Communication

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

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

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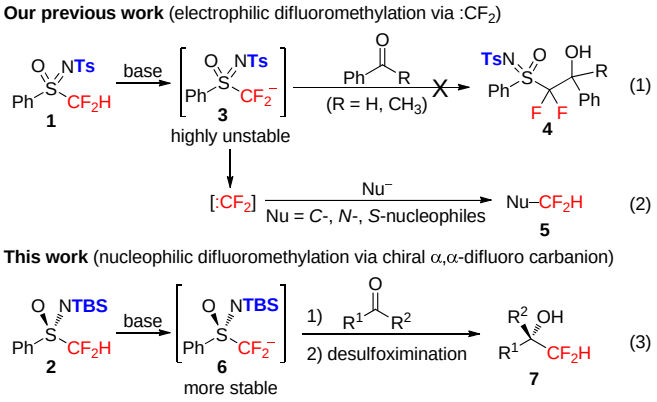
Supporting Information Placeholder

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 difluoromethyl sulfoximine to the prochiral carbon center of ketones. The present method has also been used to prepare enantiomerically enriched difluoromethyl secondary alcohols as well as two difluorinated analogues of natural products (difluorinated gossonorol **7g** and boivinian B **13**), which demonstrates 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 the 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, the difluoromethylated analogues of biologically active compounds are strong candidates for pharmaceuticals. In some cases, difluoromethylated compounds exhibit increased bioactivity compared to their trifluoromethylated counterparts.[4]

Over the past decades, a variety of protocols have been developed for introducing the trifluoromethyl group.[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 removing 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] This is mainly attributed to the instability of the difluoromethyl carbanion that 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 to aldehydes), i.e. 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 wish to disclose our recent success in tackling this interesting synthetic problem via a chiral α,α-difluoro carbanion strategy (see Scheme 1, eq 3).

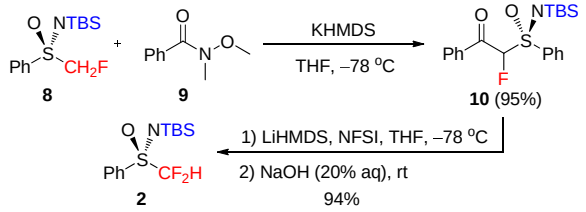
Scheme 1. Electrophilic and Nucleophilic Difluoromethylation Reactions with Different Sulfoximine Reagents



Recently, we reported the first chiral α-fluoro sulfoximine-mediated stereoselective fluoroalkylation reaction, and a series of monofluorinated cyclopropanes were synthesized in high yields and 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 found that the racemic sulfoximine **1** was not a good nucleophilic difluoromethylating agent (Scheme 1, eq 1), since its carbanion $PhSO(NTs)CF_2^-$ (**3**) is highly unstable and readily decomposes into difluorocarbene ($:CF_2$); and indeed, sulfoximine **1** can serve as an electrophilic difluoromethylating agent via difluorocarbene intermediate (Scheme 1, eq 2).[12,13] Based on these results, we surmised that in order to improve the stability of the carbanion, the structure of sulfoximine **1** should be modified by changing the Ts group (Ts = *p*-toluenesulfonyl) to a less electron-withdrawing substituent to decrease the leaving ability (nucleofugality) of the sulfonimidoyl group, and 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 TBS (*tert*-butyldimethylsilyl) as a good choice (see Scheme 1, eq 3).

(*R*)-*N*-*tert*-Butyldimethylsilyl-*S*-fluoromethyl-*S*-phenyl-sulfoximine (**8**) was readily prepared according to the literature procedures.[14] Introduction of a benzoyl group then gave

Scheme 2. Preparation of (*R*)-*N*-*tert*-Butyldimethylsilyl-*S*-Difluoromethyl-*S*-Phenylsulfoximine 2

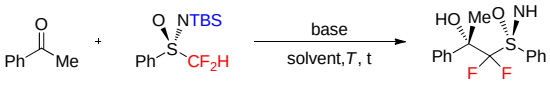


compound **10** in 95% yield. (*R*)-*N*-*tert*-Butyldimethylsilyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**2**) was obtained in 94% yield by fluorination of **10** using *N*-fluorodibenzenesulfonimide (NFSI) as the fluorinating agent, followed by removal of the benzoyl group (Scheme 2). To our knowledge, compound **2** is the first enantiopure difluoromethyl sulfoximine.

With compound **2** in hand, we investigated the diastereoselective synthesis of difluoromethyl tertiary alcohols by 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 a base, a yield of difluoromethylation products of only 25% was observed via ^{19}F NMR, 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 LiHMDS (lithium hexamethyldisilazide), 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 (sodium hexamethyldisilazide) was employed as the base (Table 1, entry 3). Furthermore, KHMDS was found to be better still for the model stereoselective difluoromethylation reaction (67% yield, 90/10 *dr*; Table 1, entry 4). The screening of solvents showed that THF was 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 co-solvent (Table 1, entry 5), indicating that alkali metal counterions are involved in the transition state of the reaction. It is remarkable that, when the 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%) and 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 supporting information).

Eventually, we chose the conditions shown under entry 13 in Table 1 as standard conditions to examine the scope of the reaction between ketones (or aldehydes) **11** and sulfoximine **2**. The results are summarized in Scheme 3. A variety of structurally diverse aromatic ketones were successfully difluoromethylated by **2**. The products **12** were obtained in good yields (77–95%) and with good diastereoselectivity (87/13–95/5 *dr*). The reaction tolerates many substituents such as fluoro, chloro, bromo and methoxy groups. 1-Phenylbutan-1-one and

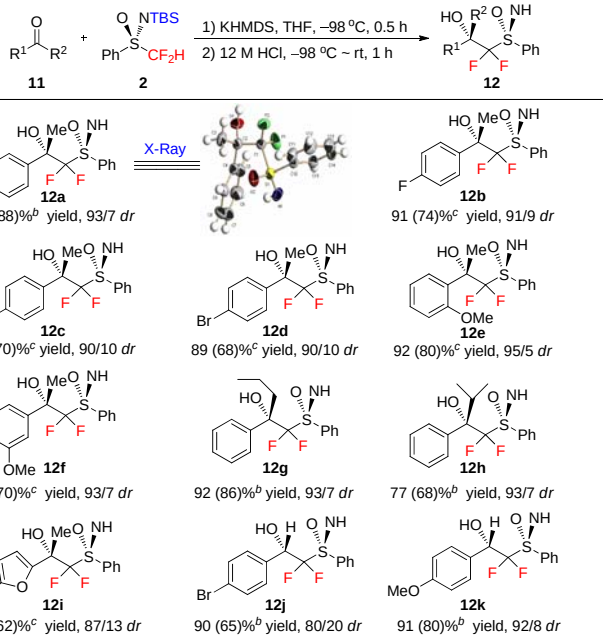
Table 1. Survey of Reaction Conditions[a]



entry	**11a**/**2**/base	base	solvent	*T* (°C)	t (h)	yield (%)[b]	*dr*[c]
1	1.5/1.0/1.2	nBuLi	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 stirred at the temperature for indicated time. [b,c] The total yield of the both diastereoisomers and *dr* were determined by ^{19}F NMR. [d] The yield in the parentheses refers to the isolated yield of the major diastereoisomer.

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

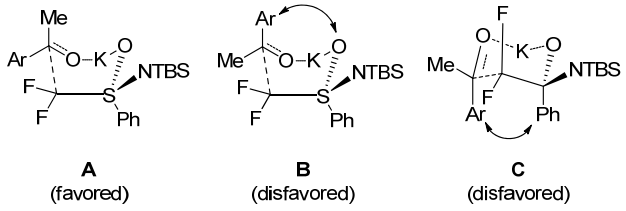


[a] Typical procedure: under N_2 atmosphere, KHMDS (1M/THF, 1.8 mL, 1.8 mmol) was added slowly into the THF (5 mL) solution of **11a** (180 mg, 1.5 mmol) and **2** (305 mg, 1 mmol) at –98 °C , and then stirred for 0.5 h, after which 12 M HCl (1 mL) was added, and the solution was stirrred for 1 h at room temperature; The isolated yield refers to the total yield of the two diastereoisomers; the dr was determined by ^{19}F NMR. [b] The yield in the parentheses refers to the isolated yield of the major diastereoisomer by colum chromatography. [c] The yield in the parentheses refers to the isolated yield of the major diastereoisomer by recrystallization.

2-methyl-1-phenylpropan-1-one are 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*, respectively. In addition, difluoromethylation of a heteroaryl-substituted ketone was also successful, giving the 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 *S*-configuration.[16] Those of the other products **12b-i** and **12k** were assigned by analogy. It is interesting that an intermolecular (sp^2)C–H···F–C interaction is observed 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 supporting information). The stereocontrol mode of the present diastereoselective difluoromethylation of ketones can be rationalized by considering different boat- or chair-like cyclic six-membered transition states such as **A**, **B**, and **C** (Figure 1). Due to the flagpole interaction between Ar group and the oxygen atom of sulfoximine,[17] transition state **B** is disfavored. Furthermore, the chair-like chelated transition state **C**, which leads to the experimentally observed major diastereoisomer **12a**, is energetically less favorable because of the severe Ar–Ph steric hindrance (see Figure 1). Our proposed transition state **A** is similar to that proposed by Pyne and co-workers regarding the reactions of lithiated (*S*)-*N*-*tert*-butyl-diphenylsilyl-*S*-methyl-*S*-phenylsulfoximine with ketones.[17] This chelated transition-state 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 a significantly decreased diastereoselectivity (Table 1, entry 5).

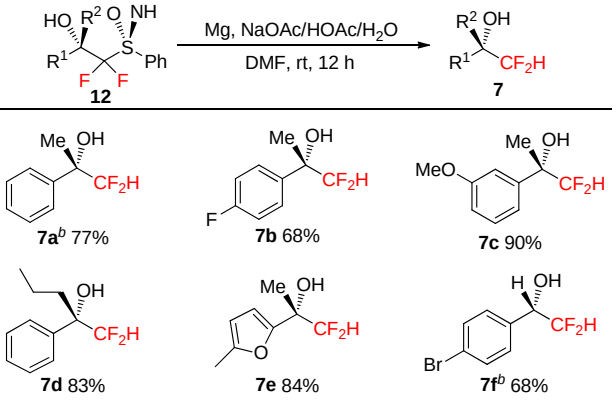
Figure 1. Proposed Transition States for Diastereoselective Difluoromethylation



The products **12** could be readily converted to enantiomerically enriched difluoromethyl alcohols **7** under the reductive desulfoximination conditions using Mg/HOAc/NaOAc.[18] The results are summarized in Scheme 4. These desulfoximination reactions proved to be efficient, and difluoromethyl alcohols **7** were obtained in good yields. The high optical purities of **7a** and **7f** (>99% *ee*) were determined by chiral HPLC, which indicates that the above procedures are reliable for the preparation of enantiomerically enriched difluoromethyl alcohols. It is worthy to note that the alcohol **7f** has been described as a key intermediate in the synthesis of 1-((*S*)-3-(((*S*)-1-(4'-((*S*)-2,2-difluoro-1-hydroxyethyl)-[1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethyl)amino)-5-fluoro-5-methyl-2-oxohexyl)cyclopropanecarbonitrile, an orally bioavailable cathepsin K inhibitor.[19]

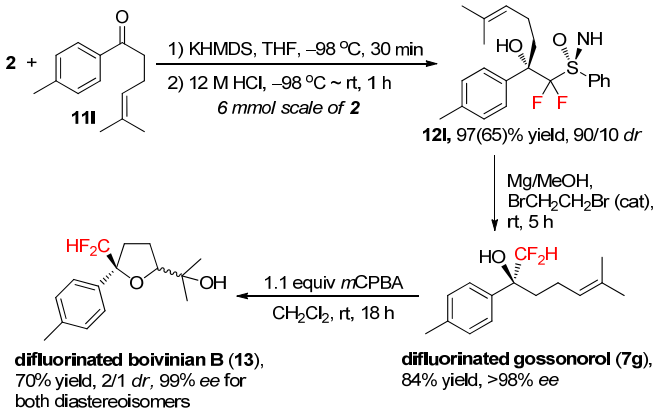
Given the fact that the incorporation of fluorine into a bioactive molecule can often impart highly interesting biological properties, we decided to use the above stereoselective difluoromethylation method to carry out the first synthesis of two enantiomerically enriched difluorinated analogues of natural products, namely difluorinated gossonorol **7g** and difluorinated boivinian B **13** (Scheme 5).[20] Under the standard conditions, the reaction between sulfoximine **2** and ketone **11l** proceeded smoothly, giving the product **12l** in 95% yield and with 90/10 *dr* even on a 6 mmol scale, which indicates that the current method can be successfully scaled up. Under the Mg/MeOH conditions, **12l** was converted to **7g** in 75% yield and with >98% *ee*. Upon treatment of **7g** with 1.1 equivalents of *m*CPBA in CH_2Cl_2 at room temperature for 18 h, compound **13** was obtained as a mixture of two diastereoisomers, both of which possess high enantiomeric purity (99% *ee*), in 2/1 *dr* and a combined yield of 70%.

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



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

Scheme 5. Synthesis of Difluorinated Analogs of Natural Products 7g and 13



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 and with good diastereoselectivity. 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-hydroxy sulfoximines **7** are promising candidates for chiral ligands in many applications, in light of the known successful applications of non-fluorinated β-hydroxy sulfoximines as chiral ligands in organic synthesis.[21] Further study in this direction is currently under way in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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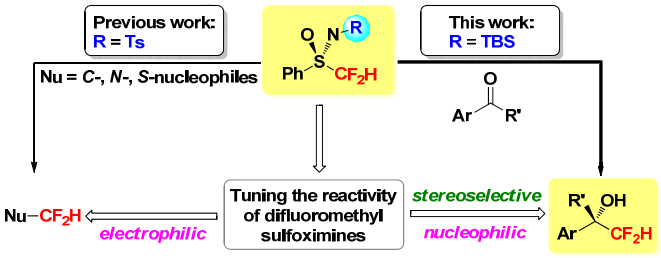
Previous work:
R = Ts
Nu = C-, N-, S-nucleophiles
This work:
R = TBS
Ar
R'
Nu–CF2H
electrophilic
Tuning the reactivity of difluoromethyl sulfoximines
stereoselective
nucleophilic
R'
OH
Ar
CF2H