ChemPubSoc Europe

DOI: 10.1002/chem.201402506

CHEMISTRY
A European Journal
Full Paper

Fluoroalkylation

Nucleophilic Difluoromethylation of Epoxides with $PhSO(NTBS)CF_2H$ by a Preorganization Strategy**

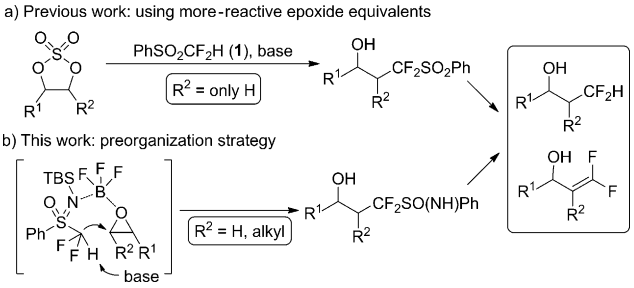
Xiao Shen, Qinghe Liu, Tao Luo, and Jinbo Hu*[a]

Abstract: Unlike the facile synthesis of β-monofluoromethyl alcohols by nucleophilic monofluoromethylation of epoxides, the synthesis of β-difluoromethyl alcohols by nucleophilic difluoromethylation of epoxides still remains a challenge. Herein, studies on tackling this problem with $PhSO(NTBS)CF_2H$ (**2**; TBS = *tert*-butyldimethylsilyl) are reported. The preorganization of **2** and epoxides with $BF_3{\cdot}Et_2O$ was found to be crucial for the reaction. The reaction shows excellent regioselectivity and has a broad substrate scope. The facile transformation of the ring-opened products to β-difluoromethyl, γ-difluoromethyl, and β-difluoromethylenyl alcohols demonstrates the synthetic utility of the reaction.

Introduction

In recent years, selective incorporation of fluorine or fluoroalkyl groups into organic compounds has become a routine and powerful strategy in the design of pharmaceuticals, agrochemicals, and materials.[1] Among various fluoroalkyl groups, the difluoromethyl (CF_2H) and 1,1-difluoromethylenyl (=CF_2) functionalities have attracted particular interest. The former group (CF_2H) has been used not only as an isostere to an OH or SH unit, but also as a hydrogen donor to form hydrogen bonding.[2] The 1,1-difluoromethylidene functionality (=CF_2), which can act as a biostere of the carbonyl group, has also been used in the design of mechanism-based enzyme inhibitors.[3] Therefore, developing methods for the synthesis of difluoromethyl- or 1,1-difluoromethylenyl-substituted compounds is highly desirable.

Over the past decades, nucleophilic fluoroalkylation, typically involving the transfer of α-fluoro carbanions or their equivalents to electrophiles, has proved to be a powerful strategy for the synthesis of fluorinated compounds.[4,5] In this respect, fluorinated sulfones have been widely used as the precursors of α-fluoro carbanions in synthetic organofluorine chemistry.[4] For example, α-difluoromethyl alcohols were easily obtained by nucleophilic difluoromethylation of carbonyl compounds with $PhSO_2CF_2^-$.[5] However, the synthesis of β-difluoromethyl alcohols by the corresponding nucleophilic difluoromethylation of epoxides is more challenging.[6,7] In our previous study, the reaction between $PhSO_2CF_2^-$ and 2-methyloxirane was unsuccessful, although $(PhSO_2)_2CF^-$ and $PhSO_2CHF^-$ were successfully reacted with epoxides to give β-monofluoromethyl alcohols.[8] The difficulty of the ring-opening reaction between the epoxides and $PhSO_2CF_2^-$ was attributed to the "negative fluorine effect", that is, fluorine substitution on the carbanion center reduces the thermal stability (lifetime) of the carbanion as well as its nucleophilicity toward epoxides.[8–10] In 2007, we reported that when 1,2-cyclic sulfates (more electrophilic epoxide equivalents) were used as substrates, the difluoromethylation with $PhSO_2CF_2H$ (**1**) could be achieved (Scheme 1a).[9a] Although this reaction provides facile access to β-difluoromethylated or β-difluoromethylenated alcohols, it is associated with some drawbacks: 1) it is not suitable for more sterically hindered 1,2-disubstituted 1,2-cyclic sulfates such as hexahydrobenzo[*d*][1,3,2]dioxathiole 2,2-dioxide;[9b] 2) the substrates (1,2-cyclic sulfates) themselves often require multi-step syntheses.[9] Therefore, a new, efficient, and direct ring-opening difluoromethylation of epoxides is highly desired. Herein, we disclose our recent success in addressing this issue with sulfoximine $PhSO(NTBS)CF_2H$ (**2**) by means of preorganization of epoxides and **2** with $BF_3{\cdot}Et_2O$ (Scheme 1b). To the best of our knowledge, this preorganization strategy has not previously been used in the ring-opening reactions between epoxides and carbanions.



Scheme 1. Strategies for the synthesis of β-difluoromethyl and β-difluoromethylenyl alcohols.

[a] *Dr. X. Shen, Q. Liu, T. Luo, Prof. Dr. J. Hu*
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai 200032 (P. R. China)
E-mail: jinbohu@sioc.ac.cn

[**] *TBS* = tert-*butyldimethylsilyl.*

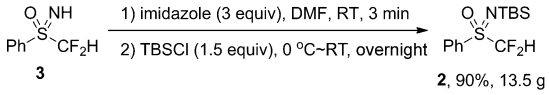
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402506.

As monoaza analogues of sulfones, sulfoximines have been widely used in organic synthesis due to their diverse chemical and biological properties.[11] Recently, various fluorinated sulfoximines have been designed, synthesized, and used as powerful fluoroalkylation reagents.[12,13] In our previous study, it was found that (*R*)-PhSO(NTBS)CF_2H ((*R*)-**2**) can serve as a difluoromethyl anion precursor and react with aryl ketones and aldehydes to give optically enriched α-difluoromethyl alcohols.[12a] In this article, we report the application of reagent **2** in the synthesis of β-difluoromethyl, γ-difluoromethyl, and β-difluoromethylenyl alcohols, which has not been achieved by the reaction of epoxides with any other difluoromethylation reagents (Scheme 1b).

Results and Discussion

Preparation of PhSO(NTBS)CF_2H (2)

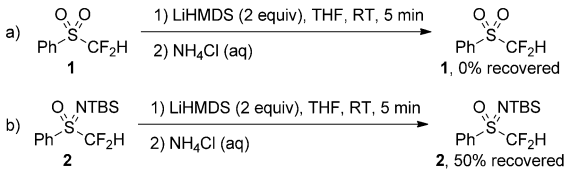
Firstly, we developed a new procedure for the synthesis of compound **2** on a relatively large scale. Sulfoximine **3** was readily synthesized according to the reported procedure.[13c] Sulfoximine **2** was obtained in 90% yield (13.5 g) by treatment of compound **3** with TBSCl and imidazole in DMF, overnight (Scheme 2).



Scheme 2. Preparation of PhSO(NTBS)CF_2H (**2**).

Thermal stabilities of PhSO(NTBS)CF_2^- and $PhSO_2CF_2^-$

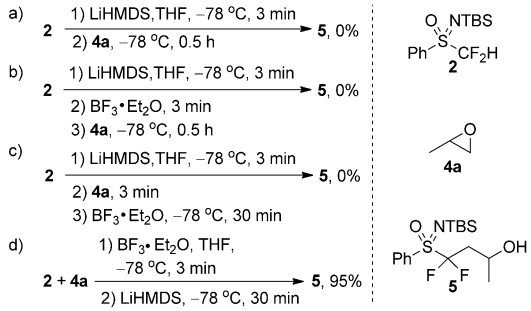
With compound **2** in hand, we examined the stability of PhSO(NTBS)CF_2^-, since the low thermal stability of $PhSO_2CF_2^-$ has been considered as one of the major reasons for the previous failure of its ring-opening difluoromethylation reaction with epoxides. It was found that $PhSO_2CF_2H$ (**1**) completely decomposed upon treatment with lithium hexamethyldisilazide (LiHMDS; 2 equiv) at −78 °C for 5 min (Scheme 3a). In contrast, 50% recovery was observed for PhSO(NTBS)CF_2H (**2**) under the same conditions (Scheme 3b), indicating a higher thermal stability of PhSO(NTBS)CF_2^- than that of $PhSO_2CF_2^-$.



Scheme 3. Investigation of the stability of $PhSO_2CF_2^-$ and PhSO(NTBS)CF_2^-.

Ring-opening difluoromethylation of epoxides

Encouraged by the above results, we started to investigate the possibility of ring-opening difluoromethylation of epoxides using sulfoximine **2**. 2-Methyloxirane (**4a**) was chosen as a model substrate to first test and then optimize the reaction conditions. To our disappointment, the reaction of PhSO(NTBS)CF_2^- with **4a** was not successful and no ring-opening difluoromethylation product **5** was found, even though PhSO(NTBS)CF_2^- is more stable than $PhSO_2CF_2^-$ (Scheme 4a). We assumed that the nucleophilicity of PhSO(NTBS)CF_2^- towards the epoxide was not high enough and that activation of **4a** would be needed to achieve the ring-opening difluoromethylation reaction. Previously, BF_3·Et_2O has often been used as a Lewis acid to activate epoxides in their reactions with carbanions.[6b,8,14] Two traditional procedures have been applied: 1) adding the epoxide to mixtures of BF_3·Et_2O and carbanions;[14] 2) adding BF_3·Et_2O immediately after the addition of the epoxide to a solution of the carbanion.[6b,8] As discussed by Ganem et al.,[14] these successful reactions would indicate that combinations of such carbanions and BF_3·Et_2O are reasonably stable under certain reaction conditions, allowing them to react independently as potent nucleophile and strong Lewis acid, respectively.[6b,8,14] However, in the case of sulfoximine **2**, compound **5** was not obtained by using either of these two procedures (Scheme 4b, c). Moreover, in neither case was any of the desired product **5** obtained, even when the reaction mixture was allowed to warm to room temperature after being stirred at −78 °C for 30 min. ^{19}F NMR experiments showed that PhSO(NTBS)CF_2H (**2**) was completely deprotonated by LiHMDS, and new ^{19}F NMR peaks at $\delta = -111.30$–111.38 ppm were observed (see the Supporting Information). We surmised that these signals might result from the reaction between BF_3·Et_2O and PhSO(NTBS)CF_2^-.[15,16] We presumed that the nucleophilicity of the newly formed species toward epoxides was still not high enough.[17]



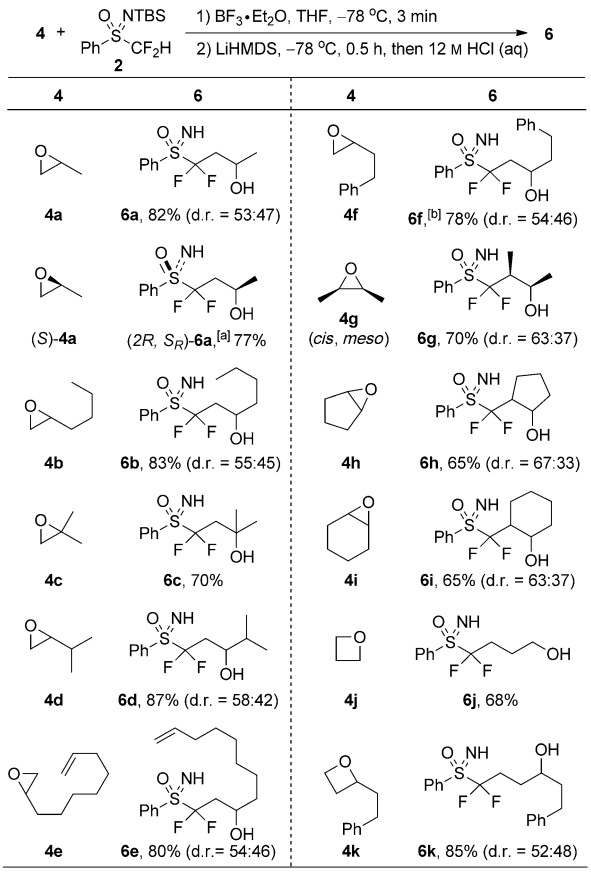
Scheme 4. Survey of reaction conditions. **4a** (1.5 equiv), LiHMDS (2 equiv), BF_3·Et_2O (2.5 equiv) were used, and the yield was determined by ^{19}F NMR with $PhCF_3$ as the internal standard.

Based on these experimental results, we considered that in order to achieve a successful ring-opening reaction between epoxide **4a** and sulfoximine **2**, the following prerequisites should be met: 1) PhSO(NTBS)CF_2^- should be generated in situ, because it will slowly decompose after formation; 2) the

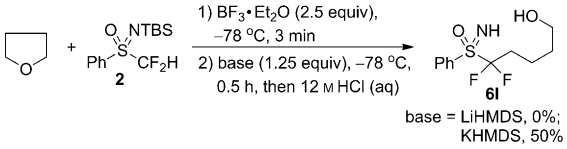
epoxide should be activated before the formation of PhSO(NTBS)CF_2^-; 3) the reaction between PhSO(NTBS)CF_2^- and the activated epoxide should be faster than that between PhSO(NTBS)CF_2^- and the activator. With these considerations in mind, we surmised that adding BF_3•Et_2O (activator) to a mixture of **2** and **4a** before the addition of LiHMDS should be the best choice. To our satisfaction, a 95% yield of product **5** was observed by ^{19}F NMR using this new "preorganization" procedure (Scheme 4d). Subsequently, several parameters, including base, solvent, and reactant ratio, were further investigated (for details, see the Supporting Information). THF was found to be a better solvent than Et_2O, $PhCH_3$, DME, or CH_2Cl_2, and LiHMDS proved to be a better base than NaHMDS, KHMDS, TMPLi, *t*BuOK, or *t*BuONa. Eventually, with a **4a**/**2**/LiHMDS/BF_3•Et_2O ratio of 1.5:1:2:2.5, THF as the solvent, and 12 M aqueous HCl to quench the reaction and remove the TBS group of the ring-opened product, compound **6a** was isolated in 82% yield (Scheme 5).

Having optimized the reaction conditions, the substrate scope of the reaction between epoxides **4** and sulfoximine **2** was investigated. Various structurally diverse epoxides were successfully difluoromethylated by reagent **2** (Scheme 5). The reaction showed excellent regioselectivity, and the substitution took place at the less hindered carbon atoms of the epoxides. For monosubstituted epoxides, the reaction worked well, giving products **6a–f** in good yields (70–87%), although the diastereoselectivities were low (53:47–58:42 d.r.). Optically pure β-difluoromethylated alcohols could be readily obtained when enantiomerically pure epoxides were used as substrates. When compound (*S*)-**4a** was subjected to the reaction with sulfoximine (*R*)-**2**, product (2*R*, S_R)-**6a** was obtained in 77% yield. The reaction could be easily scaled-up, and a 78% yield of product **6f** was obtained on a 1.5 g scale. More importantly, 1,2-disubstituted oxiranes **4g–i** also proved to be suitable substrates for the current difluoromethylation reaction, giving compound **6g** in 70% yield with 63:37 d.r., **6h** in 65% yield with 67:33 d.r., and **6i** in 65% yield with 63:37 d.r., respectively. It is worth noting that the previous reactions between $PhSO_2CF_2H$ and cyclic sulfates did not proceed with sterically hindered 1,2-disubstituted substrates such as hexahydrobenzo[*d*][1,3,2]dioxathiole 2,2-dioxide, which highlights the potency of our current difluoromethylation method.[9] Moreover, the current reaction could also be performed with four-membered oxacycles **4j** and **4k**, giving γ-difluoromethylated alcohols **6j** and **6k** in 68% and 85% yield, respectively.

After achieving reactions of difluoromethyl sulfoximine **2** with three-membered and four-membered oxacycles, we tested the possibility of the difluoromethylation of five-membered oxacycles such as tetrahydrofuran (THF). However, the anticipated product **6l** was not obtained when LiHMDS was used as the base. Interestingly, however, when LiHMDS was replaced by KHMDS, compound **6l** was formed in 50% yield (Scheme 6).

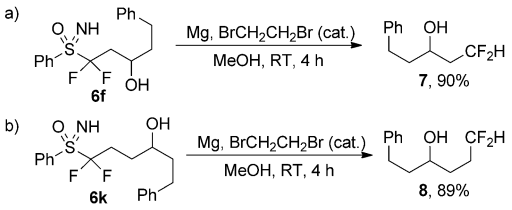


Scheme 5. Regioselective difluoromethylation of epoxides. Typical procedure: under a N_2 atmosphere, BF_3•Et_2O (0.3 mL, 2.5 mmol) was added to a solution of (*S*)-**4a** (87 mg, 1.5 mmol) and (*R*)-**2** (305 mg, 1 mmol) in THF (6 mL), at −78 °C. Three minutes later, LiHMDS (1.0 M in THF, 2.0 mL, 2 mmol) was added slowly at −78 °C. After 30 min, HCl aqueous solution (12 M, 1.5 mL) was added to quench the reaction. Yield and d.r. are based on the isolated product. [a] (*R*)-**2** was used as the reagent. [b] 1.5 g scale of **2**.

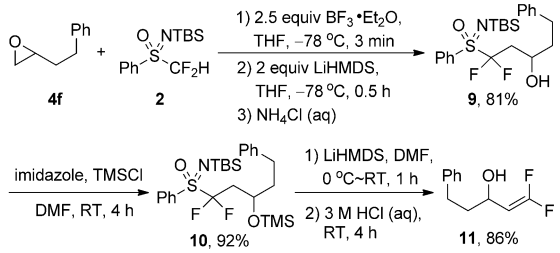


Scheme 6. Reaction of THF with sulfoximine **2**.

To demonstrate the synthetic utility of the current difluoromethylation reaction, compounds **6f** and **6k** were further transformed to β-difluoromethyl alcohol **7** and γ-difluoromethyl alcohol **8**, respectively. Under conditions of Mg/$BrCH_2CH_2Br$ (cat.)/MeOH, the sulfonimindoyl groups of compounds **6f** and **6k** were easily removed, affording products **7** and **8** in 90% and 89% yield, respectively (Scheme 7a, b). When saturated aqueous NH_4Cl was added to quench the ring-opening reaction, the TBS group was preserved, and compound **9** was obtained in 81% yield (Scheme 8). Compound **9** was transformed to compound **10** in 92% yield using TMSCl as a silylating agent. β-Difluoromethylenyl alcohol **11** was obtained in 86% yield after successive treatment of compound **10** with LiHMDS and 3 M aqueous HCl.

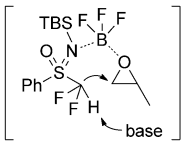


Scheme 7. Synthesis of β-difluoromethyl alcohol **7** and γ-difluoromethyl alcohol **8** by reductive desulfoximination.



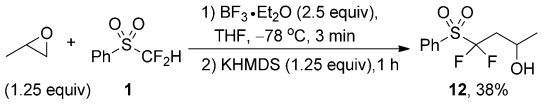
Scheme 8. Synthesis of β-difluoromethylenyl alcohol **11**.

Since the nitrogen atom in a sulfoximine is a coordination site, many sulfoximines have been used as chiral ligands in metal-catalyzed reactions.[11a,b,18] Penta- and hexacoordinate hypervalent boron species have also been reported, some of which have been synthesized in THF or Et_2O.[19] It was found that the ring-opening difluoromethylation reaction only proceeded well when the base was added after mixing **2**, **4a**, and BF_3·Et_2O (Scheme 4), indicating the crucial influence of the preorganization of the three components in this reaction. Although the details of the reaction mechanism need further investigation, we propose that BF_3 probably holds sulfoximine **2** and the epoxide in close proximity through complexation, as shown in **A**. After deprotonation of **2**, the in-situ generated carbanion should immediately attack the activated epoxide, with a reaction rate much faster than those of its decomposition or side reaction with BF_3.



A

This preorganization strategy might also be useful for the reactions of epoxides with other carbanions of low thermal stability and weak nucleophilicity. As a proof of concept, we set up the reaction between epoxide **4a** and $PhSO_2CF_2H$ (**1**). Previously, it was found that when no BF_3·Et_2O was added or when BF_3·Et_2O was added after the formation of $PhSO_2CF_2^-$, none of the desired product **12** was obtained.[8] Interestingly, by using this preorganization strategy, ring-opened product **12** was formed in 38% yield (Scheme 9). The relatively low yield of **12** compared to that of compound **6a** (76%, entry 6, Table S1 in the Supporting Information) might be attributed to the relatively lower stability of $PhSO_2CF_2^-$ compared with that of $PhSO(NTBS)CF_2^-$ and/or the lower coordinating ability of a sulfonyl group compared with a sulfoximinyl group.



Scheme 9. Reaction between **4a** and **1**.

Conclusion

In summary, an efficient and highly regioselective nucleophilic difluoromethylation of epoxides has been achieved by using an unprecedented preorganization strategy. The reaction is amenable to three-, four-, and five-membered oxacycles. Sterically hindered 1,2-disubstituted oxiranes are also suitable substrates for the reaction. The facile transformation of the ring-opened products to β-difluoromethyl, γ-difluoromethyl, and β-difluoromethylenyl alcohols shows the potential synthetic utility of this reaction. The preorganization strategy is likely to be applicable to other ring-opening reactions between epoxides and carbanions of low thermal stability and weak nucleophilicity, as demonstrated by the successful reaction between 2-methyloxirane and $PhSO_2CF_2H$ (Scheme 9).

Experimental Section

Preparation of *N*-*tert*-butyldimethylsilyl-*S*-difluoromethyl-*S*-phenylsulfoximine (2)

Under N_2 atmosphere, imidazole (10.2 g, 150 mmol) was added to a solution of $PhSO(NH)CF_2H$ (9.55 g, 50 mmol) in dry DMF (100 mL) at RT. After 5 min, the solution was cooled to 0 °C and TBSCl (11.25 g, 75 mmol) was added in two portions. The mixture was allowed to warm to RT and stirred, overnight. The reaction was then quenched by adding an excess of water, and the mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1, v/v) to give **2** (13.5 g, 90%) as a colorless oil.

Typical procedure for the ring-opening difluoromethylation of epoxides 4 with sulfoximine 2

Under N_2 atmosphere, BF_3·Et_2O (0.3 mL, 2.5 mmol) was added to a solution of (*S*)-2-methyloxirane (*S*)-**4a** (87 mg, 1 mmol) and sulfoximine (*R*)-**2** (305 mg, 1 mmol) in THF (6 mL) at −78 °C. After 3 min, LiHMDS (1.0 M in THF, 2.0 mL, 2 mmol) was slowly added at −78 °C. After a further 30 min, aqueous HCl solution (12 M, 1.5 mL, 18 mmol) was added to quench the reaction. The resulting mixture was stirred for 30 min, basified with 20% aqueous NaOH, and then extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate (3:1, v/v) to give (2*R*, S_R)-**6a** (191 mg, 77%) as a colorless oil.

Typical procedure for the reductive desulfoximination of compound 6 f

$BrCH_2CH_2Br$ (2 μL) was added to Mg chips (144 mg, 6 mmol) in dry MeOH (2 mL) at RT. When gas evolution was observed (after about 3 min), compound **6 f** (141 mg) and dry MeOH (2.5 mL) were added. After 3 h, most of the MeOH was removed under reduced pressure. Saturated aqueous NH_4Cl solution was added and the resulting mixture was extracted with diethyl ether. The organic phase was washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate to give **7** (69 mg, 90%) as a colorless oil.

Preparation of compound 9

Under N_2 atmosphere, $BF_3{\cdot}Et_2O$ (1.5 mL, 12.5 mmol) was added to a solution of 2-phenethyloxirane (1.11 g, 7.5 mmol) and sulfoximine **2** (1.51 g, 5 mmol) in dry THF (20 mL) at −78 °C. After 3 min, LiHMDS (1.0 M in THF, 10 mL, 10 mmol) was slowly added at −78 °C. After a further 30 min, the reaction was quenched by adding an excess of saturated aqueous NH_4Cl solution and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate to give **9** (1.83 g, 81%) as a colorless oil.

Preparation of compound 10 from compound 9

Under N_2 atmosphere, TMSCl (143 μL, 1.125 mmol) was added to a solution of compound **9** (335 mg, 0.74 mmol) and imidazole (130 mg, 1.875 mmol) in dry DMF (3 mL) at RT and the mixture was stirred for 4 h. The reaction was then quenched by adding an excess of water, and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate (PE/EA, 200:1) to give **10** (359 mg, 92%) as a colorless oil.

Preparation of compound 11 from compound 10

Under N_2 atmosphere, LiHMDS (1 M in THF, 0.3 mL, 0.3 mmol) was added to a solution of compound **10** (105 mg, 0.2 mmol) in dry DMF (2 mL) at 0 °C. The mixture was stirred at RT for 1 h, and then aqueous HCl solution (3 M, 1 mL) was added. The resulting mixture was further stirred at RT for 1 h, and then extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. It was then filtered, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with petroleum ether/ethyl acetate to give **11** (34 mg, 86%) as a colorless oil.

Acknowledgements

Support of our work by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the NNSFC (21372246), the Shanghai QMX program (13QH1402400), the Chinese Academy of Sciences, and the Syngenta PhD Studentship (to X.S.) is gratefully acknowledged. We thank Prof. Teruo Umemoto (Visiting Professor at Shanghai Institute of Organic Chemistry) for helpful discussions.

Keywords: alcohols · difluoromethylation · nucleophilic substitution · preorganization · sulfoximines

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Received: March 7, 2014
Published online on April 23, 2014