc reagents: a practical approach*, Oxford University Press, Oxford, New York, 1999; (*b*) P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117; (*c*) P. Knochel, J. J. Almena Perea and P. Jones, *Tetrahedron*, 1998, **54**, 8275.

13 When substrates **1b–d** were subjected to the standard reaction conditions (as described in Table 1, entry 11), 87% of **2b** (11% of **3b**), 80% of **2c** (20% of **3c**), and 65% of **2d** (23% of **3d**) were formed, respectively. All the yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCF_3$ as an internal standard.

14 The pK_a of C–H bonds collected by D.A. Evans proves to be a good reference to give constructive guide in adjusting the amount of base and $ZnCl_2$.

15 (*a*) P. R. Blakemore, W. J. Cole, P. J. Kocieński and A. Morley, *Synlett*, 1998, 26; (*b*) A. K. Ghosh and B. Zajc, *Org. Lett.*, 2006, **8**, 1553.

16 G. K. S. Prakash, F. Wang, N. Shao, T. Mathew, G. Rasul, R. Haiges, T. Stewart and G. A. Olah, *Angew. Chem., Int. Ed.*, 2009, **48**, 5358.

17 (*a*) R. M. Fabicon, M. Parvez and H. G. Richey, *J. Am. Chem. Soc.*, 1991, **113**, 1412; (*b*) A. P. Purdy and C. F. George, *Polyhedron*, 1994, **13**, 709.

18 Previously, the bis[bis(trimethylsilyl)amido] complex of zinc was reported. See: (*a*) H. Bürger, W. Sawodny and U. Wannagat, *J. Organomet. Chem.*, 1965, **3**, 113; (*b*) O. Just, D. A. Gaul and W. S. Rees Jr., *Polyhedron*, 2001, **20**, 815.