Letter

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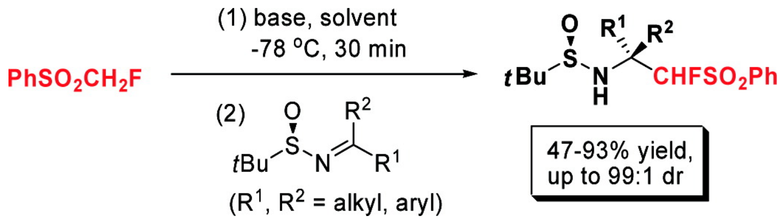

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Stereoselective Monofluoromethylation of *N-tert*-Butylsulfinyl Ketimines Using Pregenerated Fluoro(phenylsulfonyl)methyl Anion

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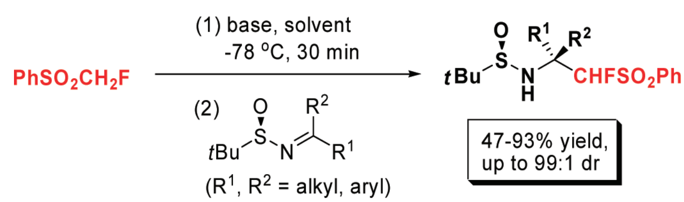
ABSTRACT



Pregeneration of fluoro(phenylsulfonyl)methyl anion ($PhSO_2CHF^-$) paves the way for the efficient and highly stereoselective monofluoromethylation of (*R*)-*N-tert*-butylsulfinyl ketimines. The stereocontrol mode of the present diastereoselective monofluoromethylation of ketimines is different from the previously known nucleophilic fluoroalkylation of (*R*)-*N-tert*-butylsulfinyl aldimines, which suggests that a cyclic six-membered transition state (rather than a nonchelation controlled one) is involved in the current ketimine reaction.

Recently, considerable attention has been directed toward the synthesis of chiral α-fluoroalkyl amines, since fluorine lowers the basicity of amines and thus enhances the metabolic stability and bioactivity of a target drug.[1] The most straightforward approach to synthesize chiral α-fluoroalkyl amines is the stereocontrolled nucleophilic additions of fluoroalkyl groups to imines. In 2001, Prakash and co-workers developed a highly diastereoselective trifluoromethylation of enantiopure *N-tert*-butylsulfinyl aldimines using Me_3SiCF_3 reagent.[2] Thereafter, similar diastereoselective trifluoromethylations of sulfinyl aldimines were reported by the groups led by Dolbier[3] and Mukaiyama.[4] We also successively demonstrated the diastereoselective difluoromethylation, monofluoromethylation, and difluoromethylenation of *N-tert*-butylsulfinyl aldimines using $PhSO_2CF_2H$, $PhSO_2CH_2F$, and Me_3SiCF_2SPh reagents.[5] More recently, Shibata and co-workers reported an enantioselective monofluoromethylation of α-amido sulfones (as aldimine precursors) with $(PhSO_2)_2CFH$.[6] However, although these stereoselective tri-, di-, and monofluoromethylations of *aldimines* have been successfully accomplished, the corresponding nucleophilic fluoroalkylations of *ketimines* are generally difficult (Scheme 1, eqs 1−3). As a result, the efficient and stereoselective synthesis of α-fluoroalkyl tertiary carbinamines by nucleophilic fluoroalkylation of *ketimines* still remains a challenging task.[7,8]

(1) (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (d) McCarthy, J. R. *Fluorine in Drug Design: A Tutorial Review*; 17th Winter Fluorine Conference (St. Petersburg, FL), Jan 9−14, 2005.

(2) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *113*, 609–610. (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847–2850. (c) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538–6539.

(3) Xu, W.; Dolbier, W. R., Jr. *J. Org. Chem.* **2005**, *70*, 4741–4745.

(4) Kawano, Y.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 894–895.

(5) (a) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882–5886. (b) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693–1696. (c) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489–2492. (d) Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119–3121.

(6) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394–6395.

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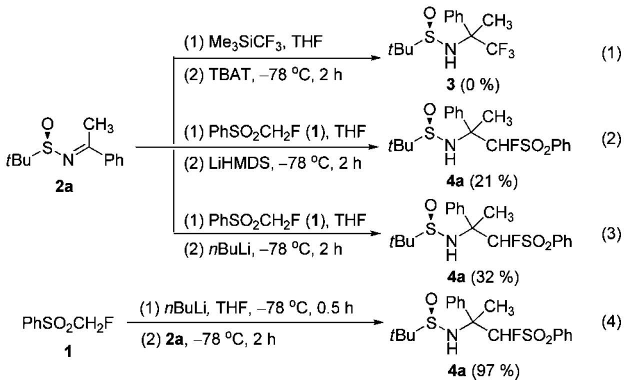
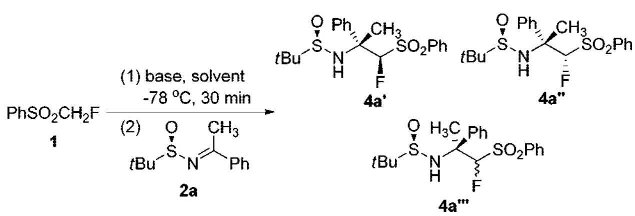
Scheme 1. Attempted Fluoroalkylation of Ketimine **2a**[9]



We envisioned that the difficulty of the fluoroalkylation of ketimines could be caused by the relatively low electrophilicity of ketimines (compared to aldimines[2−6]) and the relatively low nucleophilicity of fluorinated carbanions R_f^- (due to the "negative fluorine effect"[10]). Nucleophilic fluoroalkylation usually requires an in situ generation of the R_f^- species in the presence of an electrophilic reaction partner because many fluorinated carbanions are thermally unstable and their *pregeneration* and storage often result in decomposition (usually via α-elimination of a fluoride ion).[11] In the course of our previous study of diastereoselective fluoroalkylation of *N*-*tert*-butylsulfinyl aldimines,[5] we realized that the reactions between in situ generated anion $PhSO_2CHF^-$ and ketimine **2a** gave product **4a** in low yields (Scheme 1, eqs 2 and 3). An aza-enolization of **2a** caused by the strong base lithium hexamethyldisilazide (LiHMDS) or *n*-BuLi may account for the low product yield, and we envisaged that a *pregeneration* of anion $PhSO_2CHF^-$ could improve this monofluoromethylation reaction. Furthermore, during our previous study of "negative fluorine effect" of fluorinated carbanions,[10] we found that anion $PhSO_2CHF^-$ possesses good thermal stability and is suitable for pregeneration. Based on these considerations, we *pregenerated* $PhSO_2CHFLi$ (**5**) by mixing $PhSO_2CH_2F$ (**1**) and *n*-BuLi at −78 °C for 30 min and then allowed **5** to react with ketimine **2a** at the same temperature (Scheme 1, eq 4). To our delight, product **4a** was produced in 97% yield (determined by ^{19}F NMR), which encouraged us to further investigate this chemistry.

As shown in Table 1, by using ketimine **2a** as a model compound, we first examined the effects of different bases, reactant molar ratios, solvents, and reaction times on the chemical yield and the stereoselectivity of the product. It turned out that, when *n*-BuLi was used as a base in THF, excellent yield (92%) and good facial selectivity (dr = 95:5) were obtained (entry 6); and when KHMDS was used as a base, excellent facial selectivity (dr = 99:1) and satisfactory yield (72%) were achieved (entry 13). It should be noted that we applied several Lewis acids such as Me_3Al, $ZnBr_2$, and BF_3•Et_2O for the *n*-BuLi-mediated reaction, but no improvement of stereoselectivity was observed.

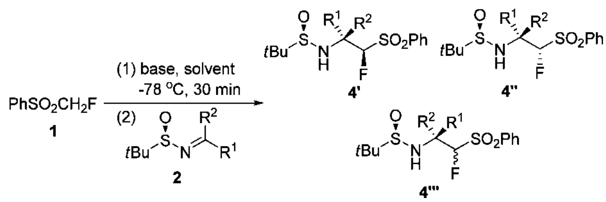
Table 1. Optimization of Reaction Conditions



entry[a]	base	molar ratio (**2a**:**1**:base)	solvent	time (h)	facial selectivity[b] [(**4a′**+**4a″**):**4a‴**]	yield (%)[c] (**4a′** + **4a″**)
1	*n*-BuLi	1:1.2:1.3	THF	2	95:5	92
2	LiHMDS	1:1.2:1.3	THF	2	94:6	37
3	NaHMDS	1:1.2:1.3	THF	2	97:3	17
4	KHMDS	1:1.2:1.3	THF	2	99:1	67
5	LDA	1:1.2:1.3	THF	2	96:4	57
6	*n*-BuLi	1:1.2:1.3	THF	1	95:5	92
7	*n*-BuLi	1:1.2:1.4	THF	1	95:5	87
8	*n*-BuLi	1:1.2:1.3	toluene	1	87:13	76
9	*n*-BuLi	1:1.2:1.3	Et_2O	1	83:17	75
10	*n*-BuLi	1:1.2:1.3	CH_2Cl_2	1	87:13	89
11	KHMDS	1:1.4:1.5	THF	2	99:1	64
12	KHMDS	1:1.1:1.2	THF	2	99:1	51
13	KHMDS	1:2:2.2	THF	2	99:1	72

[a] In all cases, **1** and base were stirred in solvent at −78 °C for 30 min first, and then **2a** was added to react with the pregenerated carbanion at −78 °C for the period of time as shown. [b] Diastereomeric ratios were determined by ^{19}F NMR of the crude reaction mixture. [c] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Table 2. Diastereoselective Monofluoromethylation of Ketimines



entry	ketimines (**2**)	condition[a]	facial selectivity [**4′** + **4″**):**4‴**][b]	yield (%)[c] (**4′** + **4″**)
1	R^1 = Ph, R^2 = CH_3 (**2a**)	A	95:5	90
		B	99:1	64
2	R^1 = 4-FC_6H_4, R^2 = CH_3 (**2b**)	A	96:4	81
		B	99:1	65
3	R^1 = 4-$CF_3C_6H_4$, R^2 = CH_3 (**2c**)	A	91:9	86
		B	97:3	60
4	R^1 = 4-$CH_3OC_6H_4$, R^2 = CH_3 (**2d**)	A	96:4	85
		B	99:1	62
5	R^1 = 4-$CH_3C_6H_4$, R^2 = CH_3 (**2e**)	A	95:5	93
		B	99:1	68
6	R^1 = 4-ClC_6H_4, R^2 = CH_3 (**2f**)	A	94:6	77
		B	98:2	69
7	R^1 = 2-naphthyl, R^2 = CH_3 (**2g**)	A	94:6	72
		B	99:1	68
8	R^1 = 2-furyl, R^2 = CH_3 (**2h**)	A	95:5	81
		B	94:6	77
9	R^1 = pyridyl, R^2 = CH_3 (**2i**)	A	87:13	81
		B	99:1	74
10	R^1 = *i*-Pr, R^2 = CH_3 (**2j**)	A	95:5	81[d]
		B	94:6	73[d]
11	R^1 = *t*-Bu, R^2 = CH_3 (**2k**)	A	95:5	77[d]
		B	99:1	47[d]
12	R^1 = Ph, R^2 = *n*Bu (**2l**)	A	91:9	88
		B	99:1	67

[a] Condition A: Using reaction conditions as mentioned in entry 6 of Table 1 (*n*-BuLi as a base). Condition B: using reaction conditions as mentioned in entry 13 of Table 1 (KHMDS as a base). [b] Diastereomeric ratios were determined by ^{19}F NMR of the crude reaction mixture. The isomeric ratios between **4′** and **4″** are 1:1−4:1 (see the Supporting Information). [c] Isolated yield. [d] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Based on these optimization results, we finally decided to choose the reaction conditions of entry 6 using *n*-BuLi as base (condition A) and entry 13 using KHMDS as base (condition B) as the standard to study the scope of nucleophilic monofluoromethylation of ketimines **2**. The results are shown in Table 2. A variety of structurally diverse (*R*)-*N*-*tert*-butylsulfinyl ketimines **2** were able to readily react with the pregenerated anion $PhSO_2CHF^-$ to give the corresponding chiral sulfinamide **4** in good to excellent yields and with high diastereoselectivity (up to 99:1). The reaction with sterically demanding ketimine **2k** also gave product **4k** (**4k** = **4k′** + **4k″**) in good yield and with satisfactory facial selectivity (Table 2, entries 11). When R^1 = phenyl and R^2 = *n*-butyl group, the ketimine **2l** still gave a high yield of product with excellent diastereoselectivity (entry 12). The absolute configurations of products **4a′** (entry 1) and **4k″** (entry 11) were determined by single-crystal X-ray analysis (see the Supporting Information), and the configurations of other products were assigned by analogy. It is particularly interesting that the stereocontrol mode of current diastereoselective (phenylsulfonyl)monofluoromethylation is completely opposite to the previously reported similar reactions with aldimines.[2−5] While the previously known fluoroalkylations of (*R*)-*N*-*tert*-butylsulfinyl aldimines prefer R_f^- species attacking the *Re* face of the aldimines (Scheme 2, TS-1), the current reaction with ketimines **2** prefers $PhSO_2CHF^-$

(7) Sorochinsky and co-workers examined the addition reaction between lithium diethyl difluoromethylphosphonate and the acetophenone-derived sulfinyl ketimine (with or without Lewis acid activation), and they found that the product yields (36−42%) were not satisfactory. See: Röschenthaler, G.-V.; Kukhar, V. P.; Belik, M. Y.; Mazurenko, K. I.; Sorochinsky, A. E. *Tetrahedron* **2006**, *62*, 9902–9910.

(8) *Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, 1999.

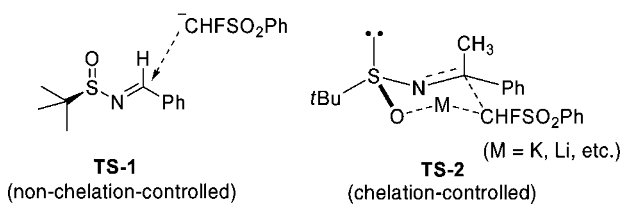
(9) The yields for eqs 1−4 were determined by ^{19}F NMR using internal standard. The reactant ratio for eq 1 was **2a**/Me_3SiCF_3/TBAT = 1:1.2:1.1, and the reactant ratios for eqs 2−4 were **2a**/**1**/base = 1:1.2:1.3.

(10) (a) Ni, C.; Li, Y.; Hu, J. *J. Org. Chem.* **2006**, *71*, 6829–6833. (b) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 786–789. (c) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713.

(11) Farnham, W. B. *Chem. Rev.* **1996**, *96*, 1633–1640. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786. (c) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930. (d) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481–2490.

species attacking the *Si* face of **2** (Scheme 2, TS-2). Although a full understanding of this unexpected "turn-over" of facial selectivity between the (phenylsulfonyl)monofluoromethylation of aldimines[5b] and ketimines **2** needs further study, we speculate that a cyclic six-membered transition state[13] TS-2 (rather than a nonchelation-controlled transition state TS-1 that was proposed for aldimine reactions[2−5]) may predominate in the current monofluoromethylation reaction with ketimines **2** (see Scheme 2).

Scheme 2. Depiction of the Transition States



As a comparison, we also examined the nucleophilic addition reaction between the pregenerated $PhSO_2CH_2Li$ and ketimine **2a** under the reaction condition A (Scheme 3, eq 5). It was found that the corresponding product **7** was obtained in 58% isolated yield with high diastereoselectivity. Single-crystal X-ray analysis showed that the absolute configuration of major isomer of product **7** is (*Rs,S*) (see Supporting Information), which indicates that the reaction proceeded via a similar cyclic transition state as above-mentioned ketimine reactions. The low chemical yield may be due to the α-deprotonation of ketimine **2a** caused by $PhSO_2CH_2^-$, which is a stronger base than $PhSO_2CHF^-$. It is also noteworthy to mention that we attempted a similar *pregeneration* protocol for the (phenylsulfonyl)difluoromethylation of ketimine **2a** (Scheme 3, eq 6), but no addition product **9** was formed (only partial decomposition of $PhSO_2CF_2H$ (**8**) was observed). These results clearly indicate that the thermal stability, good nucleophilicity, and relatively weak basicity of $PhSO_2CHF^-$ anion play important roles in the current efficient and highly stereoselctive (phenylsulfonyl)monofluoromethylation of ketimes **2**.

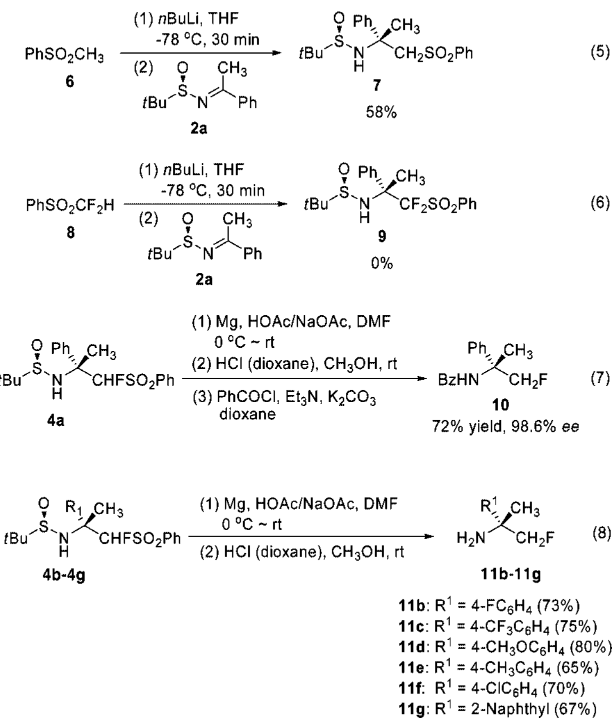
Upon reductive desulfonylation using Mg/HOAc/NaOAc reagent,[14] followed by acid-catalyzed alcoholysis and benzoylation, compound **4a** (from the reaction as shown in Table 2, entry 1, condition B) was successfully converted to benzamide derivative **10** (Scheme 3, eq 7). The high optical purity of **10** (98.6% ee) was determined by chiral HPLC, which confirms that the current monofluoromethylation methodology is reliable for the preparation of enantiomerically pure α,α-dibranched monofluoromethyl amines. Furthermore, (phenylsulfonyl)monofluoromethylated sulfinamides **4b−g** were also successfully converted to corresponding fluoromethyl amines **11b−g** in 65−80% isolated yields (Scheme 3, eq 8).

(12) Fluoromethyl phenyl sulfone ($PhSO_2CH_2F$) is commercially available, and it can also be prepared using known methods. 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.

(13) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallon, E. *Aldrichim. Acta* **2005**, *38*, 93–103. (d) Daniel, M.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8868–8905. (e) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831–840.

(14) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273–8277.

Scheme 3. Various Transformations



In summary, we have achieved the first efficient and highly diastereoselective synthesis of α,α-dibranched monofluoromethyl amines via nucleophilic monofluoromethylation of (*R*)-*N*-*tert*-butylsulfinyl ketimines. The pregeneration of $PhSO_2CHF^-$ anion from $PhSO_2CH_2F$ and a base plays a key role in this reaction, and the relatively high thermal stability and good nucleophilicity of $PhSO_2CHF^-$ anion account for the overall chemical outcome of the reaction. The stereocontrol mode of the current diastereoselective monofluoromethylation of ketimines is opposite to the other known nucleophilic fluoroalkylation of (*R*)-*N*-*tert*-butylsulfinyl aldimines, which suggests that a cyclic six-membered transition state is involved in the reaction.

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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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