JOC*Note*

Stereoselective Synthesis of Di- and Monofluoromethylated Vicinal Ethylenediamines with Di- and Monofluoromethyl Sulfones

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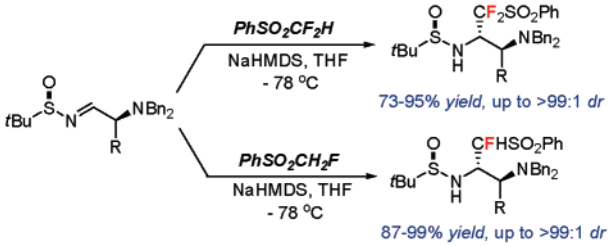

The diastereoselective nucleophilic (phenylsulfonyl)difluoromethylation and (phenylsulfonyl)monofluoromethylation of α-amino *N*-*tert*-butanesulfinimines (**3**) by using $PhSO_2CF_2H$ and $PhSO_2CH_2F$ reagents gave products **4** or **5** in high yields (73−99%) and with excellent diastereoselectivity (dr up to >99:1). After subsequent reductive desulfonylation and acid-catalyzed alcoholysis, compounds **4** and **5** could be readily transformed to chiral α-difluoromethylated or α-monofluoromethylated ethylenediamines in good yields.

Nitrogen and fluorine occupy the positions of the first and second favorite heteroelements in life-science-oriented research.[1] As a class of organic compounds possessing both nitrogen and fluorine atoms, fluorinated amines (especially chiral fluorinated amines) have received much attention as important synthetic building blocks in the design of many anticholinergic, antiemetic, antispastic drugs, and enzyme inhibitors, given the fact that fluorine lowers the basicity of the amino functionality, decreases acute toxicity, and increases the metabolic stability of a target drug.[2−4] Profound change exhibited by the amino moiety when it is placed α to a fluoroalkyl group (R_F, such as CF_3, CHF_2, CH_2F, etc.) has driven organic chemists to develop efficient synthetic methods for the preparation of chiral α-tri-, di-, and monofluoromethylated amines over the past decades.[5−8] However, although nonfluorinated chiral vicinal diamines (1,2-diamines) have increasingly become a targeted functional motif in organic synthesis owing to their ubiquity in natural products,[9] the report on the synthesis of chiral α-fluoroalkylated vicinal diamines is scarce. In 2002, Prakash and Mandal[6c] reported the first diastereoselective synthesis of chiral α-trifluoromethylated vicinal diamines with Ruppert−Prakash reagent ($TMSCF_3$). Intrigued by the unique properties of di- and monofluoromethylated organic compounds compared to their trifluoromethylated counterparts,[10] we envisioned that the chiral α-di- and monofluoromethylated vicinal diamines could be used as interesting new building blocks for drug design and as a novel type of ligands for transition-metal-catalyzed asymmetric synthesis. Previously, we have successfully applied di- and monofluoromethyl phenyl sulfones [$PhSO_2CF_2H$ (**1**) and $PhSO_2CH_2F$ (**2**)] as robust nucleophilic di- and monofluoromethylating agents.[8] In this note, we disclose a highly diastereoselective synthesis of both α-difluoromethylated and α-monofluoromethylated vicinal diamines through direct fluoroalkylation of chiral α-amino *N*-*tert*-butanesulfinimines with reagents **1** and **2**.

As the first part of experiments, we prepared a variety of structurally diverse chiral α-amino *N*-*tert*-butanesulfinimines **3**[6c] from amino aldehydes (derived from amino acids) and (*R*)-*N*-*tert*-butanesulfinamide[11] using $Ti(OEt)_4$ as a dehydrating Lewis acidic reagent. With compounds **3** in hand, we carried out the

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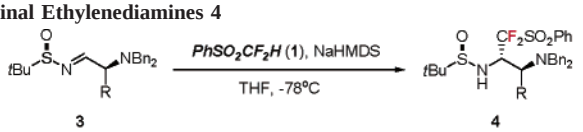
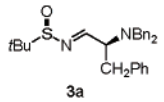
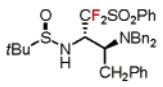
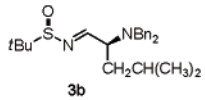
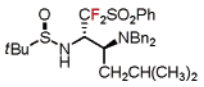
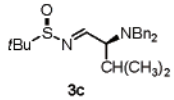
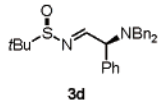
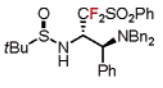
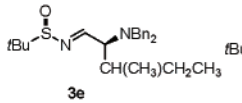
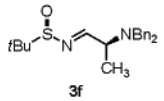
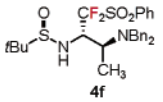
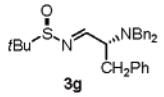
TABLE 1. Preparation of α-(Phenylsulfonyl)difluoromethylated Vicinal Ethylenediamines 4

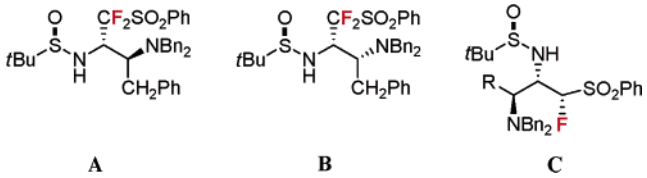


3 4

entry[a]	sulfinimine 3	product 4[b]	yield (%)[c]	dr[d]
1	 3a	 4a	80	>99:1
2	 3b	 4b	83	>99:1
3	 3c	 4c	74	>99:1
4	 3d	 4d	73	>99:1
5	 3e	 4e	83	>99:1
6	 3f	 4f	95	>99:1
7	 3g	 4g	85	95:5

[a] In all cases, NaHMDS (1.4 equiv) was added to a mixture of **1** (1.0 equiv) and **3** (1.1 equiv) in THF at −78 °C, and the reactions were usually completed in 3−5 h. [b] For entries 1 and 7, the configurations of **4a** and **4g** were determined by single-crystal X-ray analysis; the others were assigned by analogy. [c] Isolated yield. [d] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy on samples from the crude reaction mixture.

diastereoselective nucleophilic difluoromethylation between **3** and difluoromethyl phenyl sulfone ($PhSO_2CF_2H$, **1**). After a quick survey of the reaction conditions using **3a** (see Table 1) as the model compound, we found that the best diastereoselectivity of product **4a** (dr >99:1) was observed when sodium hexamethyldisilazide (NaHMDS) was used as a base. The optimized reactant ratio was **1**/**3a**/NaHMDS = 1.0:1.1:1.4, and the reactions were carried out at −78 °C and usually completed in 3−5 h. By using the optimized reaction conditions, we examined the scope of the present diastereoselective nucleophilic (phenylsulfonyl)difluoromethylation of chiral α-amino *N*-*tert*-butanesulfinimines **3**. As shown in Table 1, the (phenylsulfonyl)-difluoromethyl anion ($PhSO_2CF_2^-$), generated in situ from difluoromethyl phenyl sulfone (**1**) and NaHMDS, can readily undergo nucleophilic addition with a variety of structurally diverse chiral α-amino *N*-*tert*-butanesulfinimines **3**, giving the corresponding difluoroalkylated vicinal ethylenediamine products (**4a**−**4f**) in good to excellent yields with very high diastereoselectivities (dr >99:1). The reaction with sulfinimine (**3g**) (derived from the corresponding (*R*)-amino aldehyde) gave the corresponding product **4g** with 95:5 diastereomeric ratio and a 85% chemical yield of the major diastereomer. The very high diastereoselectivity observed in the case of entries 1−6 (in Table 1) indicates that both chiral centers present in the molecule induced the nucleophilic addition from the *re* face of imines and the stereochemistry of nucleophilic addition was non-chelation-controlled.[6,8,11] The absolute configuration of product **4a** was confirmed by single-crystal X-ray analysis (see Figure 1A and Supporting Information), and the configurations of **4b**−**4f** were assigned by analogy. The absolute configuration of the major isomer of product **4g** was also confirmed by single-crystal X-ray analysis (see Figure 1B and Supporting Information), indicating that the *tert*-butanesulfinyl group (instead of the dibenzylamino group) in substrate **3g** dominates the stereochemical outcome of the product **4g**.



A B C

FIGURE 1. Absolute configurations of products **4a** (A), **4g** (B), and **5a** (C), determined by single-crystal X-ray analysis (also see Supporting Information).

Encouraged by the above difluoromethylation results, we continued our efforts in the monofluoromethylation of α-amino *N*-*tert*-butanesulfinimines using fluoromethyl phenyl sulfone ($PhSO_2CH_2F$, **2**)[8b] as the monofluoromethylating agent. As shown in Table 2, under the similar reaction conditions, the α-amino *N*-*tert*-butanesulfinimines **3** were smoothly monofluoromethylated to give corresponding products **5** + **6** in 87−99% chemical yields with excellent diastereoselectivity [(**5** + **6**)/**7** > 99:1]. The absolute configuration of **5a** was determined by single-crystal X-ray analysis (see Figure 1C and Supporting Information), and the configurations of other products were assigned by analogy. The sense of diastereoselective induction can be depicted by the fact that the nucleophilic addition was from the *re* face of the imines with $PhSO_2CHF^-$, and a non-chelation-controlled addition step gave the Cram products **5** + **6**. It is interesting that moderate stereoselectivities (**5**/**6**= 1.5−3.3:1) were observed during the formation of another neighboring stereogenic center (the fluorine-bearing carbon), indicating that during the reaction there is a kinetic preference for one enantiomeric form of the corresponding anion.

As shown in Scheme 1, upon reductive desulfonylation using our previously developed Mg/HOAc/NaOAc reagent[12] or conventional Na(Hg) amalgam reagent, compounds **4a** and **5a** were readily converted to corresponding di- and monofluoromethylated sulfinamides **8** and **10** in 93 and 65% yield, respectively. With the treatment of the HCl/dioxane/CH_3OH system, intermediates **8** and **10** were further transformed to chiral α-di- and monofluoromethylated vicinal ethylenediamines **9** and **11** in 88 and 90% yield, respectively.

In summary, we have achieved a highly diastereoselective synthesis of chiral α-difluoromethylated and α-monofluoromethylated vicinal ethylenediamines through direct nucleophilic di- and monofluoromethylation using $PhSO_2CF_2H$ and $PhSO_2CH_2F$ reagents. The excellent diastereoselectivities and good chemical yields may enable the present synthetic methodology to find some important applications in organic synthesis.

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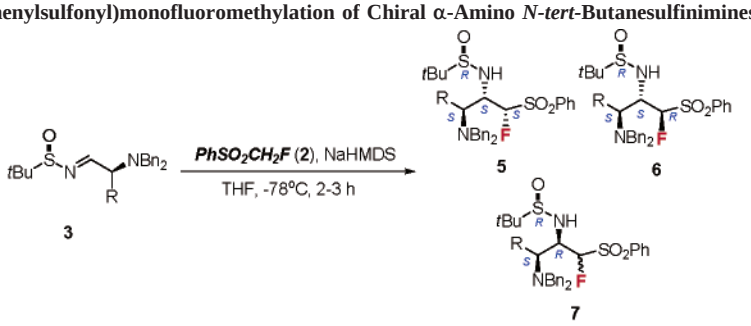
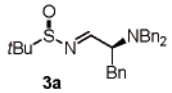
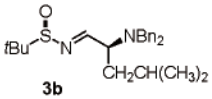
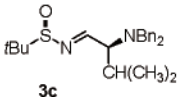
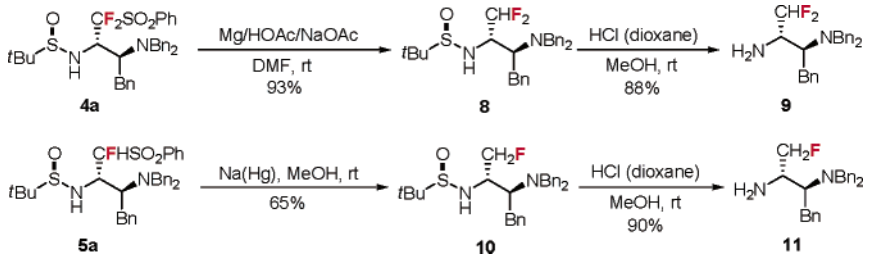
TABLE 2. Stereoselective (Phenylsulfonyl)monofluoromethylation of Chiral α-Amino *N-tert*-Butanesulfinimines 3a−c



entry[a]	sulfinimine **3**	product[b] (**5+6+7**)	yield (%)[c] (**5+6**)	facial selectivity (dr)[d] [(**5+6**):**7**]	isomeric ratio[d] (**5**:**6**)
1	 **3a**	**5a+6a+7a**	99	>99:1	1.5:1.0
2	 **3b**	**5b+6b+7b**	97	>99:1	2.2:1.0
3	 **3c**	**5c+6c+7c**	87	>99:1	3.3:1.0

[a] In all cases, NaHMDS (2.0 equiv) was added to a mixture of **2** (1.0 equiv) and **3** (1.05 equiv) in THF at −78 °C, and the reactions were usually completed in 2−3 h. [b] For entry 1, the configuration of **5a** was determined by single-crystal X-ray analysis; the others were assigned by analogy. [c] Isolated yield. [d] Both facial selectivity and isomeric ratios were determined by ^{19}F NMR spectroscopy on samples from the crude reaction mixture.

SCHEME 1. Preparation of Di- and Monofluoromethylated Vicinal Diamines 9 and 11



Experimental Section

Typical Procedure for Stereoselective Nucleophilic (Phenylsulfonyl)difluoromethylation and (Phenylsulfonyl)monofluoromethylation of Chiral α-Amino *N-tert*-Butanesulfinimines. Under N_2 atmosphere, into a 50 mL Schlenk flask containing chiral α-amino *N-tert*-butanesulfinimine (**3a**) (476 mg, 1.1 mmol) and $PhSO_2CF_2H$ (192 mg, 1.0 mmol) in THF (10 mL) at −78 °C was added a THF solution (1.4 mL) of $(TMS)_2NNa$ (NaHMDS, 1.0 M, 1.4 mmol). The reaction mixture was then stirred at this temperature until the reaction was complete (usually 3−5 h), followed by adding a saturated NaCl aqueous solution (10 mL) at this temperature. A small amount of sample from the organic phase was monitored by ^{19}F NMR, which showed that the diastereomeric ratio of the product was >99:1. After warmed to room temperature, the solution mixture was extracted with EtOAc (25 mL × 3), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under vacuum, the crude product was further purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8:1 v/v) to give product **4a** as a white solid: yield 80% (497 mg); mp 117−118 °C; $[\alpha]_D^{20}$ −69.47 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83−7.85 (m, 2H), 7.70−7.76 (m, 1H), 7.55−7.60 (m, 2H), 7.14−7.29 (m, 15H), 4.31−4.52 (m, 2H), 4.01−4.09 (m, 1H), 3.89 (d, *J* = 1.5 Hz, 2H), 3.81 (d, *J* = 1.5 Hz, 2H), 2.91−3.02 (m, 1H), 2.75−2.85 (m, 1H), 1.30 (s, 9H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −96.8 (d, *J* = 234.1 Hz, 1F), −106.6 (dd, *J* = 284.1, 18.9 Hz, 1F); ^{13}C NMR (125 MHz) δ 138.5, 138.3, 135.3, 133.6, 130.5, 129.7, 129.1, 128.5, 128.3, 127.1, 126.4, 122.4 (dd, *J* = 296.4, 291.7 Hz), 61.6, 58.4 (t, *J* = 21.3 Hz), 57.5, 33.8 (d, *J* = 3.8 Hz), 22.8; IR (KBr) 3373, 3030, 2924, 1603, 1496, 1347, 1154, 1086, 742 cm^{-1}. Anal. Calcd for $C_{34}H_{38}F_2N_2O_3S_2$: C, 65.36; H, 6.13; N, 4.48. Found: C, 65.27; H, 6.18; N, 4.30. MS (ESI, *m*/*z*): 625.2 ($M^+ + 1$).

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Supporting Information Available: General experimental information and the characterization data of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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