JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Tuning the Reactivity of Difluoromethyl Sulfoximines from Electrophilic to Nucleophilic: Stereoselective Nucleophilic Difluoromethylation of Aryl Ketones

Xiao Shen,[†] Wei Zhang,[†] Chuanfa Ni,[†] Yucheng Gu,[‡] and Jinbo Hu*[,†]

[†]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, P. R. China

[‡]Syngenta Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom

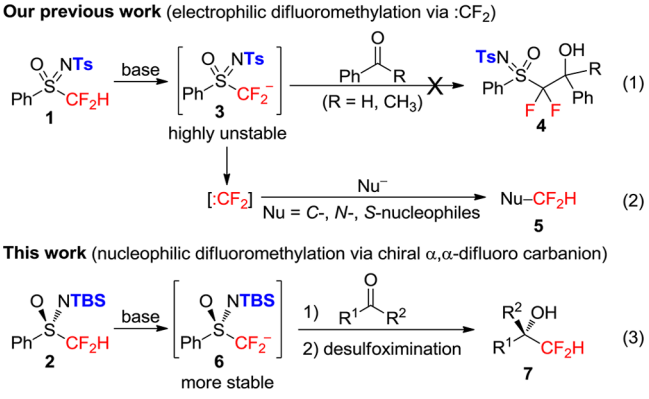
Supporting Information

ABSTRACT: A stereoselective synthesis of enantiomerically enriched difluoromethyl tertiary alcohols by tuning the reactivity of difluoromethyl sulfoximines from electrophilic to nucleophilic difluoromethylating agents is reported. The key feature of this chemistry is the diastereoselective addition of the difluoromethyl sulfoximine to the prochiral carbon of the ketone. The present method was used to prepare enantiomerically enriched difluoromethyl secondary alcohols and difluorinated analogues of the natural products gossonorol and boivinian B, demonstrating the potency of the method.

Selective incorporation of fluorine atom(s) or fluoroalkyl group(s) (such as CF_3, CF_2H, and CH_2F) into an organic molecule can often substantially change the latter's biological properties, thanks to the unique properties of fluorine.[1] Many studies have shown that fluorinated molecules offer improved metabolic stability, increased binding affinity, and improved membrane permeability and bioavailability.[2,3] As a consequence, organofluorine compounds have attracted much attention in life-science-related fields. Among various fluoroalkyl groups, the difluoromethyl (CF_2H) group is of particular interest, as it is known to be isosteric and isopolar to an OH or SH unit and can act as a hydrogen donor through hydrogen bonding.[3] Therefore, difluoromethylated analogues of biologically active compounds are strong candidates for pharmaceuticals. In some cases, difluoromethylated compounds exhibit increased bioactivity compared with their trifluoromethylated counterparts.[4]

Over the past decades, a variety of protocols for introducing the trifluoromethyl group have been developed.[5] However, there are few mild and efficient methods for difluoromethylations, and stereoselective difluoromethylation methods of carbonyl compounds are particularly sparse.[6−9] In 2008, we reported the enantioselective nucleophilic difluoromethylation of aromatic aldehydes with $PhSO_2CF_2SiMe_3$ and $PhSO_2CF_2H$ reagents catalyzed by chiral quaternary ammonium salts, with the CF_2H-substituted alcohol being obtained after removal of the $PhSO_2$ group.[7] Unfortunately, the enantioselectivity of the reaction was low (4−66% *ee*).[7] We also attempted the diastereoselective nucleophilic difluoromethylation of carbonyl compounds with $PhSOCF_2H$ and found that the diastereoselectivity was not high in these reactions either (1:1 to 1:2 *dr*).[8] The synthesis of optically pure α-difluoromethylated *tertiary* alcohols via a nucleophilic difluoromethylation strategy is even more challenging,[9] mainly because of the instability of the difluoromethyl carbanion, which is affected by the "negative fluorine effect" (NFE),[10] and the challenges associated with developing conditions for the selective addition of the difluoromethyl carbanion to ketones (compared with aldehydes), namely, the lower reactivity of ketones and the smaller steric differences between the two substituents on the prochiral carbon. To the best of our knowledge, there has been no report on the stereoselective nucleophilic difluoromethylation of ketones to obtain optically pure difluoromethyl alcohols. In this communication, we disclose our recent success in tackling this interesting synthetic problem via a chiral α,α-difluoro carbanion strategy (see eq 3 in Scheme 1).

Scheme 1. Electrophilic and Nucleophilic Difluoromethylations with Different Sulfoximine Reagents



We recently reported the first chiral α-fluorosulfoximine-mediated stereoselective fluoroalkylation reaction, and a series of monofluorinated cyclopropanes were synthesized in high yields with excellent stereoselectivity using (*R*)-$PhSO(NTs)CH_2F$.[11] In light of the ability of the PhSO(NTs) group to give high levels of chiral induction, one may envision that (*R*)-$PhSO(NTs)CF_2H$ [(*R*)-**1**] could be used to tackle the challenge of synthesizing enantiomerically enriched difluoromethyl alcohols. However, we

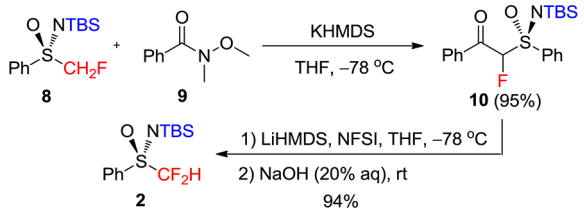
Received: August 24, 2012
Published: September 28, 2012

   dx.doi.org/10.1021/ja308419a | *J. Am. Chem. Soc.* 2012, 134, 16999−17002

found that the racemic sulfoximine **1** was not a good nucleophilic difluoromethylating agent (eq 1 in Scheme 1), since its carbanion $PhSO(NTs)CF_2^-$ (**3**) is highly unstable and readily decomposes into difluorocarbene ($:CF_2$); indeed, **1** can serve as an electrophilic difluoromethylating agent via a difluorocarbene intermediate (eq 2 in Scheme 1).[12,13] On the basis of these results, we surmised that in order to improve the stability of the carbanion, the structure of **1** should be modified by changing the *p*-toluenesulfonyl (Ts) group to a less electron-withdrawing substituent to decrease the leaving ability (nucleofugality) of the sulfonimidoyl group; a more bulky group may also favor chiral induction. In addition, the new substituent must be stable enough under the basic conditions of the nucleophilic addition and must be easily removed after the addition reaction. With these considerations in mind, we identified the *tert*-butyldimethylsilyl (TBS) group as a good choice (eq 3 in Scheme 1).

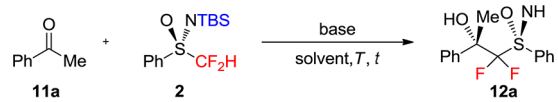
(*R*)-*N*-*tert*-Butyldimethylsilyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**8**) was readily prepared according to literature procedures.[14] Introduction of a benzoyl group then gave compound **10** in 95% yield. (*R*)-*N*-*tert*-Butyldimethylsilyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**2**) was obtained in 94% yield by fluorination of **10** using *N*-fluorodibenzenesulfonimide (NFSI) as the fluorinating agent, followed by removal of the benzoyl group (Scheme 2). To our knowledge, compound **2** is the first enantiopure difluoromethyl sulfoximine.

Scheme 2. Preparation of 2



With **2** in hand, we investigated the diastereoselective synthesis of difluoromethyl tertiary alcohols using the chiral α,α-difluoro carbanion strategy. Acetophenone (**11a**) was chosen as a model substrate on which to test and then optimize the nucleophilic difluoromethylation reaction; the results are summarized in Table 1. Typically, a base was added to the mixture of **11a** and **2**, and the ratio of **11a**, **2**, and the base was 1.5/1.0/1.2. When *n*BuLi was used as the base, a yield of difluoromethylation products of only 25% was observed via ^{19}F NMR spectroscopy, and the diastereoselectivity was only moderate (83/17 *dr*; Table 1, entry 1). The inefficiency of the reaction was probably due to the competing reaction between **11a** and *n*BuLi.[15] When the base was changed to lithium hexamethyldisilazide (LiHMDS), the yield decreased to 10% and the diastereoselectivity did not increase (Table 1, entry 2). Encouragingly, both the yield and diastereoselectivity were slightly improved (37% yield, 87/13 *dr*) when NaHMDS was employed as the base (Table 1, entry 3). Furthermore, KHMDS was found to be even better for the model stereoselective difluoromethylation reaction (67% yield, 90/10 *dr*; Table 1, entry 4). Screening of solvents showed tetrahydrofuran (THF) to be the best solvent (Table 1, entries 4–8). It was found that hexamethylphosphoramide (HMPA) was fatal to the reaction, with the yield and *dr* decreasing to 48% and 57/43, respectively, when HMPA was used as a cosolvent (Table 1, entry 5), indicating that alkali metal counterions are involved in the transition state of the reaction. It is remarkable that when the

Table 1. Survey of Reaction Conditions[a]



entry	11a/2/base	base	solvent	*T* (°C)	*t* (h)	yield (%)[b]	*dr*[c]
1	1.5/1.0/1.2	*n*BuLi	THF	–78	3	25	83/17
2	1.5/1.0/1.2	LiHMDS	THF	–78	3	10	83/17
3	1.5/1.0/1.2	NaHMDS	THF	–78	3	37	87/13
4	1.5/1.0/1.2	KHMDS	THF	–78	3	67	90/10
5	1.5/1.0/1.2	KHMDS	THF/HMPA (v/v=5/1)	–78	3	48	57/43
6	1.5/1.0/1.2	KHMDS	Et_2O	–78	3	54	84/16
7	1.5/1.0/1.2	KHMDS	$PhCH_3$	–78	3	57	83/17
8	1.5/1.0/1.2	KHMDS	CH_2Cl_2	–78	3	45	85/15
9	1.5/1.0/1.2	KHMDS	THF	–98	0.5	82	93/7
10	1.5/1.0/1.5	KHMDS	THF	–98	0.5	88	93/7
11	1.0/1.5/1.5	KHMDS	THF	–98	0.5	98	93/7
12	1.5/1.0/1.5	KHMDS	THF	–98	0.5	97	93/7
13[d]	1.5/1.0/1.8	KHMDS	THF	–98	0.5	99 (88)	93/7

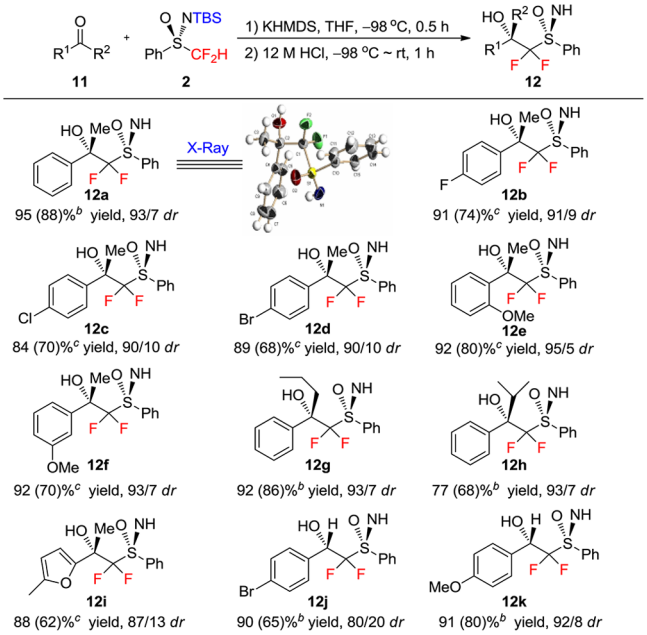
[a]Base was added slowly to the mixture of **11a** (36 mg, 0.3 mmol) and **2** (61 mg, 0.2 mmol) in the solvent (2.5 mL) at the temperature shown, and the mixture was stirred at that temperature for the indicated time. [b]Total yield of both diastereomers, as determined by ^{19}F NMR analysis. [c]Determined by ^{19}F NMR analysis. [d]The yield in parentheses is the isolated yield of the major diastereomer.

reaction temperature was lowered to −98 °C, both the yield and diastereoselectivity were substantially improved (82% yield, 93/7 *dr*; Table 1, entry 9). Further optimization of the reaction conditions by changing the ratio of **11a**, **2**, and KHMDS to 1.5/1/1.8 gave an excellent yield (99%) with 93/7 *dr* (Table 1, entry 13). It is noteworthy that *N*-methyl-, *N*-triisopropylsilyl-, *N*-tris(trimethylsilyl)silyl-, *N*-benzoyl-, and *N*-tosyl-substituted difluoromethyl sulfoximines were found to be inferior to **2** for the current stereoselective difluoromethylation reaction [for details, see the Supporting Information (SI)].

Eventually, we chose the conditions shown in entry 13 of Table 1 as the standard conditions to examine the scope of the reaction between ketones/aldehydes **11** and sulfoximine **2**. The results are summarized in Scheme 3. A variety of structurally diverse aromatic ketones were successfully difluoromethylated by **2**, and the products **12** were obtained in good yields (77–95%) with good diastereoselectivities (87/13–95/5 *dr*). The reaction tolerated many substituents, such as fluoro, chloro, bromo, and methoxy groups. 1-Phenylbutan-1-one and 2-methyl-1-phenylpropan-1-one were also suitable substrates for the difluoromethylation reaction, affording the corresponding products **12g** in 92% yield with 93/7 *dr* and **12h** in 77% yield with 93/7 *dr*. In addition, difluoromethylation of a heteroaryl-substituted ketone was also successful, giving tertiary alcohol **12i** in 88% yield with 87/13 *dr*. The reaction could also be applied to the synthesis of enantiomerically enriched difluoromethyl *secondary* alcohols, and products **12j** and **12k** were obtained in 90% yield with 80/20 *dr* and 91% yield with 92/8 *dr*, respectively. The absolute configurations of **12a** and **12j** were confirmed by X-ray crystal structure analysis, and the newly formed carbon stereocenters in **12a** and **12j** were found to be in the *S* configuration.[16] Those of the other products **12b–i** and **12k** were assigned by analogy. It is interesting that an intermolecular $C(sp^2)–H\cdots F–C$ interaction was found in the X-ray crystal structure of **12a**. The distance of the H···F interaction is 2.46 Å, which is within the sum of the van der Waals radii (ca. 2.55 Å; for details, see the SI). The stereocontrol mode of the present

dx.doi.org/10.1021/ja308419a | J. Am. Chem. Soc. 2012, 134, 16999–17002

Scheme 3. Stereoselective Difluoromethylation of Ketones and Aldehydes[a]



[a]Typical procedure: Under N_2, KHMDS (1 M in THF, 1.8 mL, 1.8 mmol) was added slowly to a THF solution (5 mL) of **11a** (180 mg, 1.5 mmol) and **2** (305 mg, 1 mmol) at −98 °C, and the mixture was stirred for 0.5 h; 12 M HCl (1 mL) was then added, and the solution was stirred for 1 h at room temperature. Total isolated yields of the two diastereomers are shown; *dr*'s were determined by ^{19}F NMR analysis. [b]The yield in parentheses is the isolated yield of the major diastereomer by column chromatography. [c]The yield in parentheses is the isolated yield of the major diastereomer by recrystallization.

diastereoselective difluoromethylation of ketones can be rationalized by considering different boat- or chairlike cyclic six-membered transition states (TSs) such as **A**, **B**, and **C** (Figure 1). Because of the flagpole interaction between the Ar group and

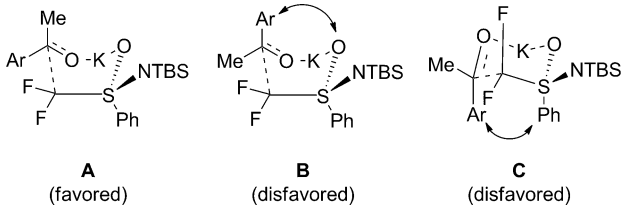
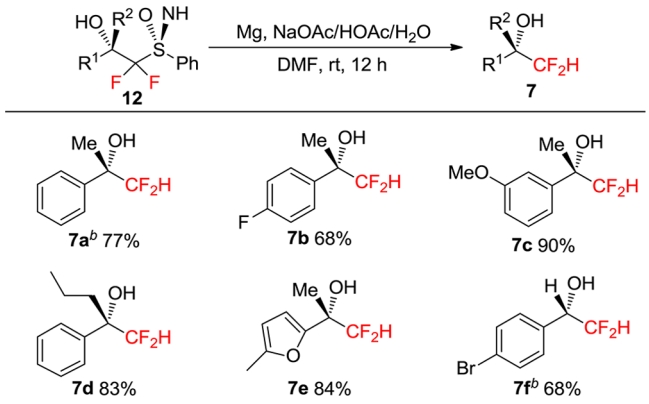


Figure 1. Proposed TSs for diastereoselective difluoromethylation.

the sulfoximine O atom,[17] **B** is disfavored. Furthermore, the chairlike chelated transition state **C** is energetically less favorable because of the severe Ar–Ph steric hindrance (Figure 1). Our proposed transition state **A** is similar to that proposed by Pyne and co-workers for the reactions of lithiated (*S*)-*N*-*tert*-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine with ketones.[17] This chelated-TS model is supported by our experimental result that the use of the coordinating solvent HMPA, which prevents the complexation of the sulfoximine oxygen atom with the metal ion (i.e., K^+), resulted in significantly decreased diastereoselectivity (Table 1, entry 5).

The products **12** could readily be converted to enantiomerically enriched difluoromethyl alcohols **7** under reductive desulfoximination conditions using Mg/HOAc/NaOAc.[18] The results are summarized in Scheme 4. These desulfoximination reactions proved to be efficient, giving **7** in good yields. The high

Scheme 4. Synthesis of Chiral Difluoromethyl Alcohols via Reductive Desulfoximination of 12[a]

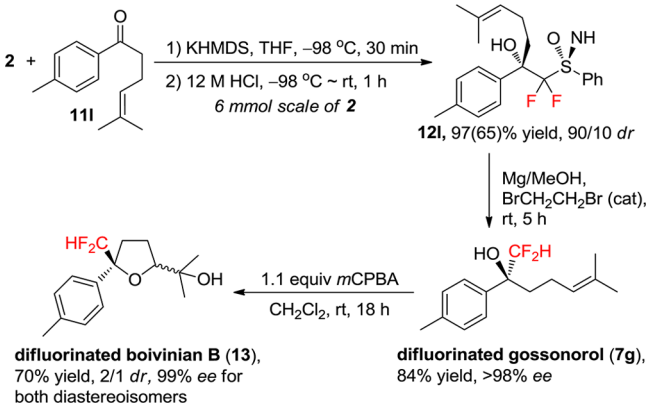


[a]Typical procedure: Mg (180 mg, 7.5 mmol) was added to the solution of **12** (0.5 mmol) in NaOAc/AcOH/H_2O (8 M [AcO^-], 3.6 mL) and DMF (5 mL) at room temperature in several portions and stirred overnight. [b]>99% *ee*.

optical purities of **7a** and **7f** (>99% *ee* as determined by chiral HPLC) indicate that the above procedures are reliable for the preparation of enantiomerically enriched difluoromethyl alcohols. It is noteworthy that **7f** has been described as a key intermediate in the synthesis of MK-0674, an orally bioavailable cathepsin K inhibitor.[19]

Since the incorporation of fluorine into a bioactive molecule can often impart highly interesting biological properties, we decided to use the above stereoselective difluoromethylation method to carry out the first synthesis of two enantiomerically enriched difluorinated analogues of natural products, namely, difluorinated gossonorol (**7g**) and difluorinated boivinian B (**13**) (Scheme 5).[20] Under the standard conditions, the reaction

Scheme 5. Synthesis of Natural Product Analogues



between sulfoximine **2** and ketone **11l** proceeded smoothly, giving **12l** in 95% yield with 90/10 *dr* even on a 6 mmol scale, indicating that the current method can be successfully scaled up. Under Mg/MeOH conditions, **12l** was converted to **7g** in 75% yield with >98% *ee*. Treatment of **7g** with 1.1 equiv of *m*-chloroperoxybenzoic acid (*m*CPBA) in CH_2Cl_2 at room temperature for 18 h gave **13** as a mixture of two diastereomers,

dx.doi.org/10.1021/ja308419a | J. Am. Chem. Soc. 2012, 134, 16999–17002

both of which possessed high enantiomeric purity (99% *ee*), in 2/1 *dr* and a combined yield of 70%.

In conclusion, an unprecedented and diastereoselective nucleophilic difluoromethylation of aryl ketones has been achieved by tuning the reactivity of difluoromethyl sulfoximines from electrophilic to nucleophilic difluoromethylating agents. The nature of the N-substituent was found to be crucial for the current reaction. The reaction was shown to be general, and a variety of structurally diverse ketones were successfully difluoromethylated to give the corresponding enantiomerically enriched difluoromethyl tertiary alcohols in good yields with good diastereoselectivities. The strategy was also amenable to the preparation of enantiomerically enriched difluoromethyl secondary alcohols. The applications of the reaction and its products illustrate the synthetic potential of the new procedure. It should be pointed out that fluorinated β-hydroxysulfoximines **7** are promising candidates for chiral ligands in many applications, in light of the known successful applications of nonfluorinated β-hydroxysulfoximines as chiral ligands in organic synthesis.[21] Further study in this direction is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and complete refs 4b and 19. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jinbohu@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of our work by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (20825209 and 20832008), the Chinese Academy of Sciences, and the Syngenta Ph.D. Studentship (to X.S.) is gratefully acknowledged. We thank Dr. John Clough of Syngenta at Jealott's Hill International Research Centre for proofreading the manuscript.

■ REFERENCES

(1) (a) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Sani, M.; Volonterio, A.; Zanda, M. *ChemMedChem* **2007**, *2*, 1693. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Fäh, C.; Mathys, R.; Hardegger, L. A.; Meyer, S.; Bur, D.; Diederich, F. *Eur. J. Org. Chem.* **2010**, 4617.

(2) (a) McCarthy, J. R. *Fluorine in Drug Design: A Tutorial Review*; 17th Winter Fluorine Conference, St. Pete Beach, FL, 2005. (b) McCarthy J. R. *Utility of Fluorine in Biologically Active Molecules*; 219th National Meeting of the American Chemical Society, San Francisco, CA, 2000; Division of Fluorine Chemistry Tutorial.

(3) (a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (b) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. (c) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701. (d) Chowdhury, M. A.; Abdellatif, K. R.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. *J. Med. Chem.* **2009**, *52*, 1525.

(4) (a) Graneto, M. J.; Philips, W. J.; U.S. Patent 5,093,347, 1992. (b) Gauthier, J. Y.; et al. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2836.

(5) For reviews, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185. (e) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(6) For reviews, see: (a) Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

(7) Ni, C.; Wang, F.; Hu, J. *Beilstein J. Org. Chem.* **2008**, *4*, 21.

(8) Zhu, L.; Li, Y.; Ni, C.; Hu, J.; Beier, P.; Wang, Y.; Prakash, G. K. S.; Olah, G. A. *J. Fluorine Chem.* **2007**, *128*, 1241.

(9) A few reactions for the synthesis of enantiomerically enriched difluoromethyl tertiary alcohols using difluoromethyl ketones as substrates have been reported, but the substrate scopes were not tested, probably because of the difficulty of obtaining a variety of difluoromethyl ketones. See: (a) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun.* **2008**, 4360. (b) Nie, J.; Zhang, G.-W.; Wang, L.; Fu, A.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2009**, 2356.

(10) For reviews, see: (a) Zhang, W.; Ni, C.; Hu, J. *Top. Curr. Chem.* **2012**, *308*, 25. (b) Ni, C.; Hu, J. *Synlett* **2011**, 770.

(11) Shen, X.; Zhang, W.; Zhang, L.; Luo, T.; Wan, X.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6966.

(12) (a) For the unsuccessful addition of **1** to benzaldehyde, see: Zhang, W. Ph.D. Dissertation, Shanghai Institute of Organic Chemistry, 2010. (b) For the unsuccessful addition of **1** to acetophenone, see the SI. (c) Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109.

(13) Many fluorinated sulfoximines and fluorinated sulfoximinium salts have been reported as electrophilic fluoroalkylating agents. See: (a) Mace, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479. (b) Nomura, Y.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 1885. (c) Prakash, G. K. S.; Zhang, Z.; Wang, F.; Ni, C.; Olah, G. A. *J. Fluorine Chem.* **2011**, *132*, 792. (d) Urban, C.; Cadoret, F.; Blazejewski, J.-C.; Magnier, E. *Eur. J. Org. Chem.* **2011**, 4862. (e) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465.

(14) Kahraman, M.; Sinishtaj, S.; Dolan, P. M.; Kensler, T. W.; Peleg, S.; Saha, U.; Chuang, S. S.; Bernstein, G.; Korczak, B.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 6854.

(15) For the effect of different bases on the nucleophilic difluoromethylation with difluoromethyl phenyl sulfone, see: Liu, J.; Hu, J. *Chem.—Eur. J.* **2010**, *16*, 11443.

(16) For the X-ray structure files of **12a** and **12j**, see the SI.

(17) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2607.

(18) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273.

(19) Isabel, E.; et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 887.

(20) Gossonorol and boivinian B, which have interesting biological properties, are two natural products widely distributed in many plants. See: (a) Elzen, G. W.; Williams, J.; Vinson, S. B. *J. Chem. Ecol.* **1984**, *10*, 1251. (b) Weyerstahl, P.; Schneider, S.; Marschall, H.; Rustaiyan, A. *Liebigs Ann. Chem.* **1993**, 111. (c) Magiatis, P.; Michaelakis, A.; Skaltsounis, A.-L.; Haroutounian, S. A. *Nat. Prod. Lett.* **2001**, *15*, 125. (d) Sun, J.; Shi, D.; Ma, M.; Li, S.; Wang, S.; Han, L.; Yang, Y.; Fan, X.; Shi, J.; He, L. *J. Nat. Prod.* **2005**, *68*, 915. (e) Cakir, A.; Kordali, S.; Kilic, H.; Kaya, E. *Biochem. Syst. Ecol.* **2005**, *33*, 245. (f) Sylvestre, M.; Pichette, A.; Longtin, A.; Nagau, F.; Legault, J. *J. Ethnopharmacol.* **2006**, *103*, 99. (g) Kartal, N.; Sokmen, M.; Tepe, B.; Daferera, D.; Polissiou, M.; Sokmen, A. *Food Chem.* **2007**, *100*, 584. (h) Saroglou, V.; Arfan, M.; Shabir, A.; Hadjipavlou-Litina, D.; Skaltsa, H. *Flavour Frag. J.* **2007**, *22*, 154. (i) Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1983**, *13*, 463. (j) Abecassis, K.; Gibson, S. E. *Eur. J. Org. Chem.* **2010**, 2938. (k) Boukpuvalas, J.; Pouliot, R.; Fréchette, Y. *Tetrahedron Lett.* **1995**, *36*, 4167.

(21) For reviews, see: (a) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (b) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 209.