Lewis Base-catalyzed Diastereoselective Strecker-type Reaction between Trimethylsilyl Cyanide and Chiral Sulfinimines

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(Received February 4, 2005; CL-050161)

Lewis base-catalyzed diastereoselective Strecker-type reaction between trimethylsilyl cyanide and chiral sulfinimines derived from commercially available (*S*)-(+)-*p*-toluenesulfinamide and aliphatic aldehydes proceeded smoothly by using a catalytic amount of tetra-*n*-butylammonium acetate in DMF to afford the corresponding α-amino nitriles with (*Ss*,*R*)-configurations in good to high yields and diastereoselectivities.

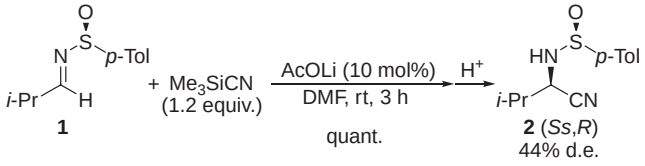
The Strecker-type reaction between trimethylsilyl cyanide (TMSCN) and an imine is one of the most important tools for the construction of α-amino nitriles which are important synthetic precursors of α-amino acids.[1] This reaction is generally performed via activation of the acceptor imines with Lewis acid and the various methods have been reported.

It was already shown that trimethylsilyl (TMS) enolates were activated with mild Lewis base catalysts such as nitrogen and oxygen containing organic-anions generated from amides, imides, or carboxylic acids. And they worked as promoters of aldol,[2] Michael,[3] and Mannich-type[4] reactions. These Lewis bases also worked as useful catalysts for the Strecker-type reaction[5] between *N*-tosylaldimines and TMSCN.

The chiral sulfinimines are obtained easily from aldehyde and chiral sulfinamide and the sulfinyl group is used as an excellent chiral auxiliary because it is easily removed from the product under mild acidic conditions after the reaction.[6] Recently, Hou and co-workers reported that Strecker-type reaction between chiral sulfinimines and TMSCN proceeded in the presence of a stoichiometric amount of cesium fluoride (CsF) to afford α-amino nitriles in good selectivity.[1o]

In this communication, we would like to report on a catalytic Strecker-type reaction between chiral sulfinimines and TMSCN by using the oxygen-containing anion generated from a carboxylic acid as a Lewis base.

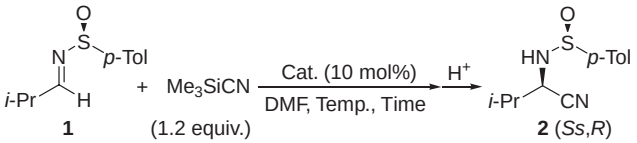
In the first place, Lewis base-catalyzed Strecker-type reaction between TMSCN and chiral sulfinimine **1** was tried in the presence of 10 mol % of AcOLi in DMF (Scheme 1). The reaction proceeded smoothly at room temperature in DMF and the corresponding α-amino nitriles **2** (*Ss*,*R*), the precursors of non-natural *D*-amino acids, were afforded as major products in quantitative yields with 44% d.e. On the contrary, the above reaction did not proceed in the absence of catalyst. This indicates that AcOLi is an effective Lewis base catalyst to promote the Strecker-type reaction when sulfinimines are employed as an acceptor. Concerning the reaction of a chiral sulfinimine, Hou and co-workers reported that α-amino nitrile having (*Ss*,*S*)-configuration was obtained as a major product when **1** was used in the presence of a stoichiometric amount of CsF.[1o,7]



Scheme 1.

In order to improve the selectivity of this Strecker-type reaction, catalysts and the reaction conditions were screened. The reaction by using various catalysts afforded the corresponding α-amino nitrile **2** (Table 1) and these results concerning reactivities are similar to our previously reported Lewis base-catalyzed Strecker-type reaction.[5] When the reaction was carried out at -45 or $-60\,^{\circ}$C by using AcOLi, the adduct **2** was obtained in high yields with good selectivities (Entries 2 and 4). The reaction completed within 2 h with the selectivity similar to that obtained by combined use of a catalytic amount of AcOLi and 100 mol % of AcOLi at $-45\,^{\circ}$C (Entry 3). Various catalysts such as AcOK, $PhCO_2Li$, potassium salt of phthalimide, AcON*n*-Bu_4, and $PhCO_2N$*n*-Bu_4 turned out to be effective ones in accelerat-

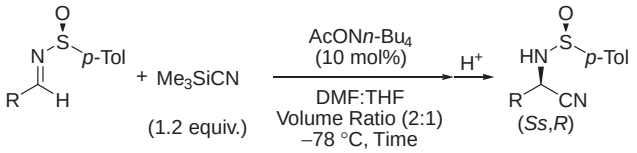
Table 1. Optimization of conditions on the Strcker-type reaction

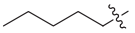


Entry	Catalyst	Temp. /°C	Time /h	Yield[a] /%	d.e. /%
1	—	–45	24	n.d.[b]	—
2	AcOLi	–45	6	97	72
3	AcOLi	–45	2	97[c]	72
4	AcOLi	–60	6	93	74
5	AcOK	–45	6	92	70
6	AcOCs	–45	6	85	64
7	Phthalimide-K[d]	–45	6	92	70
8	$PhCO_2Li$	–45	6	92	74
9	AcON*n*-Bu_4	–45	6	96	72
10	AcON*n*-Bu_4	–45	6	quant.[e]	34
11	$PhCO_2N$*n*-Bu_4	–45	6	81	70
12	AcON*n*-Bu_4	–60	6	88	76
13	AcON*n*-Bu_4	–78	12	quant.[f]	82
14	AcON*n*-Bu_4	–78	12	quant.[f,g]	82

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]n.d.; not detected. [c]100 mol % of AcOLi was used. [d]Potassium salt of phthalimide. [e]THF was used instead of DMF. [f]THF:DMF (Volume ratio 1:2) was used instead of DMF. [g]5 mol % of AcON*n*-Bu_4 was used.

Table 2. Strecker-type reaction using AcON*n*–Bu_4 with various chiral sulfinimines in DMF



Entry	R	Time /h	Yield[a] /%	d.e. /%
1		12	quant.	86
2		24	94	82
3		8	97	80
4		24	quant.	84
5		24	97	84
6		12	n.d.[b,c]	—

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]n.d.; not detected. [c]97% of starting chiral sulfinimine was recovered.

ing the present Strecker-type reaction and the selectivities were nearly the same as those of using AcOLi in DMF at −45 °C. The selectivities decreased, on the other hand, to 64 or 34% d.e. when the reactions were carried out by using AcOCs in DMF or AcON*n*-Bu_4 in THF, respectively. Further, it was found that the desired product **2** was afforded in quantitative yields with high selectivities when 10 mol % of AcO*n*–NBu_4 was used at −78 °C in a mixed solvent of THF-DMF (Entry 13).[8] Similarly, the above reaction proceeded smoothly to give the adducts when 5 mol % of AcO*n*-NBu_4 was used (Entry 14).

The reactions of TMSCN with various chiral sulfinimines were tried by using 10 mol % of AcON*n*-Bu at −78 °C (Table 2). The chiral sulfinimines having a bulky substituent such as *tert*-butyl or cyclohexyl group also reacted smoothly with TMSCN to afford the corresponding α-amino nitriles in high yields with high selectivities (Entries 1 and 2).[1o] Further, when the chiral sulfinimines derived from *n*-hexanal, *n*-butyraldehyde, or isovaleraldehyde were used, the corresponding adducts were afforded with high selectivities without accompanying their isomerizations to the corresponding enamines (Entries 3–5).[1o] The corresponding α-amino nitrile was not detected in the case where aromatic chiral sulfinimine was used (Entry 6).

It is noted that this method is quite useful because it is practically applicable to the syntheses of various *D*-amino acids. And the above catalysts have good advantages from environmental point of view because of their low toxicity and they are easy to be disposed without special treatment. Further extension of this reaction is now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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7 NMR data of these compounds [**2** (*Ss*,*R*), **2** (*Ss*,*S*)] were consistent with the data reported in Ref. 1o.

8 Typical experimental procedure is as follows (Table 1, Entry 13): to a stirred solution of AcON*n*-Bu_4 (6.0 mg, 0.02 mmol) in THF (0.4 mL) were added successively a solution of TMSCN (23.8 mg, 0.24 mmol) in DMF (0.4 mL) and a solution of fleshly prepared *N*-sulfinimine **1** (41.9 mg, 0.2 mmol) in DMF (0.4 mL) at −78 °C.

Published on the web (Advance View) March 19, 2005; DOI 10.1246/cl.2005.604