

# Magnesium-tartramide complex mediated asymmetric Strecker-type reaction of nitrones using cyanohydrin

メタデータ	言語: eng
	出版者:
	公開日: 2017-10-03
	キーワード (Ja):
	キーワード (En):
	作成者:
	メールアドレス:
	所属:
URL	<a href="https://doi.org/10.24517/00010577">https://doi.org/10.24517/00010577</a>

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 International License.



# Magnesium-Tartramide Complex Mediated Asymmetric Strecker-Type Reaction of Nitrones Using Cyanohydrin<sup>†</sup>

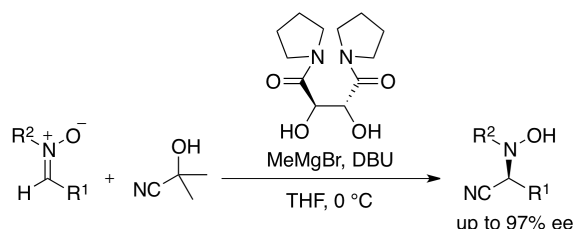
Takahiro Sakai, Takahiro Soeta, Kohei Endo, Shuhei Fujinami, Yutaka Ukaji\*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192, Japan

ukaji@staff.kanazawa-u.ac.jp

Received Date (will be automatically inserted after manuscript is accepted)

## ABSTRACT



An asymmetric Strecker-type reaction of nitrones using acetone cyanohydrin as a source of HCN has been realized. A magnesium-tartramide complex, generated from (*R,R*)-2,3-dihydroxy-1,4-di(pyrrolidin-1-yl)-butane-1,4-dione and MeMgBr, promoted transcyanation from the bromomagnesium salt of the cyanohydrin in the presence of a catalytic amount of DBU to afford the corresponding optically active (*S*)- $\alpha$ -amino nitrile derivatives. The reaction was applicable to various nitrones giving with high-to-excellent enantioselectivities.

The asymmetric hydrocyanation of imino compounds, known as the Strecker reaction, is an indispensable synthetic procedure for producing optically active  $\alpha$ -amino nitriles,<sup>1,2</sup> which are very important precursors of

natural and non-natural  $\alpha$ -amino acids, 1,2-diamines, and intermediates for several transformations.<sup>2a,3</sup> For all these reasons, the asymmetric Strecker reaction is attractive to many organic chemists, and numerous variants have been reported that use HCN or TMSCN as the cyanide source. Due to their toxicity, volatility, and hazardous handling, alternative cyanide sources are in high demand.

<sup>†</sup> This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40<sup>th</sup> anniversary of the Mukaiyama aldol reaction.

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, 75, 27–45.

(2) Reviews: (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, 29, 359–373. (b) Yet, L. *Angew. Chem., Int. Ed.* **2001**, 40, 875–877. (c) Gröger, H. *Chem. Rev.* **2003**, 103, 2795–2827. (d) Spino, C. *Angew. Chem., Int. Ed.* **2004**, 43, 1764–1766. (e) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491–1508. (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, 45, 1520–1543. (g) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, 107, 4584–4671. (h) Shibasaki, M.; Kanai, M.; Mita, T. *Org. React.* **2008**, 70, 1–119. (i) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, 42, 1117–1127. (j) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, 65, 1219–1234. (k) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, 111, 2626–2704. (l) Wang, J.; Liu,

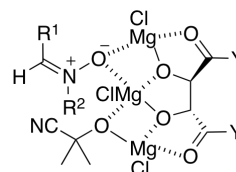
X.; Feng, X. *Chem. Rev.* **2011**, 111, 6947–6983. Recent examples: (m) Liu, Y.-L.; Shi, T.-D.; Zhou, F.; Zhao, X.-L.; Wang, X.; Zhou, J. *Org. Lett.* **2011**, 13, 3826–3829. (n) Uemura, M.; Kuroono, N.; Ohkuma, T. *Org. Lett.* **2012**, 14, 882–885. (o) Shao, Y.-D.; Tian, S.-K. *Chem. Commun.* **2012**, 48, 4899–4901. (p) Seayad, A. M.; Ramalingam, B.; Chai, C. L. L.; Li, C.; Garland, M. V.; Yoshinaga, K. *Chem. Eur. J.* **2012**, 18, 5693–5700. (q) Saravanan, S.; Sadhukhan, A.; Khan, N.-u. H.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *J. Org. Chem.* **2012**, 77, 4375–4384.

(3) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, 58, 148–162.

Furthermore, the preparation of chiral auxiliaries for these reactions is often difficult. In order to overcome the former problem, alternative inexpensive cyanide sources have been employed, such as *n*-Bu<sub>3</sub>SnCN,<sup>4</sup> Et<sub>2</sub>AlCN,<sup>5</sup> (EtO)<sub>2</sub>P(O)CN,<sup>6</sup> EtOCOCN<sup>20,24,7</sup> and CH<sub>3</sub>COCN.<sup>8</sup> Among such cyanide compounds, acetone cyanohydrin is a simple, stable, easy to handle, and readily available cyanide source.<sup>9</sup> We have already developed a Strecker-type reaction of nitrones using acetone cyanohydrin as a cyanide source by treatment with *n*-BuMgCl.<sup>10,11</sup> Among the imine analogues, nitron appears to be a promising candidate since it possesses an electronegative oxygen that can coordinate strongly to metals.<sup>12,13</sup>

We have previously investigated asymmetric nucleophilic addition reactions of nitrones based on the design of a multi-nucleating reaction system utilizing tartaric acid esters.<sup>14</sup> Herein, we will describe an asymmetric Strecker-type reaction with nitrones using acetone cyanohydrin as a cyanide source mediated by a magnesium-tartramide complex.

**Figure 1.** Original Design of Asymmetric Strecker-Type Reaction Utilizing Tartaric Acid Derivative



- (4) (a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186–3188. (b) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766.
- (5) (a) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-h. *J. Org. Chem.* **1996**, *61*, 440–441. (b) Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1513–1516.
- (6) Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, *20*, 4663–4666.
- (7) (a) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 15118–15119. (b) Kadam, S. T.; Thirupathi, P.; Kim, S. S. *Synthesis* **2011**, 919–923.
- (8) (a) Pan, S. C.; Zhou, J.; List, B.; *Angew. Chem., Int. Ed.* **2007**, *46*, 612–614. (b) Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149–1151. (c) Kanemitsu, T.; Toyoshima, E.; Miyazaki, M.; Nagata, K.; Itoh, T. *Heterocycles* **2010**, *81*, 2781–2792.
- (9) (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869–9872. (b) Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 5759–5762.
- (10) Sakai, T.; Soeta, T.; Inomata, K.; Ukaji, Y. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 231–235.
- (11) Transcyanation from cyanohydrin to carbonyl compounds promoted by metallic reagents: (a) Mori, A.; Kinoshita, K.; Osaka, M.; Inoue, S. *Chem. Lett.* **1990**, 1171–1172. (b) Mori, A.; Inoue, S. *Chem. Lett.* **1991**, 145–148. (c) Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H.; Maruoka, K. *Tetrahedron* **2001**, *57*, 867–873. (d) Watanabe, A.; Matsumoto, K.; Shimada, Y.; Katsuki, T. *Tetrahedron Lett.* **2004**, *45*, 6229–6233. (e) Yanagisawa, A.; Matsumoto, T.; Kushiara, N.; Yoshida, K. *Adv. Synth. Catal.* **2010**, *352*, 2918–2922.
- (12) (a) Breuer, E. In *Nitrones, Nitronates and Nitroxides*; Patai, S.; Rappoport, Z. Eds.; John Wiley & Sons, Inc: Chichester, 1989, Chaps. 2 and 3. (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381. (c) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695–713. (d) Merino, P. C. *R. Chim.* **2005**, *8*, 775–788. (e) Topić, D.; Aschwanden, P.; Fässler, R.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 5329–5330. (f) Grigor'ev, I. A. In *Nitrones: Novel Strategies in Synthesis, in Nitrite Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H. Ed.; John Wiley & Sons, Inc: New Jersey, **2008**, Chap. 2.
- (13) Strecker-type reactions of nitrones: (a) Tsuge, O.; Urano, S.; Iwasaki, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 485–489. (b) Gössinger, E. *Monatsh. Chem.* **1982**, *113*, 495–508. (c) Shatzmiller, S.; Shalom, E.; Lidor, R.; Tartkovski, E. *Justus Liebig's Ann. Chem.* **1983**, 906–912. (d) Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049–1052. (e) Padwa, A.; Koehler, K. F. *Chem. Commun.* **1986**, 789–790. (f) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 6469–6472. (g) Merino, P.; Tejero, T.; Revuelta, J.; Romero, P.; Cicchi, S.; Mannucci, V.; Brandi, A.; Goti, A. *Tetrahedron: Asymmetry* **2003**, *14*, 367–379. (h) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235–4238. (i) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929–2947.
- (14) (a) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A. Inomata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 447–452. (b) Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733–736. (c) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075–1087. (d) Wei, W.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2006**, *35*, 176–177. (e) Konishi, A.; Wei, W.; Kobayashi, M.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2007**, *36*, 44–45. (f) Wei, W.; Hamamoto, Y.; Ukaji, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2008**, *19*, 476–481. (g) Wei, W.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Heterocycles* **2009**, *78*, 717–724. (h) Ukaji, Y.; Inomata, K. *Chem. Rec.* **2010**, *10*, 173–187.

**Table 1.** Asymmetric Strecker-Type Reaction with **1a** Promoted by Bis(chloromagnesium)salt of Tartaric Acid Derivatives

entry	Y	solvent	t (h)	yield (%)	ee (%) <sup>a</sup>
1	Oi-Pr	THF	26	76	0
2	NMe <sub>2</sub>	THF	21	71	14
3	NBn <sub>2</sub>	THF	48	99	11
4	NPh <sub>2</sub>	THF	44	93	17
5	pyrrolidinyl	THF	44	70	44
6	piperidinyl	THF	21	84	–3
7	morpholinyl	THF	25	72	0
8	pyrrolidinyl	DME	45	57	24
9	pyrrolidinyl	Et <sub>2</sub> O	45	12	3
10	pyrrolidinyl	toluene	20	53	4
11	pyrrolidinyl	CH <sub>2</sub> Cl <sub>2</sub>	20	81	18
12	pyrrolidinyl	MeCN	21	42	38

<sup>a</sup>Enantioselectivity was determined by HPLC analysis (Daicel CHIRALPAK IA).

First, the asymmetric Strecker-type reaction of (*Z*)-*N*-(benzylidene)benzylamine *N*-oxide (**1a**) was examined with acetone cyanohydrin (**2**) based on our general design of the multi-nucleating chiral reaction system as depicted in Figure 1.<sup>14c,14h</sup> Thus, a mixture of **2** and diisopropyl (*R,R*)-tartrate was treated with 3.0 equiv of *n*-BuMgCl in THF at 0 °C followed by the addition of **1a**. The reaction gave  $\alpha$ -hydroxylamino nitrile **3a** in 76% yield; however, no chiral induction was observed (Table 1, entry 1). With a view to promoting strong coordination of the carbonyl

oxygen in the tartaric acid moiety to magnesium metal and/or for sterical bulkiness, the tartramide was employed instead of the tartaric acid ester.<sup>15</sup> By the use of *N,N,N',N'*-tetramethyl-*(R,R)*-tartramide, a slight enantiofacial differentiation was realized (entry 2). Several tartramides were then probed. Although tetrabenzyl- and tetraphenyltartramides showed low levels of enantioselection (entries 3 and 4), an amide derived from pyrrolidine, 2,3-dihydroxy-1,4-di(pyrrolidin-1-yl)-butane-1,4-dione (BTMTA),<sup>16</sup> enhanced the enantioselectivity to 44% ee (entry 5). Amides derived from piperidine and morpholine showed little stereoselection (entries 6 and 7). Next, the effect of solvent was examined using BTMTA. Among the ethereal solvents examined, THF was better than DME and Et<sub>2</sub>O (entries 5, 8, and 9). Less polar solvents, toluene and CH<sub>2</sub>Cl<sub>2</sub>, showed lower enantioselectivities (entries 10 and 11). While the reaction in MeCN gave the product in slightly lower 38% ee (entry 12), the reaction did not proceed in much polar solvents, DMF and DMSO.

In our previous work,<sup>10</sup> gradual generation of the chloromagnesium salt of cyanohydrin by the use of 0.2 equiv of *n*-BuMgCl made the reaction proceed smoothly. When the transcyanation was performed with 2.2 equiv of *n*-BuMgCl, enantioselectivity was improved, although the chemical yield decreased (Table 2, entry 1). With only 2.0 equiv of *n*-BuMgCl, transcyanation did not occur (entry 2). When 0.2 equiv of TMEDA was employed as an extra organic base in addition to 2.0 equiv of *n*-BuMgCl, **3a** was obtained with enhanced chemical and optical yields (entry 3). The reaction using other organic bases also gave **3a** in good enantioselectivities, though chemical yields were not enhanced (entries 4 and 5). DBU was the base of choice to give **3a** with 92% ee in moderate chemical yield (entry 6). Finally, in order to examine the effect of the Lewis acidity of the magnesium salt, MeMgBr instead of *n*-BuMgCl was used. The chemical yield was enhanced up to 80% without any remarkable decrease in enantioselectivity (entry 7).<sup>17</sup>

The influence of the substituents on the nitrogen atom of the nitrones was investigated next and *N*-benzyl nitrone **1a** showed higher enantioselectivity than *N*-methyl and *N*-phenyl nitrones **1b** and **1c** (Table 3, entries 1–3). Although the addition reaction to a *N*-diphenylmethyl nitrone **1d** was sluggish, a cyanated product **3d** was obtained with excellent enantioselectivity (entry 4). The asymmetric Strecker-type reaction of various *N*-benzyl nitrones **1** was performed with 1.0 equiv of acetone cyanohydrin (**2**) utilizing 1.0 equiv of *(R,R)*-BTMTA as a chiral auxiliary by the treatment of 2.0 equiv of MeMgBr

**Table 2.** Reaction Conditions for Asymmetric Strecker-Type Reaction to Nitrone **1a**

entry	RMgX	base	<i>t</i> (h)	yield (%)	ee (%) <sup>a</sup>
1 <sup>b</sup>	<i>n</i> -BuMgCl	<i>n</i> -BuMgCl	39	15	79
2 <sup>b</sup>	<i>n</i> -BuMgCl	--	21	nr	--
3 <sup>c</sup>	<i>n</i> -BuMgCl	TMEDA	21	49	87
4 <sup>c</sup>	<i>n</i> -BuMgCl	Et <sub>3</sub> N	45	31	86
5 <sup>c</sup>	<i>n</i> -BuMgCl	DTBMP <sup>d</sup>	45	13	73
6 <sup>c</sup>	<i>n</i> -BuMgCl	DBU	45	50	92
7 <sup>c</sup>	MeMgBr	DBU	22	80	89

<sup>a</sup>Enantioselectivities were determined by HPLC analysis (Daicel CHIRALPAK IA). <sup>b</sup>To a mixture of *(R,R)*-BTMTA and **2** was added *n*-BuMgCl at 0 °C. After 1 h, the nitrone **1a** was added. <sup>c</sup>To a mixture of *(R,R)*-BTMTA and **2** was added RMgX at 0 °C. After 1 h, base and **1a** was successively added. <sup>d</sup>2,6-Di(*t*-butyl)-4-methylpyridine.

**Table 3.** Asymmetric Strecker-Type Reaction of Nitrones **1**

entry	R <sup>1</sup>	R <sup>2</sup>	<i>t</i> (h)	yield (%)	ee (%) <sup>a</sup>	
1	Ph	Bn	<b>a</b>	22	80	89
2	Ph	Me	<b>b</b>	21	47	72
3	Ph	Ph	<b>c</b>	21	6	63
4	Ph	Ph <sub>2</sub> CH	<b>d</b>	21	58	96
5	4-(MeO)C <sub>6</sub> H <sub>4</sub>	Bn	<b>e</b>	21	72	90
6	4-ClC <sub>6</sub> H <sub>4</sub>	Bn	<b>f</b>	21	75	96
7	4-BrC <sub>6</sub> H <sub>4</sub>	Bn	<b>g</b>	23	63	96
8	1-Nap	Bn	<b>h</b>	41	89	85
9	2-Nap	Bn	<b>i</b>	41	73	96
10	Me	Bn	<b>j</b>	4	95	79
11	Me	Ph <sub>2</sub> CH	<b>k</b>	2	94	97
12	<i>c</i> -Hex	Bn	<b>l</b>	6	97	73
13	<i>c</i> -Hex	Ph <sub>2</sub> CH	<b>m</b>	21	87	90
14	<i>t</i> -Bu	Bn	<b>n</b>	22	90	87
15	<i>t</i> -Bu	Ph <sub>2</sub> CH	<b>o</b>	21	88	93

<sup>a</sup>Enantioselectivities were determined by HPLC analysis (Daicel CHIRALPAK IA).

(15) Asymmetric reactions using tartramides: (a) Ukaji, Y.; Soeta, T.; In *Comprehensive Chirality*, Carreira, E. M.; Yamamoto, H. Eds. Elsevier, Amsterdam, 2012, Section. 3.6.4. One of the most successful examples: (b) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

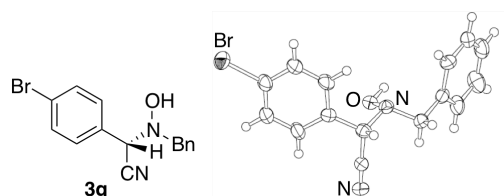
(16) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559–3572. BTMTA is an abbreviation derived from an alternative name, *N,N,N',N'*-bis(tetramethylene)tartramide.

(17) When 0.1 and 0.4 equiv of DBU were used, chemical yield was decreased to 55% and 73%, respectively, with the same 89% ee.

and 0.2 equiv of DBU. In the case of aromatic nitrones, most of the  $\alpha$ -hydroxylamino nitrile derivatives **3e–3i** were obtained in over 90% ee (entries 5–9). The Strecker-type reaction of aliphatic nitrones proceeded faster than that of aromatic nitrones to give the cyanated products with lower but still good enantioselectivities (entries 10, 12, and 14). In the case of aliphatic nitrones, a diphenylmethyl substituent on the nitrogen improved the stereoselection to afford the adducts in high chemical yields with excellent enantioselectivities up to 97% (entries 11, 13, and 15).

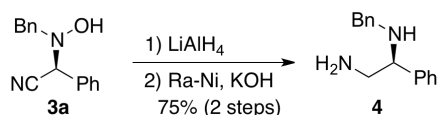
The absolute configuration of **3g** was determined to be *S* by X-ray crystallographic analysis of its single crystal (Figure 2). The absolute configurations of other products were tentatively determined to also be *S*.

**Figure 2.** X-ray Structure of **3g** (Flack parameter = 0.03)



The obtained product **3a** (90% ee) was readily converted to a diamine **4** by sequential reduction (Scheme 1). The absolute stereochemistry of **4** was confirmed to be also *S* by comparison of the specific rotation of the obtained product ( $[\alpha]_D^{25} +57$  ( $c$  0.91,  $\text{CCl}_4$ ) [lit.<sup>18</sup> (*S*)-isomer:  $[\alpha]_D^{23} +62$  ( $c$  1,  $\text{CCl}_4$ )].<sup>19</sup>

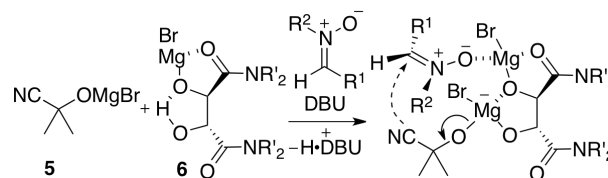
**Scheme 1.** Conversion of **3a** to a Diamine **4**



Although the precise reaction mechanism is not yet clear, one possible reaction pathway is shown in Scheme 2. When **2** and (*R,R*)-BTMTA are treated with 2 equiv of  $\text{MeMgBr}$ , bromomagnesium salts **5** and **6** are formed. By the addition of 0.2 equiv of DBU, deprotonation from **6** might occur to furnish a tartramide-magnesium ate complex, to which the nitrone **1** coordinates. The subsequent transcyanation proceeds from the *re*-face of the nitrone to afford the product **3** with preference for the

(*S*)-enantiomer. However, the effect of amide substituents is still not well-elucidated.

**Scheme 2.** A Possible Reaction Pathway



In conclusion, the magnesium-tartramide complex mediated asymmetric Strecker-type reaction of nitrones using acetone cyanohydrin has been developed. Various types of nitrones were applicable to this reaction. The present method is very simple and avoids using dangerous cyanide sources such as  $\text{HCN}$  and  $\text{TMSCN}$ . Furthermore, both enantiomers of  $\alpha$ -amino nitrile derivatives, which are versatile synthetic intermediates, are readily synthesized because both enantiomers of BTMTA are easily prepared from commercially available (*R,R*)- and (*S,S*)-diethyl tartrates in one step.<sup>16</sup> Further studies on this reaction are in progress in our laboratory.

**Acknowledgment.** The present work was financially supported in part by a Grant-in-Aid for Scientific Research (B) (No. 24350022) from the Japan Society for the Promotion of Science (JSPS) and an Adaptable and Seamless Technology Transfer Program through Target-driven R&D (No. AS242Z02711Q) from the Japan Science and Technology Agency (JST).

**Supporting Information Available.** Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(18) Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3747–3757.

(19) (*R*)-Antipode **4** was reported to be used as a building block for the exploration of drugs which could have anxiolytic or hypnotic activities: Horwell, D. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Aranda, J. *Eur. Pat. Appl.* **1991**, EP 405537 A1.