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On-Step Synthesis of a Bifunctional BINOL Ligand for the Highly Enantioselective Cyanation of Aliphatic Aldehydes

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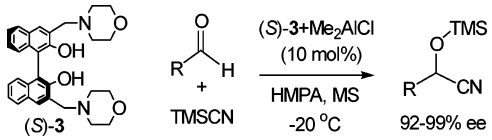
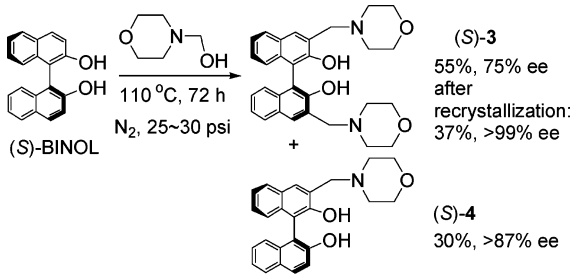
ABSTRACT

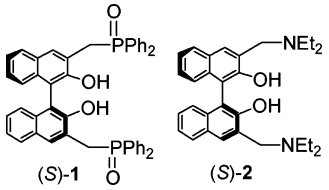


An efficient one-step synthesis of the optically active bifunctional BINOL ligand (*S*)-3 has been developed. It was found that (*S*)-3 in combination with Me_2AlCl is a highly enantioselective catalyst for the addition of TMSCN to aliphatic aldehydes of diverse structures and is also among the most practical ones. A remarkable positive nonlinear effect was found for this chiral ligand.

In recent years, a number of 1,1′-bi-2-naphthol (BINOL)-based bifunctional chiral catalysts that contain both Lewis acidic and basic sites have been successfully applied in asymmetric reactions.[1−3] For example, the aluminum complexes of chiral ligands (*S*)-**1**[2a] and (*S*)-**2**[2b] have been used to catalyze the enantioselective reaction of aldehydes with trimethylsilylcyanide (TMSCN) to generate the synthetically useful chiral cyanohydrins. These bifunctional ligands require either a six-step synthesis from the optically active BINOL[2a] or optical resolution in a multistep synthesis from a naphthalene derivative.[2b] Although the synthesis of the 3,3′-bis(alkylaminomethyl)-substituted BINOLs from the reaction of BINOL with α-alkoxyamines was reported by Cram et al.,[4] the high temperature of this reaction (160 °C) prohibited the preparation of the optically active ligands. Herein, we wish to report an efficient one-step synthesis of the optically active 3,3′-bismorpholinomethyl-substituted BINOL (*S*)-**3** (Scheme 1) and its application in the highly enantioselective cyanohydrin synthesis.

Scheme 1. One-Step Synthesis of the Optically Active (*S*)-**3**





As shown in Scheme 1, we conducted the direct reaction of (*S*)-BINOL with morpholinomethanol.[5] This one-step

(1) For a review of bifunctional chiral catalysts: Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882.
(2) (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. (b) Casas, J.; Náera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589−2592.
(3) (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *J. Chem. Soc., Chem. Commun.* **2002**, *18*, 1989−1999. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1641−1644.
(4) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930−1946.

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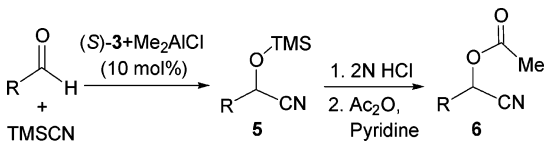
reaction at 110 ± 2 °C under ~30 psi nitrogen produced the optically active (*S*)-**3** with 55% yield and 75% ee. Separation of the racemic crystals from the solution in CH_2Cl_2/CH_3OH (3:1) led to the optically pure (*S*)-**3** (>99% ee, 37% from BINOL). The specific optical rotation of (*S*)-**3** was $[\alpha]_D$ −152.1 (*c* 1.0, CH_2Cl_2). At lower temperatures, a much longer reaction time was needed, and lower yields were achieved; higher temperatures led to the completely racemized product. The side product of this reaction was the monomorpholinomethyl-substituted compound (*S*)-**4**, which could be converted to (*S*)-**3** by further treatment with morpholinomethanol.

With the readily available (*S*)-**3**, we examined the use of its aluminum complex in the catalytic asymmetric reaction of TMSCN with aldehydes (Scheme 2). The silyl ether

Scheme 2. Asymmetric Reaction of Aldehydes with TMSCN Catalyzed by (*S*)-**3**+Me_2AlCl



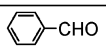
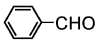
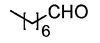
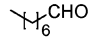
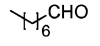
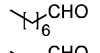
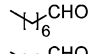
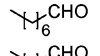
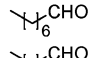
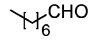
product (**5**) of this reaction was converted to the acetate **6** for ee determination with a GC−β-cyclodextrin column. Applying the conditions developed by Saá and co-workers for (*S*)-**2**,[2b] we first tested the use of (*S*)-**3** for the reaction of benzaldehyde with TMSCN in the presence of Me_2AlCl (Table 1, entry 1). This gave an excellent result (95% ee) similar to the use of (*S*)-**2**. We also found that changing the additive Ph_3PO to HMPA greatly accelerated this reaction while still maintaining the high enantioselectivity (Table 1, entry 2).

Although (*S*)-**2** was previously reported to be highly enantioselective for the reaction of aromatic aldehydes with TMSCN, it gave much lower ees for the reaction of *aliphatic* aldehydes.[2b] For example, even at −40 °C, (*S*)-**2** catalyzed the addition of TMSCN to heptaldehyde with only 66% ee. In general, very few catalysts could give consistently good results for the asymmetric reaction of *aliphatic* aldehydes with TMSCN despite a good number of highly enantioselective catalysts for the reaction of aromatic aldehydes.[2,6,7]

Therefore, we explored the application of (*S*)-**3** for the asymmetric reaction of *aliphatic* aldehydes with TMSCN. In entries 3−10 of Table 1, the results for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**3** and Me_2AlCl under various conditions are summarized. In these reactions, HMPA replaced Ph_3PO as the additive because it offered a higher reaction rate. In toluene solution, (*S*)-**3** showed up to 91% ee for this reaction (entry 3). Changing the solvent to THF reduced the ee (entry 4). In diethyl ether, however, a significant enhancement in ee was observed (97% ee, entry 5). Without the additive HMPA, a somewhat lower ee was observed (entry 6). Absence of molecular sieves led to a large reduction in enantioselectivity (entry 7). The room temperature reaction gave a lower but still significant ee (entry 8). Increasing the amount of molecular sieves at room temperature greatly decreased the enantioselectivity even with the increased amount of the chiral catalyst (entry 9). Changing the solvent to hexanes at room temperature diminished the enantioselectivity (entry 10).

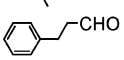
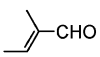
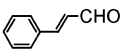
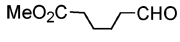
We applied the optimized conditions of entry 5 in Table 1 for the reaction of a variety of aliphatic aldehydes with TMSCN. As the results summarized in Table 2 show, in the

Table 1. Asymmetric Addition of TMSCN to Benzaldehyde and Octyl Aldehyde in the Presence of (*S*)-**3** and Me_2AlCl[a]

entry	aldehyde	solvent	4Å MS	*t*(h)	ee (%)
1[b]		Toluene	5mg	48	95
2		Toluene	5mg	24	94
3		Toluene	5mg	24	91
4		THF	5mg	24	87
5		**Et_2O**	**5mg**	**24**	**97**
6[c]		Toluene	5mg	24	82
7		Toluene	None	24	46
8[d]		Et_2O	5mg	3	76
9[d,e]		Et_2O	15mg	4	31
10[d]		Hexane	5mg	24	6

[a] Following procedure was used unless otherwise indicated: (*S*)-**3** (0.025 mmol, 10 mol %), 4 Å molecular sieves, and Me_2AlCl (10 mol %, 1 M in hexanes) in a solvent (1 mL) were stirred under nitrogen at room temperature for 3 h. The mixture was then combined with the additive HMPA (40 mol %) and cooled to −20 °C. TMSCN (3.0 equiv) and an aldehyde were added. [b] Ph_3PO was used as the additive. [c] No additive. [d] Reaction at room temperature. [e] Performed with 20 mol % (*S*)-**3** and 20 mol % Me_2AlCl.

Table 2. Asymmetric Addition of TMSCN to Aliphatic Aldehydes in the Presence of (*S*)-**3** and Me_2AlCl

entry	aldehyde[a]	isolated yield (%)[b]	ee (%)[b]
1		91	97
2		92	98
3		87	96
4		90	99
5		65	97
6		72	96
7		86	95
8		70	98
9		74	94
10		67	96
11		90	92

[a] Freshly distilled. [b] For the acetates **6**.

presence of (*S*)-**3** (10 mol %) and Me_2AlCl (10 mol %), high enantioselectivities have been achieved for the reactions of TMSCN with diverse aliphatic aldehydes, including linear (entries 1−3), branched (entries 4−7), α,β-unsaturated (entries 8 and 9), and functionalized substrates (entries 10 and 11). The absolute configurations of the products from hydrocinnamaldehyde and cinnamaldehyde were determined to be *R* by comparing their optical rotations with those in the literature.

The effect of the optical purity of (*S*)-**3** on the ee of the asymmetric cyanation product was studied. A large positive nonlinear effect was observed for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**3** and Me_2AlCl (Figure 1). As shown in Figure 1, a chiral ligand of only 40% ee could generate the product of the same high ee as that by the ligand of high optical purity. This finding further demonstrates the practical value of this chiral ligand and its efficient one-step synthesis. The remarkable nonlinear effect also indicates that the catalytic process may involve intermolecularly aggregated Al complexes.

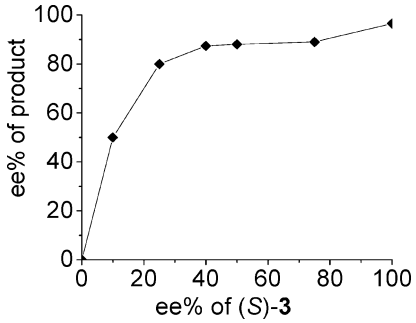


Figure 1. Correlation of the ee of (*S*)-**3** and that of its catalytic product from the reaction of octyl aldehyde with TMSCN.

When (*S*)-**3** was treated with Me_2AlCl in toluene-d_8, the ^1H NMR spectrum showed a complete disappearance of the signals of the ligand accompanied with the formation of a white precipitate, indicating the aggregation of the produced aluminum complexes. A singlet at δ 0.16 in the spectrum was attributed to methane generated from the protonation of Me_2AlCl by the chiral ligand. Further mechanistic study will be conducted in order to better understand the catalysis by (*S*)-**3**.

We tested the use of the optically pure 3-monosubstituted BINOL ligand (*S*)-**4** to catalyze the reaction of TMSCN with both benzaldehyde and octyl aldehyde. Under the same conditions as the use of (*S*)-**3**, only diminished enantioselectivity was observed (7−20% ee). Thus, both the 3,3′-morpholinomethyl substituents of (*S*)-**3** are very important for the observed high enantioselectivity.

In summary, we have developed an efficient one-step synthesis of the optically active bifunctional BINOL ligand (*S*)-**3**. We have discovered that (*S*)-**3** in combination with Me_2AlCl is a highly enantioselective catalyst for the addition of TMSCN to aliphatic aldehydes of diverse structures and is also among the most practical ones. A remarkable positive nonlinear effect was found for this chiral ligand.

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Supporting Information Available: Synthesis and characterization of (*S*)-**3**, (*S*)-**4**, and the catalytic reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Morpholinomethanol was in situ generated from the addition of morpholine to paraformaldehyde. 2,2′-Biphenol was reacted with morpholinomethanol: Fabris, F.; Lucchi, O. D.; Lucchini, V. *J. Org. Chem.* **1997**, *62*, 7156−7164. (b) A partially hydrogenated BINOL was reacted with morpholinomethanol: Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427−7430.

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