Synthetic Methods

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# Facile Synthesis of Chiral α-Difluoromethyl Amines from *N*-(*tert*-Butylsulfinyl)aldimines**

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*Dedicated to Professor George A. Olah*

Fluorinated amines are important synthetic building blocks in the design of antimetabolites and drugs because fluorine causes minimal structural changes and maximal shifts in electron distribution.[1,2] Fluorine lowers the basicity of amines and improves oral absorption, suppresses metabolism, and thus increases the bioavailability of a target drug.[3–5] Among the fluorinated amines, α-difluoromethyl amines are of particular interest as the $CF_2H$ functionality is isosteric to a carbinol ($CH_2OH$) unit and also, as a lipophilic group, it shares much of the dipolar nature of the latter.[6,7] Therefore, α-difluoromethyl amines can be regarded as more lipophilic bioisosteres of corresponding α-aminocarbinols (or β-amino alcohols), which may feature some significant properties within biologically active molecules.

Despite its importance for applications related to life sciences, the synthesis of α-difluoromethyl amines has not been well explored. The few known methods are mainly based on the use of difluoromethyl carbonyl compounds or their imine derivatives as precursors.[8–12] Pey and Schirlin reported the multistep synthesis of α-difluoromethyl amines from substituted malonate esters with $CHF_2Cl$ followed by a Curtius rearrangement.[13] However, the general and efficient asymmetric synthesis of α-difluoromethyl amines still remains a challenge although it has drawn many synthetic endeavors.[9–12,14] The asymmetric hydrogenation of fluorinated imines are usually difficult, and recently Uneyama and coworkers reported that the palladium-catalyzed asymmetric hydrogenation of difluoromethyl imino esters proceeded with poor enantioselectivity (30% *ee*).[9] Hydride reduction of the C=N bond of chiral difluoromethyl β-sulfinyl-*N*-arylimine only gave 82% diastereomeric excess.[10] Difluoropyruvaldehyde *N*,*S*-ketal was synthesized in three steps from difluoroacetic esters and chiral methyl *p*-tolyl sulfoxide in only 72% enantiomeric excess.[11] Conversion of optically pure β-

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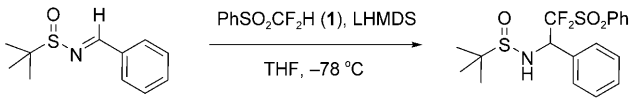
bromo-β,β-difluoroalanine derivatives into corresponding β,β-difluoroalanine products led to a decrease in the optical purity (with 80% *ee*).[14] Funabiki et al. attempted L-proline-catalyzed asymmetric Mannich-type reactions with difluoromethyl aldimine, but prolonged reaction times (7 days) were required and the reactions lacked generality.[12] On the other hand, although Prakash et al. elegantly developed the asymmetric synthesis of α-trifluoromethyl amines using $TMSCF_3$ (TMS = trimethylsilyl) and *N*-(*tert*-butylsulfinyl)aldimines,[15] similar asymmetric synthesis of α-difluoromethyl amines using $R_3SiCF_2H$ and *N*-(*tert*-butylsulfinyl)imines proved problematic due to the low reactivity of $R_3SiCF_2H$ reagents.[16] To the best of our knowledge, there is no synthetic method available for the highly stereoselective synthesis of α-difluoromethyl amines using a direct difluoromethylation strategy. Previously, one of us was involved in the development of difluoromethyl phenyl sulfone (**1**) as a versatile reagent for the selective transfer of difluoromethyl, difluoromethylene, and difluoromethylidene building blocks.[17] Herein, we report the first highly stereoselective nucleophilic difluoromethylation reaction using difluoromethyl phenyl sulfone and *N*-(*tert*-butylsulfinyl)aldimines which has enabled us to efficiently synthesize enantiomerically pure α-difluoromethyl amines through a simple and reliable protocol.

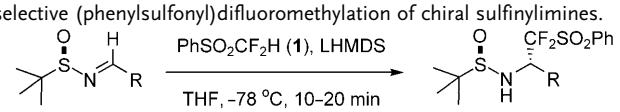
In previous investigations, we found that difluoromethyl phenyl sulfone (**1**) can be used as a convenient difluoromethylating agent for alkyl halides and carbonyl compounds, commonly accomplished through a (phenylsulfonyl)difluoromethylation–reductive desulfonylation strategy.[17d,e] The (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$, **2**), generated in situ from **1** and a base such as lithium hexamethyldisilazide (LHMDS) or *t*BuOK, is an excellent nucleophile that can readily undergo addition or substitution reactions with carbonyl compounds, disulfides, and primary alkyl halides.[17] Anion **2**, although difficult to isolate owing to its slow decomposition into difluorocarbene and benzenesulfinate, showed both higher thermal stability and sometimes better nucleophilicity (in the case of alkyl halides) than the trifluoromethyl anion ($CF_3^-$). Nucleophilic addition reactions between **2** and imines **3** have not been reported, and we envisioned that the reactions would proceed smoothly as a result of the reasonable stability of anion **2** to decomposition and the matched hard-/softness between **2** and imines.[18,19] With these in mind, first we prepared racemic *N*-(*tert*-butylsulfinyl)aldimine **4**[20] as a model compound to test the reaction with difluoromethyl phenyl sulfone (Scheme 1). When LHMDS (2 equiv, dissolved in THF) was added to a solution of aldimine **4** (2 equiv) and $PhSO_2CF_2H$ (1 equiv) in THF at −78 °C, a facile addition reaction occurred and sulfone **1** was quantitatively transformed into product **5** (detected by NMR spectroscopy and TLC) in 15 minutes. More interestingly, analysis of the crude reaction mixture by $^{19}F$ NMR spectroscopy showed that the reaction proceeded highly diastereoselectively and only



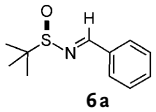
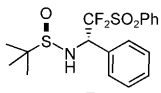
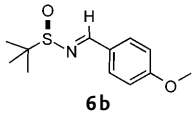
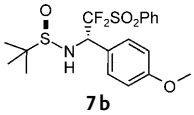
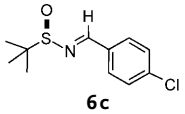
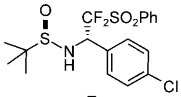
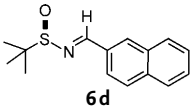
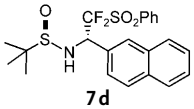
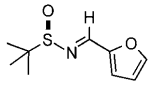
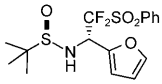
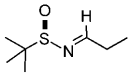
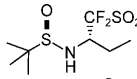
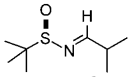
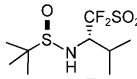
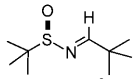
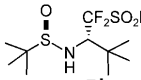

**4** **5**

***Scheme 1.*** Nucleophilic (phenylsulfonyl)difluoromethylation of *N*-(*tert*-butylsulfinyl)imine (**4**).

***Table 1:*** Stereoselective (phenylsulfonyl)difluoromethylation of chiral sulfinylimines.




**6** **7**

| Entry[a] | Sulfinylimine **6** | Product **7**[b] | Yield [%][c] | d.r. [%][d] | $[\alpha]_D^{25}$ [e] |
|---|---|---|---|---|---|
| 1 |  **6a** |  **7a** | 95 | >99 | −27.4 (*c*=0.8) |
| 2 |  **6b** |  **7b** | 96 | >99 | −20.7 (*c*=0.7) |
| 3 |  **6c** |  **7c** | 95 | >99 | −17.8 (*c*=0.6) |
| 4 |  **6d** |  **7d** | 98 | >99 | −5.6 (*c*=1.0) |
| 5 |  **6e** |  **7e** | 90 | >99 | −45.5 (*c*=1.0) |
| 6 |  **6f** |  **7f** | 95 | >99 | −25.0 (*c*=0.8) |
| 7 |  **6g** |  **7g** | 94 | >99 | −54.3 (*c*=0.9) |
| 8 |  **6h** |  **7h** | 85 | >99 | −9.7 (*c*=1.0) |

[a] In all cases, LHMDS (1.2 equiv) was added to a mixture of **1** (1.0 equiv) and **6** (1.1 equiv) in THF at −78 °C, and the reactions were usually complete in 10–20 min. [b] For entry 1, the configuration was determined by single-crystal X-ray analysis; the others were assigned from transition-state models. [c] Yields of isolated analytically pure material. [d] Diastereomeric ratios were determined by $^{19}F$ NMR spectroscopy of the crude reaction mixture. [e] Optical rotations were measured in chloroform.

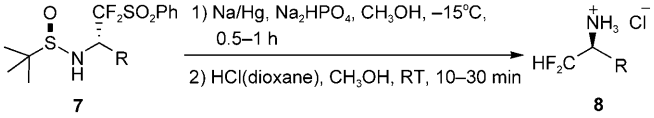
  

one single diastereomer (racemic) of **5** was formed. The reactant ratio **4**/**1**/LHMDS was further optimized to 1.1:1.0:1.2, and product **5** was isolated in 95% yield as a single diastereomer (racemic). Potassium *tert*-butoxide was also found to be effective for the reaction, however, slightly lower yields (80–85%) of product were obtained.

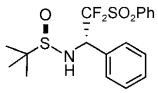
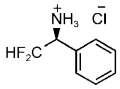
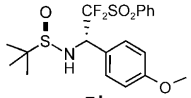
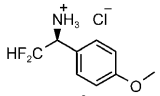
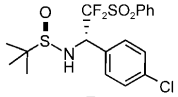
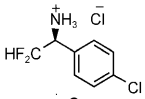
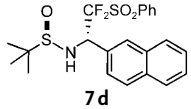
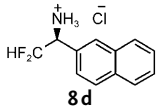
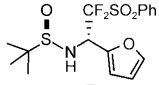
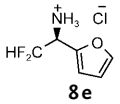
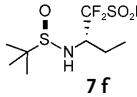
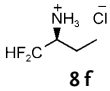
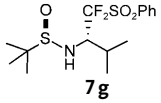
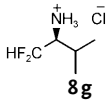
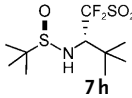
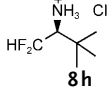
Encouraged by the above results, we predicted that when a homochiral sulfinylimine is subjected to this reaction, enantiomerically pure sulfinamide product could be obtained. The chiral sulfinamide can be further converted into enantiomerically pure α-difluoromethyl amines after deprotection of both *tert*-butylsulfinyl and phenylsulfonyl groups under mild conditions. Therefore, we prepared optically pure (*R*)-(*tert*-butylsulfinyl)aldimines **6**[21] and applied them in this nucleophilic (phenylsulfonyl)difluoromethylation reaction. The optimized reaction conditions as described above were used (**6**/**1**/LHMDS = 1.1:1.0:1.2, −78 °C, 10–20 min), and the results are summarized in Table 1. A variety of structurally diverse (*R*)-(*tert*-butylsulfinyl)aldimines **6** reacted with (phenylsulfonyl)difluoromethyl anion (generated in situ from sulfone **1** and LHMDS) to give the corresponding chiral sulfinamides **7** in excellent yields and with very high diastereoselectivities. Remarkably, the reactions were carried out under basic conditions but were still amenable to sulfinylimines bearing α hydrogen atoms (see entries 6 and 7, Table 1), which is in sharp contrast to their known trifluoromethylation chemistry.[15,18] Prakash et al.[15] and Dolbier and co-workers[18] reported that trifluoromethylation reactions of chiral sulfinylimines (with $TMSCF_3$ or $CF_3I$/tetrakis(dimethylamino)ethylene) were very sensitive to base (such as CsF), and that sulfinylimines bearing α hydrogen atoms usually gave lower yields. Sterically demanding sulfinylimine **6h** also gave a high yield of product (85%), which is superior to that obtained in the analogous trifluoromethylation reaction.[15,18] In each case as shown in Table 1, the product **7** was obtained as a single diastereomer, as determined by $^{19}F$ and $^{1}H$ NMR spectroscopy. Indeed, we observed that the present nucleophilic (phenylsulfonyl)difluoromethylations of sulfinylimines worked even more efficiently than those of carbonyl compounds as previously reported.[17e] The thermal stability, good nucleophilicity, and the softness of the (phenylsulfonyl)difluoromethyl anion generated in situ account for the short reaction times (10–20 min) and excellent chemo- and stereoselectivities. The absolute configuration of sulfinamide **7a** was determined by single-crystal X-ray analysis (see Figure 1a), and the configurations of **7b**–**7h** were assigned by analogy. The sense of diastereoselective induction can be depicted by a nonchelation-controlled addition step to give the Cram products **7** (Figure 1b).[15,18,21b,22]

All of the (phenylsulfonyl)difluoromethylated sulfinamides **7** were selectively deprotected under mild conditions following reported procedures[17,21] to give the corresponding amine salts **8**. Reductive desulfonylation using Na/Hg amalgam followed by acid alcoholysis provided a convenient and facile preparation of **8** from **7**. The results are summarized in Table 2. In all cases, near-quantitative conversions from **7** into **8** (in two continuous deprotection steps) were observed by

***Table 2:*** Preparation of amine salts **8** from **7**.




**7** **8**

| Entry[a] | Sulfinylimine **7** | Product **8**[b] | Yield [%][c] | $[\alpha]_D^{25}$ |
|---|---|---|---|---|
| 1 |  **7a** |  **8a** | 83 | 25.4 ($c$=1.0)[d] |
| 2 |  **7b** |  **8b** | 96 | 26.3 ($c$=0.7)[d] |
| 3 |  **7c** |  **8c** | 82 | 24.9 ($c$=0.5)[d] |
| 4 |  **7d** |  **8d** | 97 | 32.9 ($c$=0.6)[d] |
| 5 |  **7e** |  **8e** | 88 | 9.2 ($c$=0.55)[d] |
| 6 |  **7f** |  **8f** | 70 | −19.7 ($c$=0.2)[e] |
| 7 |  **7g** |  **8g** | 72 | −26.3 ($c$=0.3)[e] |
| 8 |  **7h** |  **8h** | 94 | −17.6 ($c$=0.2)[e] |

[a] No purification was necessary between two deprotection steps. [b] The configurations were determined by the fact that no racemerization occurred during the deprotection step. [c] Yields of the isolated analytically pure material. [d] Optical rotations were measured in methanol. [e] Optical rotations were measured in acetone.

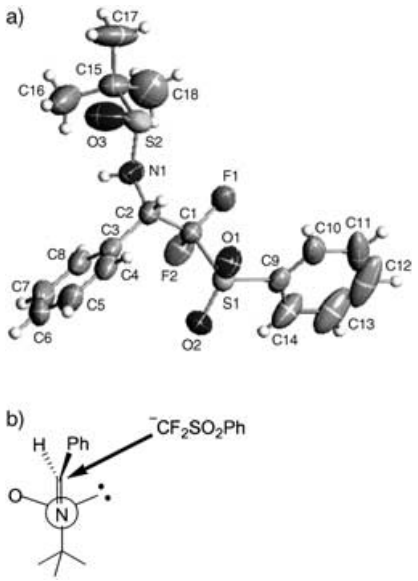
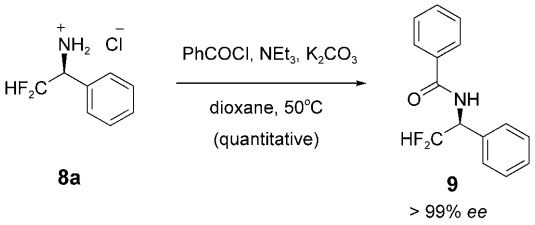



***Figure 1.*** a) X-ray crystal structure of **7a**, and b) depiction of its stereoselective formation.

NMR spectroscopy and the isolated yields of **8** were somewhat affected by the hydroscopicity of the products (see entries 6 and 7, Table 2). To ensure that there was no racemization during the deprotection process, we converted amine salt **8a** into benzamide derivative **9** (Scheme 2). The




***Scheme 2.*** Conversion of amine hydrochloride salt **8a** into chiral benzamide derivative **9**.

high optical purity of **9** (> 99 % *ee*) was determined by chiral HPLC and indicated that the above deprotection procedures are reliable for the preparation of enantiomerically pure α-difluoromethyl amines.

In summary, we have reported the first highly stereoselective and facile synthesis of α-difluoromethyl amines using a nucleophilic difluoromethylation strategy. Nucleophilic (phenylsulfonyl)difluoromethylation of (*R*)-(*N*-*tert*-butylsulfinyl)aldimines with difluoromethyl phenyl sulfone affords the corresponding products in excellent yields and with high diastereoselectivity
(d.r. > 99 %). The facile and convenient deprotection of both *tert*-butylsulfinyl and phenylsulfonyl groups gives the target α-difluoromethyl amines with high enantiomeric purity (*ee* > 99 %). The experimental data reported herein indicate that in a nucleophilic fluoroalkylation reaction, the stability, nucleophilicity, and hard-/softness of a fluorine-bearing carbon nucleophile substantially affect the overall chemical outcome of that reaction. The present synthetic methodology provides a convenient and useful synthetic tool for many applications related to life sciences.

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