Diastereoselective Trifluoromethylation of Chiral *N*-(Tolylsulfinyl)imines in the Presence of Lewis Bases

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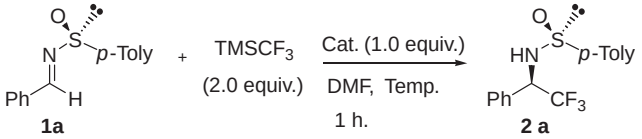
A diastereoselctive trifluoromethylation of chiral *N*-(tolylsulfinyl)imines with (trifluoromethyl)trimethylsilane in the presence of Lewis bases such as tetrabutylammonium acetate or phenoxide proceeded smoothly to afford the corresponding trifluoromethylated adducts in good yields.

The introduction of a trifluoromethyl group into organic molecules dramatically influences on the polarity, solubility, and biological activity of thus formed fluorinated compounds. Trifluoromethylated amines are important building blocks for biologically active drugs and agrochemicals, and also useful precursors for the synthesis of α-trifluoromethyl α-amino acid analogues. In spite of their usefulness in synthetic reaction, only a few examples have been reported on the syntheses of trifluoromethylated amines including chiral ones.[1–3] Prakash and coworkers reported on the nucleophilic addition of the trifluoromethyl group to chiral *N*-sulfinylimines, that is one of the most straightforward methods for syntheses of chiral trifluoromethylated amines.[4]

In our previous communication, a catalytic trifluoromethylation of various carbonyl compounds or imines with $TMSCF_3$ in the presence of lithium acetate was reported.[5] In order to demonstrate the utilities of these Lewis bases such as the acetate anion in synthetic reactions, the trifluoromethylation of chiral *N*-sulfinylimines, easily prepared from commercially available sulfinamide, was studied. In this communication, we would like to describe the trifluoromethylation of chiral *N*-sulfinylimine with $TMSCF_3$ under mild conditions by using a Lewis base such as AcON*n*-Bu_4.

In the first place, a trifluoromethylation of (*S*)-*N*-benzylidene-*p*-toluenesulfinamide **1a** with $TMSCF_3$ was tried in the presence of an equimolar amount of AcOLi at 0 °C in DMF and the desired product was obtained in moderate yield with low diastereoselectivity (Table 1). The effect of counter cations of the acetate was also examined in order to improve the yield and diastereoselectivity of the above reaction. As a result, it was found that the counter cations played important roles on yields and stereoselectivities of this reaction, and as the nucleophilicity of acetate anion increased, yield and diastereoselectivity of the adduct became higher (Entries 1–5). Further, various tetrabutylammonium salts were screened and reaction conditions were optimized in order to improve the diastereoselectivity (Entries 6–11). The corresponding trifluoromethylated adduct was obtained in high yield with good diastereoselectivity when the reaction was carried out by using an equimolar amount of tetrabutylammonium acetate (AcON-*n*-Bu_4) at −40 °C (Entry 8). On the other hand, the trifluoromethylation reactions did

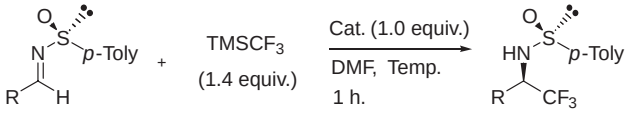
Table 1. Screening of catalysts



Entry	Cat.	Temp./°C	Yield/%[a]	$(S_S,R{:}S_S,S)$[b]
1	AcOLi	0	56	52:48
2	AcONa	0	68	46:54
3	AcOK	0	77	63:37
4	AcOCs	0	89	75:25
5	AcON-*n*-Bu_4	0	92	92:8
6	AcON-*n*-Bu_4	−20	97	95:5
7	AcON-*n*-Bu_4	−40	94	96:4
8	AcON-*n*-Bu_4	−40	93	96:4[c]
9	PhON-*n*-Bu_4	−40	87	94:6
11	$PhCO_2N$-*n*-Bu_4	−40	51	95:5
10	SuccinN-*n*-Bu_4[d]	−40	6	96:4
12	none	0	0	—

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Diastereomeric ratios were determined by ^{19}F NMR analysis. [c]1.4 equiv. of $TMSCF_3$ were used. [d]Tetrabutylammonium succinimide.

Table 2. Trifluoromethylation of various aldimines



Entry	R		Cat.	Temp./°C	Yield[a]/%	$(S_S,R{:}S_S,S)$[b]
1	C_6H_5	(**2a**)	AcON-*n*Bu_4	−40	91	96:4
2	4-$MeOC_6H_4$	(**2b**)	AcON-*n*Bu_4	−20	81	92:8[c,d]
3	4-MeC_6H_4	(**2c**)	AcON-*n*Bu_4	−40	90	95:5
4	2-ClC_6H_4	(**2d**)	AcON-*n*Bu_4	−40	92	96:4
5	3-ClC_6H_4	(**2e**)	AcON-*n*Bu_4	−40	93	95:5
6	4-ClC_6H_4	(**2f**)	AcON-*n*Bu_4	−40	94	95:5
7	4-BrC_6H_4	(**2g**)	AcON-*n*Bu_4	−40	94	94:6
8	1-Naphthyl	(**2h**)	AcON-*n*Bu_4	−40	92	96:4[c]
9	3-Pyridyl	(**2i**)	AcON-*n*Bu_4	−40	85	94:6
10	2-Furyl	(**2j**)	AcON-*n*Bu_4	−40	93	95:5
11	*t*-Bu	(**2k**)	AcON-*n*Bu_4	−40	91	96:4
12	*c*-C_6H_5	(**2l**)	PhON-*n*Bu_4	−40	75	95:5[e]
13	$PhCH_2CH_2$	(**2m**)	PhON-*n*Bu_4	−40	53	92:8[e]

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^{19}F NMR analysis. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis. [d]2.0 equiv. of $TMSCF_3$ were used. [e]The combined solution of imine and $TMSCF_3$ in DMF was added slowly to the DMF solution of PhON-*n*Bu_4.

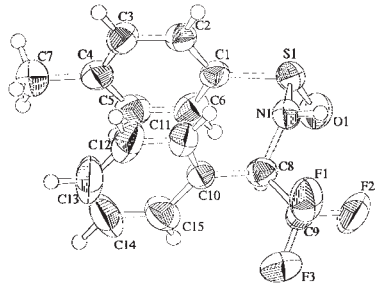
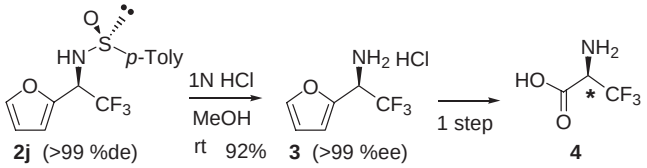


Figure 1. An ORTEP representation of the structure of **2a**.



Scheme 1. Synthesis of 3,3,3-Trifluoroalanine.

not proceed effectively when the reactions were tried by using $TMSCF_3$ in the presence of a catalytic amount of a Lewis base. The reason for these results is not made clear yet.

Next, the reaction of various chiral *N*-sulfinylimines with $TMSCF_3$ was tried by using an equimolar amount of AcON-*n*-Bu_4 in DMF (Table 2). Aromatic aldimines having electron-donating or -withdrawing groups reacted smoothly to afford the trifluoromethylated adducts in high yields with good diastereoselectivities (Entries 1–10). Aliphatic aldimine having no α-proton adjacent to the imino group reacted smoothly to afford the desired adduct in high yield whereas those having α-protons gave the adducts in low yields because the abstraction of an α-proton took place competitively (Entry 11). However, when the reactions were carried out in the coexistence of an equimolar amount of PhON-*n*-Bu_4, the corresponding trifluoromethylated adducts were obtained in moderate yields with good diastereoselectivities (Entries 12 and 13).

These trifluoromethylated adducts were easily purified by recrystallization of the crude mixture from hexane–AcOEt and, optically pure major diastereomers were obtained (Scheme 1).[6] The absolute configuration of newly formed stereogenic carbon was determined by X-ray analysis of compound **2a**[7] and the configurations of **2b** and **2m** were assigned by comparing ^{19}F NMR chemical shifts of **2a** with that of **2b** and **2m** (Figure 1).[8]

Thus, obtained amines were known as useful precursors for the synthesis of α-trifluoromethyl α-amino acids. Since Demir et al. reported that 2,2,2-trifluoro-1-(furan-2-yl)ethylamine **3** was converted into 3,3,3-trifluoroalanine **4** by oxidative cleavage of the furan ring (Scheme 1),[9] the synthesis of **3** implies a formal synthesis of 3,3,3-trifluoroalanine.[10]

It is noted that AcON-*n*-Bu_4 behaved as an effective Lewis base catalyst in trifluoromethylation of chiral *N*-sulfinylimines. This method is quite practical since the reaction proceeded by using mild and readily available Lewis base catalysts such as AcON-*n*-Bu_4 and PhON-*n*-Bu_4, and the adducts can be purified easily by crystallization because the catalyst is removed just by treating with water. Further study on this reaction is now in progress.

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References and Notes

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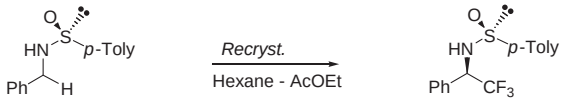
6 Recrystallization of compound **2a**.



7 Crystal data: $C_{15}H_{14}NOF_3S$ (FW = 313.34), monoclinic, $P2_1$, $a = 8.621(1)$ Å, $b = 8.315(1)$ Å, $c = 11.0901(8)$ Å, $\beta = 107.489(6)^\circ$, $V = 758.2(1)$ Å^3, $Z = 2.0$, $D_{calcd} = 1.372$ g cm^{-3}, $T = 295$ K. X-ray intensities were measured on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo Kα radiation. The final *R* factors was 0.052 ($Rw = 0.101$ for all data) for 1519 reflections with $I > 2\sigma(I)$.

8 Structure assignment of diastereomer was based on the ^{19}F NMR chemical shift, which resonates at a higher field in the (*Ss*,*R*)-isomer than in the (*Ss*,*S*)-isomer.

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10 Compound **3**: Determined by HPLC (CHIRALCEL OD-H, hexane/^{i}PrOH = 50:1, flow rate = 1.0 ml/min): ^{t}R = 11.3 min. $[\alpha]_D^{21} = -6.7$ (*c* 1.01, MeOH).

11 Typical experimental procedure is as follows (Table 2, Entry 1); to a stirred solution of AcON-*n*-Bu_4 (60.3 mg, 0.2 mmol) in DMF (1.0 mL) were added successively a solution of chiral *N*-benzylidene-*p*-toluenesulfinamide (48.7 mg, 0.2 mmol) in DMF (0.2 mL) and $TMSCF_3$ (43.7 µL, 0.28 mmol, 95% content) at -40 °C. The mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the resulted residue was purified by preparative TLC to give the desired product (57.1 mg, 91%) as a colorless prisms.

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