# A New Bifunctional Asymmetric Catalysis: An Efficient Catalytic Asymmetric Cyanosilylation of Aldehydes

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Developing efficient asymmetric catalytic addition reactions to carbonyl compounds is an intensely studied area.[1] The catalysis by chiral Lewis acids activating the electrophile is among the most successful approaches.[1] Recently, chiral Lewis bases coordinating to and activating silylated nucleophiles have been introduced into this field.[2] We have been involved in developing a new asymmetric catalyst from the concept of multifunctional catalysis,[3] whereby activation of substrates and nucleophiles occurs simultaneously at the Lewis acid and the Brönsted base moieties in the catalyst, thus affording high enantioselectivities in a variety of reactions. Therefore, it seemed rational to design a new bifunctional asymmetric catalyst consisting of Lewis acid and Lewis base moieties, which activate both electrophiles and nucleophiles at defined positions simultaneously.[4] Using this concept, we designed the chiral Lewis acid−Lewis base catalyst **1**. We assumed that the aluminum would work as a Lewis acid to activate the carbonyl group, and the oxygen atom of the phosphine oxide would work as a Lewis base to activate the silylated nucleophiles.[5,6] We report herein that catalyst **1** is a highly efficient catalyst for the cyanosilylation[7] of aldehydes with broad generality, affording products in excellent chemical yields and excellent enantioselectivities.
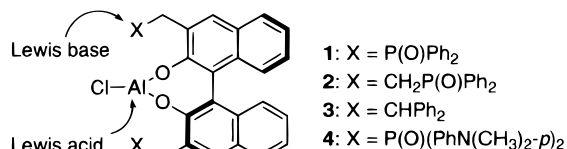
(1) (a) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(2) (a) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998,** *120,* 12990−12991. (b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998,** *120,* 6419−6420. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998,** *39,* 2767−2770.

(3) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 1236−1256.

(4) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998,** *37,* 1986−2012. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991,** *30,* 49−69. (c) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991,** 541−544.

(5) We have found that phosphine oxides promote the cyanosilylation of aldehydes: TMSCN reacted with **5a** to give **6a** in 81% yield in the presence of 40 mol % of Bu₃P(O) *at ambient temperature* for 7.5 h. In the absence of Bu₃P(O), the yield was 12% under the same conditions. *At −40 °C for 40 h,* however, the reaction did not proceed at all.

(6) As phosphines catalyze the cyanosilylation of aldehydes (Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991,** 537−540), we first investigated 3,3′-phosphinomethylnaphthol (X = PPh₂). However, the naphthol moieties of this ligand were partly silylated during the reaction, whereas catalyst **1** was stable against silylation under the reaction conditions.

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One of the key issues for designing a Lewis acid−Lewis base catalyst is how to prevent the internal complexation of these moieties. Molecular modeling studies suggested that **1** would avoid such a problem, because the coordination of the Lewis base, attached to the 3,3′-position of the binaphthol, to the internal aluminum seemed to be torsionally unfavorable. When considering **2**, however, which has an ethylene linker, the internal coordination seemed to be quite stable without strain. In accordance with this expectation, the reaction of TMSCN with benzaldehyde **5h**, catalyzed by **2** (9 mol %), proceeded slowly at −40 °C (37 h) and gave the cyanohydrin **6h** in only 4% yield after hydrolysis. In this case, strong intramolecular coordination of the phosphine oxide should reduce the Lewis acidity of the aluminum, therefore diminishing the catalytic efficiency of **2**. However, a solution of **1** (9 mol %), **5h**, and TMSCN, at −40 °C (37 h), afforded **6h** in 91% yield. Therefore, in the case of **1**, the intramolecular binding of the phosphine oxide to the aluminum seems to be labile enough to allow coordination of the aldehyde to the aluminum. Conversion of **6h** to the corresponding ethoxy-carbonate, followed by chiral HPLC analysis, revealed that **6h** had 87% ee.[8] The absolute configuration was determined to be *S* by optical rotation.[7d]

Encouraged by the result of benzaldehyde with catalyst **1**, we next investigated the reaction of aliphatic aldehydes. Surprisingly, aliphatic aldehydes afforded very low ee values: **5a** gave *S*-**6a** in 90% yield and in 9% ee; **5c** gave *S*-**6c** in 80% yield and in 25% ee.[8] We anticipated that there would be competition between two reaction pathways in the case of the more reactive aliphatic aldehydes. The desired pathway involves the dual interaction between the Lewis acid and the aldehyde and between the Lewis base and TMSCN, whereas the undesired pathway involves mono-activation by the Lewis acid. We assumed that these two pathways could differ more significantly if the Lewis acidity of the catalyst was decreased, and so we investigated the effect of additives which coordinate to the aluminum to reduce its Lewis acidity. Moreover, the additive could change the geometry of aluminum from tetrahedral to trigonal bipyramidal,[9] which should allow the phosphine oxide to exist in a more favorable position relative to the aldehyde. After several attempts, we found that electron donating phosphine oxides had a beneficial effect on ee.[10,11] In the case of **5a**, the ee values of **6a** significantly increased from 9% to 41% and 56% by the addition of 36 mol % of CH₃P(O)-Ph₂ and Bu₃P(O), respectively. Further improvement of ee (up to 97%) was achieved by the slow addition of TMSCN (10 h), via syringe pump, in the presence of Bu₃P(O) (Table 1, entry 1). In the case of **5h**, however, addition of Bu₃P(O) resulted in a very sluggish reaction, affording only a trace amount of the product. However, the reaction proceeded in 98% yield and in 96% ee in the presence of CH₃P(O)Ph₂ (entry 7). Therefore, we used Bu₃P-(O) as the additive for aliphatic and α,β-unsaturated aldehydes, and CH₃P(O)Ph₂ as the additive for aromatic aldehydes.

This catalyst is practical and has a broad generality with respect to the variety of aldehydes that can be used (Table 1).[12] Since cyano groups can be easily converted into carboxyl groups, this

(8) The products of the opposite configuration were generally obtained by **3** (9 mol %) (−40 °C, 37 h): **5g** gave *R*-**6g** (50% yield and 12% ee); **5a** gave *R*-**6a** (56% yield and 10% ee); **5c** gave *R*-**6c** (36% yield and 4% ee) with **3**.

(9) (a) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997,** *119,* 5754−5755. (b) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997,** *119,* 11713−11714.

(10) Addition of ether, dimethyl sulfoxide, Hünig base, or acetonitrile gave lower ee values. Since the reaction pathway involving activation by the external phosphine oxide is negligible at −40 °C (ref 5), only an internal phosphine oxide can function as an activator of TMSCN, because the phosphine oxide exists at the appropriate position close to TMSCN in the reactive complex.

(11) The reaction rate in the presence of the additive phosphine oxide is slower than that in the absence of the additive (the relative reaction rate; $k_{\text{additive}}/k_{\text{no-additive}} = 0.6$, in the reaction of **6a** in the presence or absence of Bu₃P(O)), as expected from the lower Lewis acidity.

Table 1.   Asymmetric Cyanosilylation of Aldehydes Catalyzed by **1**[a]

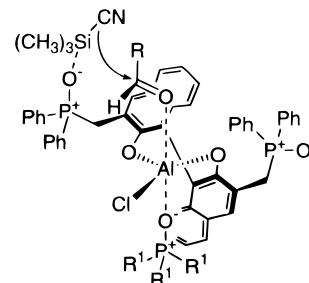| entry	R	aldehyde	product	additive	h	yield/%[b]	ee/%[c]	*S/R*
1	$Ph(CH_2)_2$	**5a**	**6a**	$Bu_3P(O)$	37	97	97	*S*
2	$CH_3(CH_2)_5$	**5b**	**6b**	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	**5c**	**6c**	$Bu_3P(O)$	45	96	90	*S*
4	$(CH_3CH_2)_2CH$	**5d**	**6d**	$Bu_3P(O)$	60	98	83	*S*
5	*trans*-$CH_3(CH_2)_3CH=CH_2$	**5e**	**6e**	$Bu_3P(O)$	58	94	97	$-$[g]
6	$PhCH=CH$	**5f**	**6f**	$Bu_3P(O)$	40	99	98	*S*
7[d]	(thiazole structure)	**5g**	**6g**	$Bu_3P(O)$	36	91	97	$-$[g]
8[e]	Ph	**5h**	**6h**	$CH_3P(O)Ph_2$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	**5i**	**6i**	$CH_3P(O)Ph_2$	79	87	90	*S*
10[f]	(furyl structure)	**5j**	**6j**	$CH_3P(O)Ph_2$	70	86	95	*S*

[a] The method for preparation of the catalyst and the general procedure of the reaction, see ref 12. TMSCN (1.8 equiv) was added over 10 h via syringe pump unless otherwise mentioned. [b] Isolated yield. [c] Determined by HPLC analysis. Configuration assigned by comparison to literature values of optical rotation. See Supporting Information. [d] 20 mol % of **1** and 80 mol % of the additive were used. [e] TMSCN (1.2 equiv) was added dropwise over 1 min. [f] 18 mol % of **1** and 72 mol % of the additive were used. [g] The absolute configuration was not determined.

catalytic asymmetric process is an efficient entry to access chiral α-hydroxy carboxylic acids, which consitute one of the most synthetically useful chiral building blocks.

Although more detailed investigations of the reaction mechanism are currently underway, preliminary kinetic studies, using catalyst **4** which contains a more electron-rich phosphine oxide, seem to support the dual Lewis acid−Lewis base activation pathway. The initial reaction rate with **4** (10 mol %) is 1.2 times faster than that with **1** (10 mol %) ($k_4/k_1 = 1.2$), reflecting the higher Lewis basisity of the phosphine oxide in the reaction of **6a** in the presence of $Bu_3P(O)$ (40 mol %).[13] Thus, the enantio-selctivity of the reaction catalyzed by **1** may be explained by the working model depicted in Figure 1, with the external phosphine oxide coordinating to the aluminum, thus giving a pentavalent aluminum. This geometry would allow the aldehyde to position itself at the apical site close to the internal phosphine oxide.

Figure 1.

TMSCN, interacting with the internal phosphine oxide, could then transfer cyanide to the aldehyde thus giving the observed *S*-product.

In summary, we have shown that a new Lewis acid−Lewis base bifunctional catalyst is highly efficient in the cyanosilylation of aldehydes. This concept could provide a guide for designing new asymmetric catalysts for the reaction of a variety of nucleophiles, including silylated ones, with carbonyl compounds.

Supporting Information Available: Experimental details for the synthesis of **1** and **4**, ee analysis of compounds **6a−6j**, and kinetic studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Procedure**: To a stirred solution of a well-dried achiral phosphine oxide (69 µmol) in CH_2Cl_2 (0.1 mL) was added Et_2AlCl (18 µL, 17.28 µmol, 0.96 M in hexane) at room temperature, followed by the addition of the chiral ligand (13 mg, 18.2 µmol) in CH_2Cl_2 (0.35 mL). The resulting mixture was stirred for 1 h at room temperature and cooled to −40 °C. After the addition of an aldehyde (0.192 mmol), TMSCN (46 µL, 0.346 mmol) was slowly added over 10 h. After the time shown in Table 1, 2 N HCl (1.0 mL) was added to hydrolyze the product. The crude cyanohydrin was purified by flash chromatography on silica gel.

(13) By the one-portion addition of TMSCN, catalyst **4** (10 mol %) gave *S*-**6g** in 86% yield and in 68% ee in the presence of $Bu_3P(O)$ (40 mol %) (−40 °C for 36 h), whereas **1** gave *S*-**6g** in 60% yield and in 56% ee under the same conditions.