Diastereoselective Cyanomethylation of Chiral *N*-(*tert*-Butylsulfinyl)imines Promoted by Lewis Bases

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Cyanomethylation of chiral *N*-(*tert*-butylsulfinyl)imines with 2-trimethylsilylacetonitrile ($TMSCH_2CN$) in the presence of a Lewis base such as tetrabutylammonium phenoxide ($PhONn$-Bu_4) proceeds smoothly to afford the corresponding β-amino nitriles in good to high yields with excellent diastereoselectivities.

Chiral β-amino nitriles are known as the useful building blocks since they are easily converted into optically active β-amino acids or 1,3-diamines. These derivatives are useful for the preparations of chiral ligands, peptides, and of some natural products.[1] β-Amino nitriles are generally prepared by the Michael-type addition of primary and secondary amines to α,β-unsaturated nitriles:[2] however, the stereoselective reactions of this addition have not yet been reported. For the synthesis of optically active β-amino nitriles, ring-opening reactions of aziridine derivatives with metal cyanides such as NaCN, KCN, and TMSCN are practical though the chiral aziridines are essential for this reaction.[3] On the other hand, the stereoselective addition of a cyanomethyl group to imines is one of the direct methods for the synthesis of chiral β-amino nitriles, but it have not been reported.

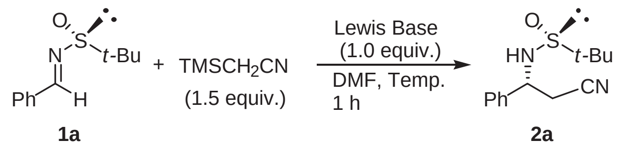
In our previous papers, it was shown that the nitrogen- or oxygen-containing anions generated from amides, imides, carboxylic acids, or alcohols behaved as effective Lewis base catalysts in the activation of trimethylsilyl (TMS) derivatives[4] and successful diastereoselective addition reactions of chiral *N*-sulfinimines such as trifluoromethylation, Strecker-type, and Mannich reactions were carried out in the presence of a Lewis base.[5]

Recently, cyanomethylation of carbonyl compounds or imines with $TMSCH_2CN$, which was carried out in the presence of AcOLi, was also reported from our laboratory.[6] In order to extend the utility of this reaction, diastereoselective cyanomethylation of chiral *N*-sulfinimines, that were easily prepared from commercially available sulfinamides, was considered since the sulfinyl group worked as an useful chiral auxiliary[7] to construct the adduct with the desired configuration if an appropriate chiral sulfinamide was chosen. Further, there was expected that the sulfinyl group would easily be removed from the product under mild acidic conditions. In this communication, we would like to report on diastereoselective cyanomethylation of chiral *N*-sulfinimines with $TMSCH_2CN$ by using Lewis bases such as $PhONn$-Bu_4.

In the first place, reactions of chiral *N*-sulfinimine **1a** with $TMSCH_2CN$ were tried in the presence of an equimolar amount of various Lewis bases in DMF (Table 1). When the Lewis base was absent, the cyanomethylated adduct was not detected (Entry 1). In the cases when AcOLi or AcONa was used, the desired product was obtained in low yields, respectively (Entries 2 and 3). The effect of counter cations of the acetate was further examined, and the yield of the adduct became higher as the nucleophilicity of the anion increased (Entries 4–6). In these cases, however, large amount of cynnamonitrile was formed as a by-product due to the β-elimination of the cyanomethylated adduct. In order to prevent this elimination, the reaction was next carried out at −20 °C and then both the yield and diastereoselectivity increased (Entry 7).

The effects of solvents were further examined in the presence of an equimolar amount of $PhONn$-Bu_4 (Table 2).

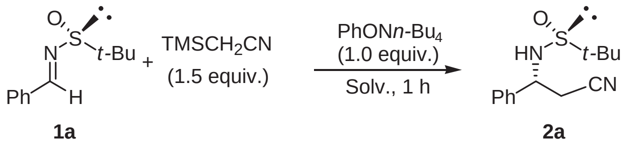
Table 1. Effects of Lewis bases



Entry	Lewis Base	Temp/°C	Yield[a]/%	(*Rs*/*R*) /(*Rs*/*S*)[b]
1	none	0	N.D.	—
2	AcOLi	0	trace	—
3	AcONa	0	7	93:7
4	AcOK	0	19	94:6
5	$AcONBu_4$	0	26	91:9
6	$PhONBu_4$	0	28	92:8
7	$PhONBu_4$	-20	69	98:2

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^1H NMR analysis.

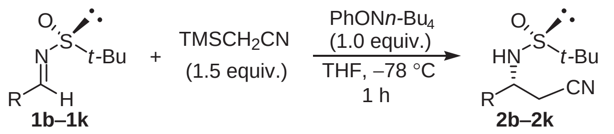
Table 2. Effects of solvents



Entry	Solv.	Temp/°C	Yield[a]/%	(*Rs*/*R*) /(*Rs*/*S*)[b]
1	CH_2Cl_2	−20	26	96:4
2	Toluene	−20	51	93:7
3	Et_2O	−20	55	96:4
4	THF	−20	85	97:3
5	THF	−45	88	97:3
6	THF	−78	94	98:2
7[c]	THF	−78	61	98:2

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^1H NMR analysis. [c]0.6 equiv. of $PhONn$-Bu_4 were used.

Table 3. Cyanomethylation of various chiral sulfinimines



Entry	R		Yield^a/%	(Rs/R) $/(Rs/S)^b$
1	2-ClC_6H_4	(**2b**)	95	90:10
2	3-ClC_6H_4	(**2c**)	95	94:6
3	4-ClC_6H_4	(**2d**)	93	96:4
4	4-MeC_6H_4	(**2e**)	92	99:1
5	4-$MeOC_6H_4$	(**2f**)	79	>99:1
6	1-Naphthyl	(**2g**)	90	>99:1
7	2-Furyl	(**2h**)	88	97:3
8	3-Pyridyl	(**2i**)	93	88:12
9	*t*-Bu	(**2j**)	88	>99:1
10	*c*-Hex	(**2k**)	22	96:4

^{a}Isolated yield. ^{b}Diastereomeric ratios were determined by ^{1}H NMR analysis.

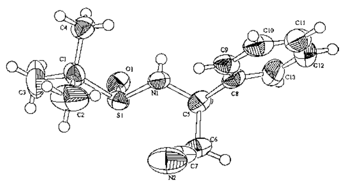


Figure 1. An ORTEP representation of the structure of **2a**.

The corresponding product was afforded in moderate to good yields with high diastereoselectivities when the reactions were carried out at $-20\,°C$ in the above solvents (Entries 1–4). It was then found that THF is the most suitable solvent, and that the yield was improved at lower temperature (Entries 4 and 5). Further, the undesirable β-elimination of the product was completely prevented as shown in Entry 6 when the reaction was carried out at $-78\,°C$ and the best result was obtained.[8] In addition, the reactions proceeded to give **2a** depending on the amount of the Lewis base (Entry 7). Thus, it is noted that the reaction did not proceed catalytically.

Then, reactions of various chiral *N*-sulfinimines and $TMSCH_2CN$ by using an equimolar amount of PhON*n*-Bu_4 were tried (see Table 3). Aromatic chiral *N*-sulfinimines having electron-donating or electron-withdrawing groups reacted smoothly with $TMSCH_2CN$ to afford the adducts in good to high yields with high diastereoselectivities (Entries 1–8). Similarly, aliphatic chiral *N*-sulfinimine having no protons at α-position of imino group reacted as smoothly as well to afford the desired adduct (Entry 9) while the substrate having an α-proton gave the poor result because of the deprotonation that took place under the conditions (Entry 10). These cyanomethylated adducts were easily purified by recrystallization from hexane–AcOEt, and optically pure major diastereomers were obtained.[9]

The absolute configration of newly formed stereogenic carbon of compound **2a** was determined by X-ray analysis (Figure 1).[10] Configurations of **2b**–**2k** were assigned by comparing ^{1}H NMR chemical shifts of **2a** with that of **2b**–**2k**.

Thus, a diastereoselective cyanomethylation by the addition between chiral *N*-sulfinimines and $TMSCH_2CN$ in the presence of Lewis bases such as PhON*n*-Bu_4 proceeded smoothly to afford the chiral β-amino nitriles with high diastereoselectivities. It is noted that the chiral β-amino nitriles with the desired configurations were easily constructed by choosing an appropriate chiral auxiliary.

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References and Notes

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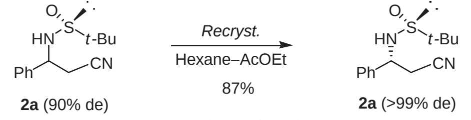
8 Typical experimental procedure is as follows (Table 2, Entry 6): To a stirred solution of PhON*n*-Bu_4 (100.7 mg, 0.30 mmol) and (*R*)-*N*-benzylidene-*tert*-butylsulfinamide (**1a**) (62.8 mg, 0.30 mmol) in THF (3.0 mL) were added $TMSCH_2CN$ (61 µL, 0.45 mmol) at $-78\,°C$. The reaction mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 1/1) to give the desired product (70.3 mg, 94%) as a white solid.

9 Recrystallization of **2a**.



10 Crystal data: $C_{13}H_{18}N_2OS$ (fw 250.36), orthorhombic, $P2_12_12_1$, $a = 13.524(2)$, $b = 16.554(2)$, $c = 6.286(2)$ Å, $V = 1407.2(6)$ Å^3, $Z = 4.0$, $D_{calcd} = 1.182\,g\,cm^{-3}$, $T = 295$ K. X-ray intensities were measured on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.710690$ Å). The final *R* factors was 0.045 ($Rw = 0.179$ for all data) for 2547 reflections with $I > 2\sigma(I)$.