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Stereoselective Nucleophilic Monofluoromethylation of *N*-(*tert*-Butanesulfinyl)imines with Fluoromethyl Phenyl Sulfone

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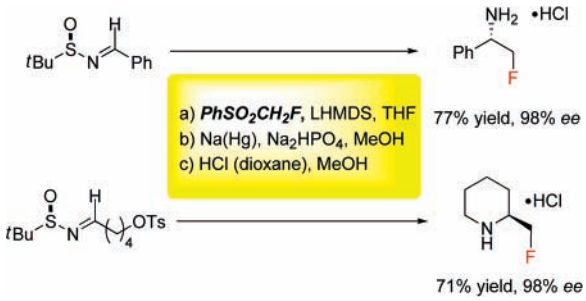
ABSTRACT



Highly stereoselective nucleophilic monofluoromethylation of (*R*)-(*tert*-butanesulfinyl)imines with fluoromethyl phenyl sulfone was achieved to afford α-monofluoromethylamines with a nonchelation-controlled stereoselectivity mode. By using the same chemistry, (*R*)-(*tert*-butanesulfinyl)-imines bearing a terminal tosylate (OTs) group can be converted to α-monofluoromethylated cyclic secondary amines with high stereoselectivity.

Fluorine is truly "a small atom with a big ego", and in many cases the replacement of a hydrogen atom with fluorine in a drug molecule can cause 10-fold enhancement of its biological potency and bioavailability.[1] Today, selective incorporation of fluorine atom(s) into organic molecules to modulate their biological properties has become a routine and powerful strategy in drug design. Since Kollonitsch's first report of α-monofluoromethylamines as selective inhibitors of biosynthesis of aminergic neurotransmitters,[2] α-monofluoromethylamines have been extensively used as important building blocks in the design of many anticholinergic, antiemetic, and antispastic drugs and enzyme inhibitors, given the fact that the fluorine atom lowers the basicity of the amine functionality, decreases acute toxicity, and increases the metabolic stability of a target drug.[1−5] However, there are very few synthetic methods available to effectively synthesize α-monofluoromethylamines,[6] mostly based on the fluorination reactions with toxic reagents such as SF_4,[7] HF,[8] and FCH_2CN.[9] Other preparative methods of α-monofluoromethylamines with fluoromethyl ketones[10] and cyclic sulfamidates[11] suffer from multistep transformations and unavailability of the precursors.

(1) (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 Turtorial.

(2) Kollonitsch, J.; Perkins, L. M.; Patchett, A. A.; Doldouras, G. A.; Marburg, S.; Duggan, D. E.; Maycock, A. L.; Aster, S. D. *Nature* **1978**, *274*, 906−908.

(3) Grunewald, G. L.; Caldwell, T. M.; Li, Q.; Slavica, M.; Criscione, K. R.; Borchardt, R. T.; Wang, W. *J. Med. Chem.* **1999**, *42*, 3588−3601.

(4) Silverman, R. B.; Nanavati, S. M. *J. Med. Chem.* **1990**, *33*, 931−936.

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(6) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishman, S., Eds.; Wiley: New York, 1991.

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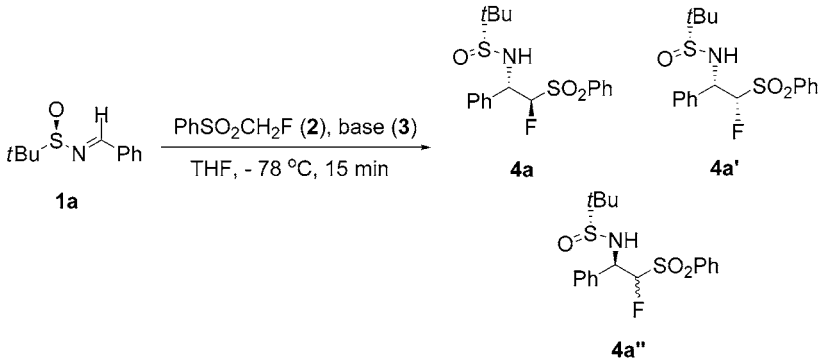
Table 1. Survey of Reaction Conditions



entry	base **3**	molar ratio (**1**:**2**:**3**)	facial selectivity[a] ((**4a** + **4a′**):**4a″**)	isomer ratio[a] (**4a**:**4a′**)	unreacted **2** (equiv)[a]	yield (%)[b] (**4a** + **4a′**)
1[c]	*n*-BuLi	1.0:1.2:1.2	99:1	1:1.6	0.14	95
2[c]	LHMDS	1.0:1.2:1.2	99:1	1:1.9	0.14	98
3[c,d]	LHMDS	1.0:1.2:1.2	99:1	1:2.2	0.19	99
4[e]	LHMDS	1.0:1.2:1.2	99:1	1:1.3	0.19	99
5[e]	LHMDS	1.0:1.0:1.05	99:1	1:2.0	trace	99

[a] Facial selectivity, isomer ratio, and unreacted **2** were determined by ^{19}F NMR spectroscopy of the crude products. Compounds **4a** (−179 ppm) and **4a′** (−188 ppm) were also identified by ^{19}F NMR. [b] Isolated yield of **4a** and **4a′**. [c] Method A: The mixture of base and **2** was stirred at −78 °C for 3 min, then **1a** was added. [d] The reaction temperature was −90 °C. [e] Method B: The base was added dropwise into the mixture of **1a**, **2**, and THF at −78 °C.

Nucleophilic fluoroalkylation is a straightforward way to introduce fluoroalkyl groups into the target molecules, and with this strategy both nucleophilic trifluoromethylation and difluoromethylation have been tamed.[12] To the best of our knowledge, however, owing to the lack of efficient nucleophilic monofluoromethylating agents, nucleophilic monofluoromethylation (nucleophilic incorporation of a CH_2F group into electrophiles) has never been reported. As part of our continuing effort in selective fluoroalkylation chemistry,[13] we wish to disclose the unprecedented stereoselective synthesis of α-monofluoromethylamines by nucleophilic monofluoromethylation of Ellman's *N*-(*tert*-butanesulfinyl)-imines[14] using fluoromethyl phenyl sulfone ($PhSO_2CH_2F$)[15] as the monofluoromethylating agent.

In the first set of experiments, we chose (*R*)-(*tert*-butanesulfinyl)benzaldimine **1a** as a model compound to study the reaction with fluoromethyl phenyl sulfone **2**. The reaction conditions were carefully tuned as shown in Table 1. In all cases, the facial selectivities [(**4a** + **4a′**):**4a″**], i.e., the diastereoselectivity during the nucleophilic addition of in situ generated (phenylsulfonyl)fluoromethyl anion into imine functionality of **1a**, were excellent (99:1). The absolute configuration of sulfinamide **4a** was confirmed by single-crystal X-ray analysis (see Figure 1), which indicates that

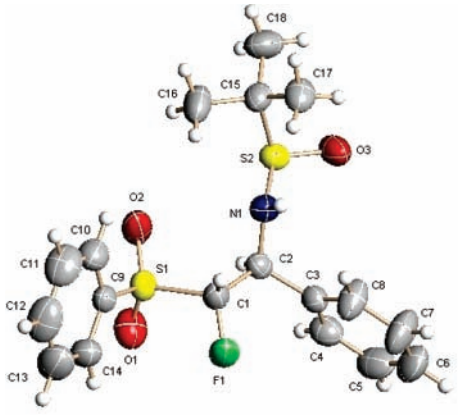


Figure 1. ORTEP drawing for sulfinamide **4a**.

the stereochemistry of nucleophilic addition was nonchelation controlled.[13,14] Interestingly, we found that there were some moderate stereoselectivities (**4a**:**4a′** = 1:1.3−2.2) during the formation of another neighboring stereogenic center (the fluorine-bearing carbon). The chemical yields of all experi-

(8) Alvernhe, G.; Lacombe, S.; Laurent, A. *J. Fluorine Chem.* **1980**, *16*, 526−527.
(9) Bey, P.; Gerhart, F.; Jung, M. *J. Org. Chem.* **1986**, *51*, 2835−2838.
(10) (a) Kanai, M.; Ueda, K.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Ootsuka, T.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *J. Fluorine Chem.* **2005**, *126*, 377−383. (b) Bravo, P.; Cavicchio, G.; Crucianelli, M.; Poggiali, A.; Zanda, M. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2811−2815.
(11) (a) Ok, D.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **1999**, *40*, 3831−3834. (b) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 766−770.
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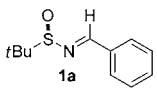
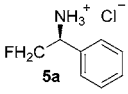
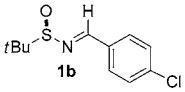
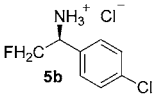
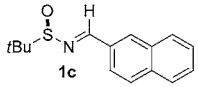
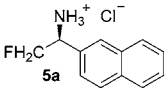
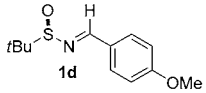
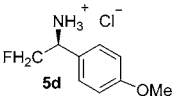
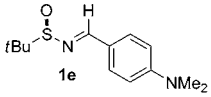
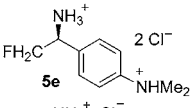
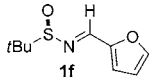
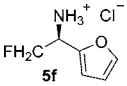
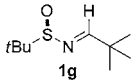
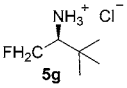
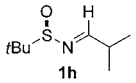
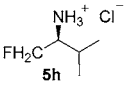
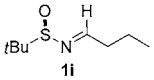
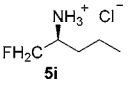
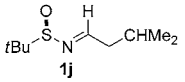
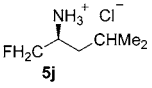
(13) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882−5886.
(14) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995 and references therein.
(15) Fluoromethyl phenyl sulfone is commercially available, and it can also be readily prepared with known methods. It has been used to prepare fluoroolefins. However, its application as a CH_2F^- equivalent has never been reported. See: (a) Matthews, D. P.; Persichetti, R. A.; McCarthy, J. R. *Org. Prep. Proced. Int.* **1994**, *26*, 605−608. (b) Inbasekaran, M.; Peet, N.; McCarthy, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 678−679.

ments were high within 15 min (entries 1−5), and finally we decided to choose the reaction condition of entry 5 as the standard condition (1.05 equiv of lithium hexamethyldisilazide (LHMDS) was added dropwise into the mixture of 1.0 equiv of **1** and **2** in THF at − 78 °C) to study the reactions of **2** with other (*R*)-(*tert*-butanesulfinyl)imines **1**. The results were summarized in Table 2. A variety of

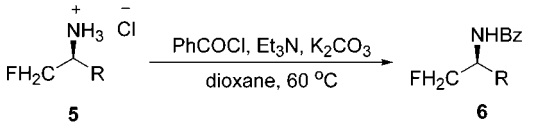
Table 2. Facile Synthesis of α-Monofluoromethyl Amines

entry[a]	sulfinylimine **1**	product **5**	facial selectivity (yield, %)[b] **4**	yield (%)[c] **5**
1	 **1a**	 **5a**	99 : 1 (99)	77
2	 **1b**	 **5b**	99 : 1 (98)	73
3	 **1c**	 **5a**	99 : 1 (95)	74
4	 **1d**	 **5d**	99 : 1 (99)	76
5	 **1e**	 **5e**	98 : 2 (99)	75
6	 **1f**	 **5f**	99 : 1 (98)	71
7	 **1g**	 **5g**	99 : 1 (99)	73
8	 **1h**	 **5h**	99 : 1 (91)	70
9	 **1i**	 **5i**	99 : 1 (94)	70
10	 **1j**	 **5j**	99 : 1 (96)	74

[a] The synthesis of **5** from **1** was carried out in three continuous steps without purification of the intermediate products such as (phenylsulfonyl)fluoromethylated sulfinamides **4**. [b] Both the facial selectivity data and the yield (for the first step) of **4** were determined by ^{19}F NMR spectroscopy. [c] Isolated overall yield of **5** from **1**. The configurations of **5** were assigned from the X-ray structure of **4a** and the transition state models.

structurally diverse (*R*)-(*tert*-butanesulfinyl)imines **1** reacted with (phenylsulfonyl)fluoromethyl anion (generated in situ from **2** and LHMDS) to give the corresponding (phenylsulfonyl)fluoromethylated homochiral sulfinamides **4** in excellent chemical yields (for the first step) with high stereoselectivity (facial selectivity = 99:1 or 98:2). Without purification, compounds **4** were readily converted into α-monofluoromethylamine salts **5** in good overall yields via reductive desulfonylation (with Na−Hg in methanol) and removal of the *tert*-butanesulfinyl group (with HCl in dioxane).[13] It is still noteworthy to mention that the first nucleophilic addition step was performed under the strong basic condition in the presence of LHMDS, but was still amenable to sulfinylimines bearing α hydrogen atoms (see entries 8−10). To ensure that there was no racemization during the deprotection process, we converted amine salts **5a** and **5g** into the corresponding benzamide derivatives **6a** and **6g** (see Scheme 1). The high optical purity of **6a** (98.4%

Scheme 1. Preparation of Benzamide Derivatives **6a** and **6g**



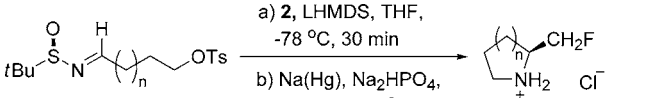
5 **6**

5a (R= Ph); **6a** (R= Ph): 98.4% *ee;*
5g (R= *t*Bu). **6g** (R= *t*Bu): 98.2% *ee*.

ee) and **6g** (98.2% ee) was determined by chiral HPLC, indicating that the current synthetic method promises to be a general and convenient approach for the preparation of enantiomerically pure α-monofluoromethylamines.

Taking into consideration that the (phenylsulfonyl)fluoromethylated sulfinamide anion species (the nitrogen-anion species of **4**) generated from the first nucleophilic addition step (before protonation) could further attack other electrophilic sites, we synthesized the tosylate (OTs)-bearing (*R*)-(*tert*-butanesulfinyl)imines **1k** and **1*l*** and applied them in a nucleophilic addition−substitution tandem reaction (see Scheme 2).[16] To our satisfaction, α-(phenylsulfonyl)fluoro-

Scheme 2. Synthesis of α-Monofluoromethylated Cyclic Amines



1k (n=1)
1l (n=2)

5k (n=1): 52 % yield;
5l (n=2): 71 % yield.

methylated cyclic amines formed smoothly with excellent stereoselectivity (in both cases, facial selectivity = 99:1), which were further converted into corresponding homochiral α-monofluoromethylated pyrrolidine **5k** and piperidine **5*l*** in 52% and 71% overall yield, respectively.

In conclusion, the unprecedented nucleophilic monofluoromethylation of *N*-(*tert*-butanesulfinyl)imines with fluoromethyl phenyl sulfone has been shown to be a highly stereoselective and convenient method for the synthesis of enantiomerically pure α-monofluoromethylamines. The same methodology can also be used to synthesize homochiral α-monofluoromethylated cyclic secondary amines by using tosylate (OTs)-bearing (*R*)-(*tert*-butanesulfinyl)imine precur-

(16) The same experimental procedures were applied as those for Table 2, except that 1.2 equiv (instead of 1.0 equiv) of **1k** and **1*l*** were used.

sors. The application of the present synthetic methodology in the synthesis of biologically interesting molecules is currently under investigation in our laboratory.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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