Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 566–573

Catalytic asymmetric cyano-phosphorylation of aldehydes using a YLi_3tris(binaphthoxide) complex (YLB)

Noriyuki Yamagiwa, Yumi Abiko, Mari Sugita, Jun Tian, Shigeki Matsunaga* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan

Received 9 November 2005; accepted 21 December 2005
Available online 10 March 2006

Abstract—A highly enantioselective cyano-phosphorylation of aldehydes catalyzed by a YLi_3tris(binaphthoxide) complex YLB **1** is described. The slow addition of diethyl cyanophosphonate **4** to aldehydes **5** in the presence of YLB **1** (10 mol %), H_2O (30 mol %), tris(2,6-dimethoxyphenyl)phosphine oxide **3a** (10 mol %), and BuLi (10 mol %) afforded cyanohydrin *O*-phosphates **6** in up to 98% yield and 97% ee. Mechanistic studies revealed that the addition of cyanide to aldehydes is irreversible and determines the enantioselectivity. The reaction mechanism is also discussed in detail.
© 2006 Elsevier Ltd. All rights reserved.

1. Introduction

The catalytic asymmetric cyanation reaction of carbonyl compounds is one of the most powerful tools available for supplying useful chiral building blocks. Much effort, therefore, has been devoted to develop asymmetric catalysis to realize the enantioselective cyanation reaction of aldehydes and prochiral ketones.[1] Although various methods have been developed over the last two decades, $(CH_3)_3SiCN$ (TMSCN) and/or HCN are the most often used cyanide sources to afford cyanohydrins and their TMS ethers. The intrinsic instability of cyanohydrins and their TMS ethers, however, is sometimes problematic for further transformations. Therefore, the development of a one-pot cyanation-O-protection reaction with a stable protecting group is desirable. To address this issue, Deng,[2] our group,[3] Nájera and Saá,[4] North and Belokon',[5] and Moberg[6] recently developed a catalytic asymmetric cyano-ethoxycarbonylation reaction of aldehydes[3–6] and ketones[2] using ethyl cyanoformate **2** as the cyanide source, affording the chiral cyanohydrin *O*-carbonates in one pot. In our system, the YLi_3tris(binaphthoxide) complex[7–9] YLB **1** (Fig. 1) effectively promoted the reaction in the presence of three additives; H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide **3a**, and BuLi. The cyanohydrin *O*-carbonates were obtained in high yields (up to 100% yield) and ees (up to 98% ee).[3]

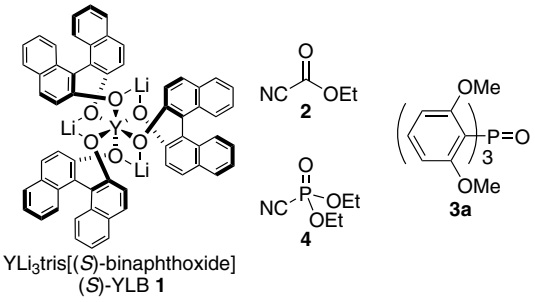


Figure 1. Structures of YLi_3tris(binaphthoxide) YLB **1**, ethyl cyanoformate **2**, tris(2,6-dimethoxyphenyl)phosphine oxide **3a**, and diethyl cyanophosphonate **4**.

To extend the utility of our catalyst system, we investigated the use of other cyanide sources. Cyanohydrin *O*-phosphate is a useful building block in pesticides.[10] Although efficient one-pot racemic syntheses of cyanohydrin *O*-phosphate were reported over two decades ago, in which diethyl cyanophosphonate **4** was used as the cyanide source,[11] enantioselective variants are still limited. Recently, Nájera and Saá et al. reported a catalytic asymmetric cyano-phosphorylation reaction using a chiral aluminum catalyst.[12] We also presented a preliminary report of a catalytic asymmetric cyano-phosphorylation reaction of aldehydes using YLB **1**.[13]

* Corresponding authors. Tel.: +81 3 5684 0651; fax: +81 3 5684 5206 (M.S.); e-mail addresses: smatsuna@mol.f.u-tokyo.ac.jp; mshibasa@mol.f.u-tokyo.ac.jp

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.12.038

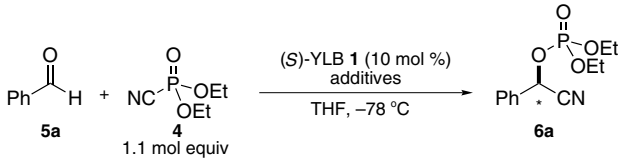
Cyanohydrin *O*-phosphates were obtained in up to 97% yield and 97% ee. Herein, we report in full detail the catalytic asymmetric cyano-phosphorylation reaction. The reaction mechanism is also discussed.

2. Results and discussion

2.1. Catalytic asymmetric cyano-phosphorylation of aldehydes

Initially, we applied the optimized conditions for the catalytic asymmetric cyano-ethoxycarbonylation reaction[3] to the cyano-phosphorylation reaction. Compound (*S*)-YLB **1** (10 mol %) with H_2O (30 mol %), $Ar_3P(O)$ **3a** (10 mol %), and BuLi (10 mol %) promoted the reaction of aldehyde **5a** and **4** at −78 °C, affording cyanohydrin *O*-phosphate **6a** in 66% yield and 86% ee, together with the corresponding cyanohydrin (11% yield) (Table 1, entry 1). The results, as shown in entries 2–4, suggested that all three additives [H_2O, $Ar_3P(O)$ **3a**, and BuLi] were essential for good enantioselectivity. During the optimization studies, we encountered reproducibility problems in terms of both reactivity and selectivity. We hypothesized that **4** would partially decompose YLB complex **1**, because **4** is a good phosphorylating reagent of phenolic OH groups.[14] Moreover, excess **4** would also prevent the interaction of $Ar_3P(O)$ **3a** with the active catalyst, because of structural similarities. Thus, **4** was added slowly to maintain a low concentration of **4** throughout the reaction. As shown in entry 5, both the chemical yield and enantiomeric excess were improved when **4** was added slowly over 1 h to the reaction mixture at −78 °C. Cyanohydrin *O*-phosphate **6a** was obtained in 97% yield and 92% ee after 2 h under the optimized conditions.

Table 1. Optimization of reaction conditions

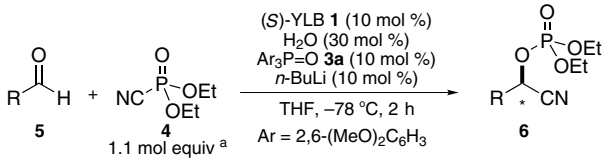


Entry	Additive (mol %)			Time (h)	Yield (%)	ee (%)
	H_2O	Ar_3P=O **3a**	BuLi			
1[a]	30	10	10	1	66	86
2	0	10	10	4	58	19
3	30	0	10	4	54	29
4	30	10	0	4	63	75
5[b]	30	10	10	2	97	92

[a] 11% of cyanohydrin was obtained.
[b] Compound **4** was slowly added over 1 h.

The scope and limitations of the substrates are summarized in Table 2. In all entries, the reactions were performed at −78 °C for 2 h, with the slow addition of **4** over 1 h. Aromatic aldehydes gave high yields (95–98%) and good enantiomeric excesses (81–93% ee) (entries 1–4). Linear and branched aliphatic aldehydes (entries 5–8) also gave good chemical yields (82–90%) and good enantiomeric excesses (82–97% ee). Aldehyde **5h** gave the highest enantioselectivity amongst the aldehydes examined (97% ee, entry 8). On the other hand, aldehyde **5i** gave **6i** in moderate enantioselectivity, probably due to steric factors (entry 9). α,β-Unsaturated aldehydes **5j** gave **6j** in only 24% ee (entry 10), although a high enantiomeric excess was obtained in the cyano-ethoxycarbonylation reaction of **5j** (100% yield, 91% ee).[3] We assumed that product **6j** would competitively inhibit the desirable interaction of $Ar_3P(O)$ **3a** with the catalyst, resulting in low ee.

Table 2. Catalytic asymmetric cyano-phosphorylation of various aldehydes



Entry	Aldehyde (R)		Product	Yield (%)	ee (%)
1	C_6H_5–	**5a**	**6a**	97	92
2	4-$CH_3C_6H_4$–	**5b**	**6b**	98	93
3	2-Naphthyl–	**5c**	**6c**	98	81
4[b]	1-Naphthyl–	**5d**	**6d**	95	89
5[b]	*n*-C_6H_{11}–	**5e**	**6e**	90	92
6	$C_6H_5CH_2CH_2$–	**5f**	**6f**	83	82
7	$(CH_3)_2CH$–	**5g**	**6g**	82	96
8	*c*-C_6H_{11}–	**5h**	**6h**	82	97
9	$C_6H_5CH_2C(CH_3)_2$–	**5i**	**6i**	81	76
10	*trans*-C_6H_5CH=CH–	**5j**	**6j**	71	24

[a] Compound **4** was slowly added over 1 h.
[b] Tris(2,4,6-trimethoxyphenyl)phophine oxide **3c** was used instead of **3a**.

2.2. Mechanistic studies

2.2.1. Effects of H_2O. Our previous NMR studies of the YLB **1** complex in the presence and absence of H_2O revealed that the anhydrous-YLB and YLB-H_2O complexes are in equilibrium (Fig. 2).[3c,7c] Aspinall et al. reported the X-ray crystallographic structure of both $[Li(Et_2O)]_3[Eu(binol)_3]$ (anhydrous-EuLB) and $[Li(Et_2O)]_3[Eu(binol)_3(H_2O)]$ (EuLB-H_2O).[8] The anhydrous-EuLB has nearly D_3-symmetry, while EuLB-H_2O has bent C_3-symmetry due to the coordination of H_2O with the europium metal center. H_2O is thought to be effective for finely tuning the chiral environment of the europium complex. We assumed that H_2O would coordinate with the yttrium metal center of YLB **1** in solution and have effects similar to those observed in the europium complex. Based on the coordination number (CN = 6 or 7) of rare earth–alkali metal heterobimetallic complexes observed *in crystal structures*,[15] only one H_2O molecule would coordinate with the yttrium.

2.2.2. Generation of LiCN. The present cyano-phosphorylation reaction of aldehydes is postulated to proceed via the same active species as that in the cyano-ethoxycarbonylation reaction using the same YLB **1**.[3] Based on our previous mechanistic studies,[3c] LiCN **7** is the key nucleophilic species generated in the reaction

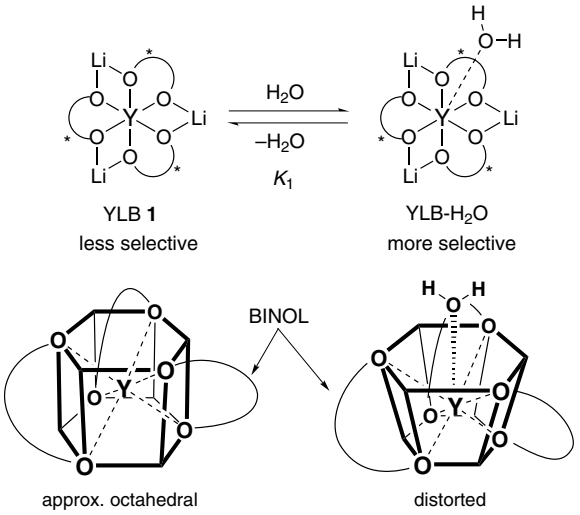
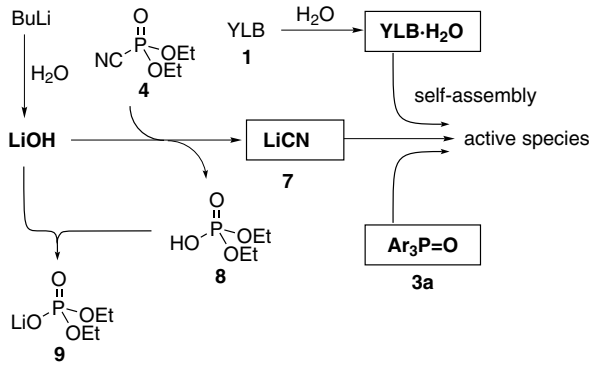


Figure 2. Effects of H_2O as seventh ligand on the structure of YLB **1**.

mixture. As shown in Scheme 1, LiOH generated from BuLi and H_2O reacts with the cyanide source **4** to generate LiCN **7**, and the co-product **8**. The active species of the asymmetric cyanation reaction would consist of YLB **1**-H_2O, LiCN **7**, and phosphine oxide **3a**. The co-product **8** had an acidic OH group, which reacted with LiOH to generate lithium salt **9**. Therefore, only half the amount of LiOH was transformed to LiCN **7** while the other half was consumed to neutralize **8**.

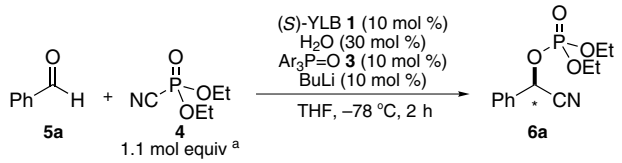


Scheme 1. Postulated mechanism to generate LiCN and active species.

To avoid wasting half of the LiOH, we examined acetone cyanohydrin as an initiator to generate LiCN, because a catalytic amount of acetone cyanohydrin effectively improved the reaction rate and enantiomeric excess of the product in the related cyano-ethoxycarbonylation reaction. LiCN was readily generated from LiOH and acetone cyanohydrin to initiate the reaction.[3c] In the present reaction, however, the addition of 10 mol % of acetone cyanohydrin had no positive effects. Compound **6a** was obtained in 99% yield and 89% ee after 2 h with acetone cyanohydrin, whereas **6a** was obtained in 97% yield and 92% ee after 2 h without acetone cyanohydrin. A notable advantage of using acetone cyanohydrin was not observed, probably because the slow addition of phosphorylating reagent **4** determines the overall reaction rate in the present reaction.

2.2.3. Substituent effects of phosphine oxide 3. The substituent effects of the phosphine oxide are summarized in Table 3.[16] Triphenylphosphine oxide **3b** resulted in a slightly lower ee and reactivity (88% ee, 85% yield, entry 2). Tris(2,4,6-trimethoxyphenyl)phosphine oxide **3c** afforded a comparable enantioselectivity and reactivity (95% yield, 91% ee, entry 3). On the other hand, tris(2,4,6-trimethylphenyl)phosphine oxide **3d** produced worse results (75% yield, 79% ee, entry 4), indicating the importance of the MeO– group rather than the steric bulkiness at the *ortho*-position. The methoxy group substituted on the *ortho*-position of the aromatic ring of phosphine oxide **3** is important for achieving highest catalyst efficiency.

Table 3. Substituents effects of phosphine oxide **3**



Entry	Phosphine oxide (Ar)		Yield (%)	ee (%)
1	2,6-$(MeO)_2C_6H_3$–	**3a**	97	92
2	C_6H_5–	**3b**	85	88
3	2,4,6-$(MeO)_3C_6H_2$–	**3c**	96	91
4	2,4,6-$(Me)_3C_6H_2$–	**3d**	75	79

[a] Compound **4** was slowly added over 1 h.

2.2.4. Catalytic cycle and structure of the active species. Based on mechanistic studies of the related asymmetric cyano-ethoxycarbonylation reaction[3c] and the present study, the YLB **1**/H_2O/LiCN/$Ar_3P(O)$ **3a** = 1:1:1:1 complex was assumed to be the active species. The structure of the postulated active species is shown in Figure 3a. H_2O would coordinate to the yttrium center and modify the chiral environment of YLB **1**. Phosphine oxide **3a** might coordinate to the lithium cation of LiCN in a bidentate manner, thus increasing the nucleophilicity of the cyanide anion[17] as well as affecting the enantioselectivity. Both LiCN and phosphine oxide **3a** self-assemble with YLB **1**, meaning the racemic pathway without YLB was negligible. In fact, neither phosphine oxide **3a** alone nor a mixture of **3a** and LiCN had good solubility in THF, even at room temperature, while a mixture of YLB, **3a**, and LiCN easily dissolved in THF, even at −78 °C. The difference in solubility would assist self-assembly and suppress the racemic pathway.

The postulated catalytic cycle of the reaction is shown in Figure 3b. The catalytic cycle occurs in three steps: a reversible interaction between aldehyde **5** and catalyst species **cat-1** (step A); cyanide addition to the aldehyde activated by the catalyst, affording the cyanohydrin-catalyst complex **cat-3** (step B); and trapping of the cyanohydrin intermediate to form product **6** and regenerate **cat-1**. The rate-determining step is probably step C, because **4** was added slowly to the reaction mixture. Both product **6** and cyanide source **4** have a P=O moiety, thus **6** and **4** might adversely interact with the active species. Trials to reduce catalyst loading failed in the present reaction.

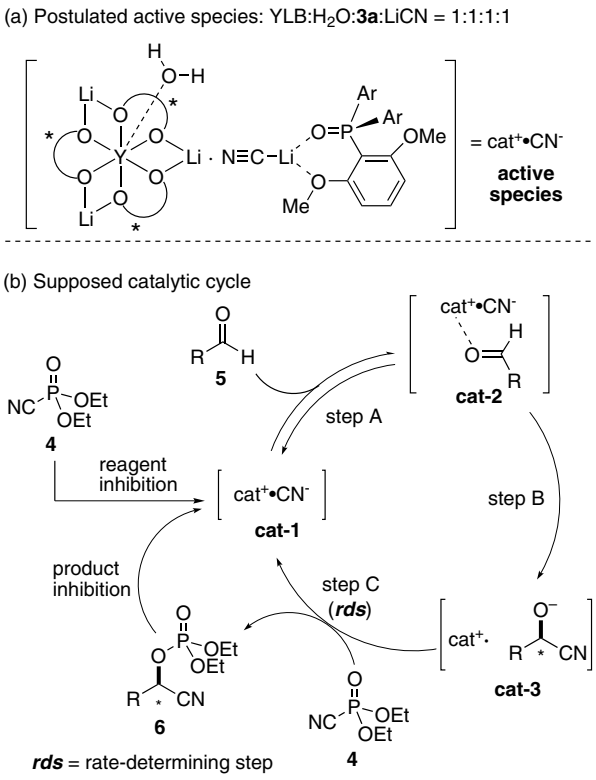
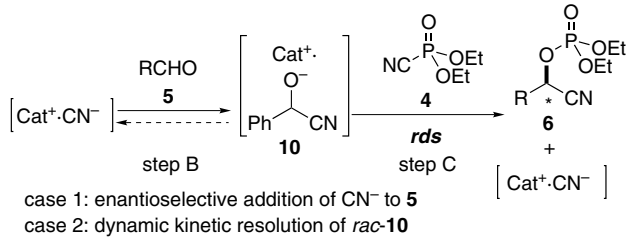
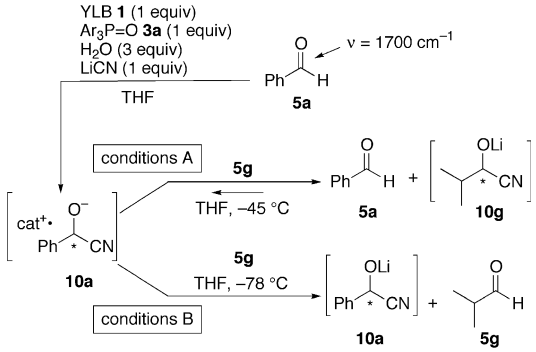


Figure 3. (a) Postulated active species and (b) supposed catalytic cycle.

In the catalytic cycle in Figure 3b, there are two possibilities to transfer chirality from the chiral catalyst to product **6**, as shown in Scheme 2. One possibility is the irreversible formation of the chiral cyanohydrin intermediate **10**, where enantioselective addition of cyanide to aldehyde in step B would determine the enantiomeric excess of the products. The other possibility is a dynamic kinetic resolution of racemic cyanohydrin intermediate. As the reaction conditions are supposed to be somewhat basic, step B in Figure 3b might be reversible. In this case, enantioselectivity is induced during the reaction of the racemic cyanohydrin-catalyst complex with **4** (step C). To determine the actual reaction pathway and enantiomer-recognizing step of the reaction, the reversibility of step B in Figure 3b was examined using in situ IR analysis. The experiments are summarized in Scheme 3, while the results of in situ IR analysis are summarized in Figure 4. When benzaldehyde **5a** was treated with 1 mol equiv of YLB **1**, 3 mol equiv of H_2O, 1 mol equiv of **3a**, and 1 mol equiv of LiCN,[18] IR



Scheme 2. Enantioselective cyanide addition versus dynamic kinetic resolution.



Scheme 3. React IR experiment to determine reversibility of cyanide addition.

absorption of aldehyde **5a** ($\nu = 1700\ cm^{-1}$) immediately disappeared, suggesting the generation of cyanohydrin intermediate **10a**. Then, 1 mol equiv of aldehyde **5g** was added to the reaction mixture. The mixture was stirred at either −45 °C (conditions A in Scheme 3 and Fig. 4a-1 and a-2) or −78 °C (conditions B in Scheme 3 and Fig. 4b), and the IR spectra profile was monitored. As shown in Figure 4a, the absorption of **5a** ($\nu = 1700\ cm^{-1}$) was gradually regenerated at −45 °C, suggesting that the cyanide group was reversibly transferred from **10a** to **5g** affording **10g**. On the other hand, at −78 °C, the peak corresponding to **5a** was not detected (Fig. 4b).[19] These results indicated that cyanide

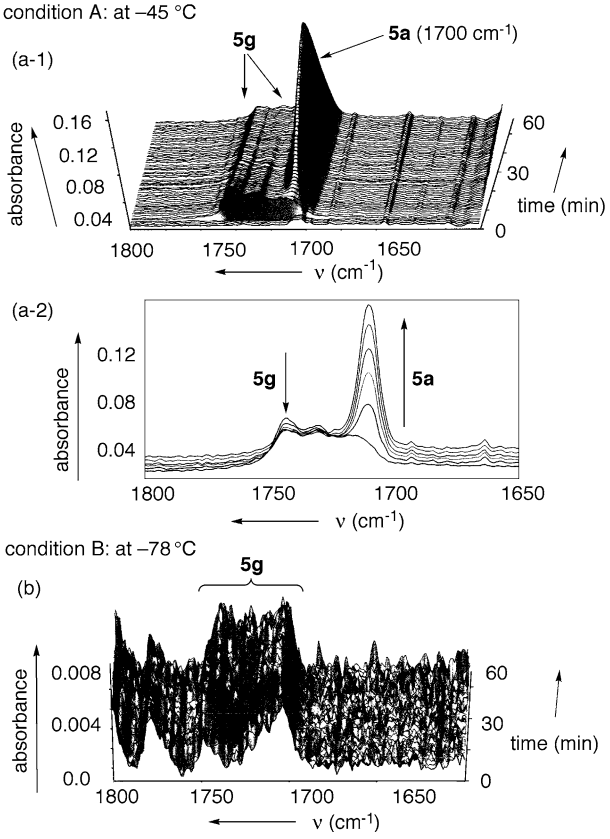


Figure 4. React IR experiment to determine reversibility of cyanide addition.

addition to the aldehyde is irreversible at −78 °C, while the addition is reversible at −45 °C. Thus, the possibility of a dynamic kinetic resolution pathway under the optimized reaction conditions at −78 °C was excluded.[20] In the present asymmetric catalysis, the catalyst recognized the enantioface of aldehydes in the cyanide addition step (step B in Fig. 3b and Scheme 2).

3. Conclusion

In summary, we have developed a catalytic asymmetric cyano-phosphorylation reaction promoted by the YLB complex. Cyanohydrin *O*-phosphates were obtained with good yields (up to 98%) and enantiomeric excesses (up to 97% ee). Mechanistic studies suggested that cyanide addition to aldehyde is highly enantioselective.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 and JEOL ECX-500 spectrometers, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0) or in the scale relative to $CHCl_3$ (7.24 ppm for ^{1}H NMR) and $CDCl_3$ (77.0 ppm for ^{13}C NMR) as internal references. Chemical shifts in THF-d_8 were reported in the scale relative to THF-d_8 residual peak (1.73 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to THF-d_8 (25.5 ppm and/or 67.7 ppm) as internal references. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra (for LRMS) were measured on a Waters ZQ4000 spectrometer. FAB mass spectra (for HRMS) were measured on a JEOL JMS-700 spectrometer. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis (JASCO HPLC systems consisting of the following: pump, PU-980 or PU-2080plus; detector, UV-970, or UV-2075plus, measured at 254 nm; column, DAICEL CHIRALCEL AD-H, OD, OD-H) and gas chromatography (Shimadzu GC-14A with Varian Chirasil DEX CB column [0.25 mm × 25 m); carrier gas, nitrogen (4 kPa)]. Reactions were carried out in dry solvent under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. $Y[N\{Si(CH_3)_3\}_2]_3$ was purchased from Aldrich Co. Ltd. and used as received. (*S*)-1,1′-Bi-2-naphthol [(*S*)-BINOL] was recrystallized from diethyl ether and hexane. A hexanes solution of BuLi (1.6 M) was purchased from Aldrich Co. Ltd.

4.2. Procedure for preparation of water containing (*S*)-YLi$_3$[tris(binaphthoxide)] complex [(*S*)-YLB 1-H_2O]

To a stirred solution of (*S*)-BINOL (1.237 g, 4.32 mmol) in THF (20 mL) at 0 °C was added BuLi (2.72 μL, 4.32 mmol, 1.59 M in hexanes). To the resulting suspension was added a solution of $Y[N\{Si(CH_3)_3\}_2]_3$ (820 mg, 1.44 mmol) in THF (20 mL). After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in THF (24 mL), and H_2O (78 μL, 4.32 mmol) added to give the (*S*)-YLB **1**-H_2O solution (60 mM, in THF). The YLB solution was stored at room temperature under Ar.

4.3. Typical procedure for the catalytic asymmetric cyano-phosphorylation reaction of aldehydes promoted by YLi$_3$tris(binaphthoxide) (YLB 1) complex

To **3a** (164.6 mg, 0.3 mmol) in a test tube were added the (*S*)-YLB **1**-H_2O solution (5.0 mL, 0.3 mmol, 0.06 M, THF) and BuLi (0.3 mmol) in hexane at room temperature. After dissolving **3a** completely, the mixture was cooled to −78 °C, and aldehyde **5a** (3.0 mmol) in THF (4.5 mL) was added to the catalyst mixture. After stirring for 10 min at −78 °C, **4** (0.55 mL, 3.6 mmol) in THF (0.5 mL) was slowly added to the reaction mixture over 1 h, and the reaction mixture then stirred at −78 °C for an additional 1 h. Acetic acid in THF cooled to −78 °C was added to the solution, and then the mixture diluted with water. The organic component was extracted with ethyl acetate. The organic layer was washed with satd aq $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. After evaporating the solvent, the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 7:1) to give chiral-*O*-protected cyanohydrin **6a**.

4.3.1. (*R*)-1-Cyano-1-phenylmethyl diethyl phosphate 6a. Colorless oil, IR (neat) ν 1269, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (dt, $J_{(H,P)} = 0.6$ Hz, $J = 7.0$ Hz, 3H), 1.32 (dt, $J_{(H,P)} = 0.6$ Hz, $J = 7.0$ Hz, 3H), 3.92–3.99 (m, 2H), 4.12–4.17 (m, 2H), 6.02 (d, $J_{(H,P)} = 8.6$ Hz, 1H), 7.39–7.40 (m, 3H), 7.49–7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (d, $J_{(C,P)} = 7.3$ Hz), 16.0 (d, $J_{(C,P)} = 7.1$ Hz), 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 64.8 (d, $J_{(C,P)} = 6.1$ Hz), 66.5 (d, $J_{(C,P)} = 4.1$ Hz), 116.1 (d, $J_{(C,P)} = 6.3$ Hz), 127.5, 129.2, 130.6, 132.4 (d, $J_{(C,P)} = 4.1$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.93; LRMS (ESI, methanol) *m*/*z* 292 [M+Na$^+$]; HRMS (FAB) *m*/*z* 270.0894 [M+H$^+$] calcd for $C_{12}H_{17}NO_4P^+ = 270.0890$; $[\alpha]_D^{21.7} = +18.9$ (*c* 1.2, $CHCl_3$); HPLC (DAICEL CHIRALPAK) AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 14.5 min (*S*)/17.1 min (*R*). The absolute configuration of **6a** was determined comparing retention time in HPLC analysis with that of the authentic product synthesized from commercially available (*R*)-mandelonitrile (Aldrich Co. Ltd.) with **4**.

4.3.2. 1-Cyano-1-(4-methylphenyl)methyl diethyl phosphate 6b. Colorless oil; IR (neat) ν 1270, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $J = 7.0$ Hz, 3H), 1.38 (t, $J = 7.0$ Hz, 3H), 2.39 (s, 3H), 3.96–4.04 (m, 2H), 4.14–4.26 (m, 2H), 6.02 (d, $J_{(H,P)} = 8.9$ Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 2H), 7.44 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, $J_{(C,P)} = 6.3$ Hz), 15.8 (d, $J_{(C,P)} = 7.1$ Hz), 21.1, 64.4 (d, $J_{(C,P)} = 6.1$ Hz), 64.6 (d, $J_{(C,P)} = 6.1$ Hz), 66.3 (d, $J_{(C,P)} = 5.1$ Hz), 116.1 (d,

$J_{(C,P)} = 6.3$ Hz), 127.4, 129.4 (d, $J_{(C,P)} = 5.1$ Hz), 129.7, 140.7; ^{31}P NMR ($CDCl_3$) δ −1.86; LRMS (ESI, methanol) m/z 306 [M+Na$^+$]; HRMS (FAB) m/z 284.1050 [M+H$^+$] calcd for $C_{13}H_{19}NO_4P = 284.1046$; $[\alpha]_D^{23.0} = +16.5$ (c 1.4, $CHCl_3$); HPLC DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 16.0 min (minor)/17.4 min (major).

4.3.3. 1-Cyano-1-(2-naphthyl)methyl diethyl phosphate 6c. Colorless oil; IR (neat) ν 1273, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, $J = 7.0$ Hz, 3H), 1.35 (t, $J = 7.0$ Hz, 3H), 3.95–4.02 (m, 2H), 4.14–4.25 (m, 2H), 6.22 (d, $J_{(H,P)} = 8.9$ Hz, 1H), 7.50–7.51 (m, 2H), 7.57–7.59 (m, 1H), 7.80–7.84 (m, 2H), 7.86–7.88 (m, 1H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6 (d, $J_{(C,P)} = 7.1$ Hz), 15.8 (d, $J_{(C,P)} = 6.1$ Hz), 64.4 (d, $J_{(C,P)} = 6.1$ Hz), 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 66.5 (d, $J_{(C,P)} = 5.1$ Hz), 116.0 (d, $J_{(C,P)} = 6.1$ Hz), 123.6, 126.8, 127.3, 127.4, 127.6, 128.2, 129.2, 129.4 (d, $J_{(C,P)} = 5.1$ Hz), 132.5, 133.7; ^{31}P NMR ($CDCl_3$) δ −1.67; LRMS (ESI, methanol) m/z 342 [M+Na$^+$]; HRMS (FAB) m/z 320.1051 [M+H$^+$] calcd for $C_{16}H_{19}NO_4P = 320.1046$; $[\alpha]_D^{22.3} = +10.8$ (c 1.0, $CHCl_3$); HPLC DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 22.6 min (minor)/34.3 min (major).

4.3.4. 1-Cyano-1-(1-naphthyl)methyl diethyl phosphate 6d. Colorless oil; IR (neat) ν 1273, 1031, 2359 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, $J = 7.0$ Hz, 3H), 1.35 (t, $J = 7.0$ Hz, 3H), 3.83–3.96 (m, 2H), 4.14–4.27 (m, 2H), 6.64 (d, $J_{(H,P)} = 8.9$ Hz, 1H), 7.45 (m, 1H), 7.52 (m, 1H), 7.60 (m, 1H), 7.76 (d, $J = 6.7$ Hz, 1H), 7.87 (d, $J = 7.9$ Hz, 1H), 7.91 (d, $J = 8.2$ Hz, 1H), 8.22 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5 (d, $J_{(C,P)} = 7.1$ Hz), 15.7 (d, $J_{(C,P)} = 6.3$ Hz), 64.4 (d, $J_{(C,P)} = 5.1$ Hz), 64.7 (d, $J_{(C,P)} = 6.1$ Hz), 65.1 (d, $J_{(C,P)} = 5.1$ Hz), 116.0 (d, $J_{(C,P)} = 5.1$ Hz), 122.6, 124.8, 126.4, 127.1, 127.4, 127.5 (d, $J_{(C,P)} = 6.3$ Hz), 128.8, 129.6, 131.5, 133.7; ^{31}P NMR ($CDCl_3$) δ −1.80; LRMS (ESI, methanol) m/z 342 [M+Na$^+$]; HRMS (FAB) m/z 320.1051 [M+H$^+$] calcd for $C_{16}H_{19}NO_4P = 320.1046$; $[\alpha]_D^{22.9} = +67.7$ (c 1.1, $CHCl_3$); HPLC DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 15.7 min (minor)/23.1 min (major).

4.3.5. 1-Cyanohexyl diethyl phosphate 6e. Colorless oil; IR (neat) ν 1275, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89–0.92 (m, 3H), 1.34–1.40 (m, 10H), 1.53–1.55 (m, 2H), 1.92–1.96 (m, 2H), 4.14–4.22 (m, 4H), 4.97–5.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.9 (d, $J_{(C,P)} = 7.1$ Hz), 22.2, 23.7, 30.7, 34.0 (d, $J_{(C,P)} = 6.1$ Hz), 64.5 (d, $J_{(C,P)} = 5.1$ Hz), 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 64.7 (d, $J_{(C,P)} = 6.1$ Hz), 116.8 (d, $J_{(C,P)} = 4.1$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.62; LRMS (ESI, methanol) m/z 286 [M+Na$^+$]; HRMS (FAB) m/z 264.1364 [M+H$^+$] calcd for $C_{11}H_{23}NO_4P = 264.1359$; $[\alpha]_D^{23.7} = +21.0$ (c 0.9, $CHCl_3$); GC, initial temp 110 °C, initial time 10 min, program rate 0.1 °C/min, final temp 150 °C, final time 30 min, injection temp 200 °C, detection temp 250 °C, retention time 89.1 min (minor)/90.9 min (major).

4.3.6. 1-Cyano-3-phenylpropyl diethyl phosphate 6f. Colorless oil; IR (neat) ν 1274, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36–1.39 (m, 6H), 2.21–2.33 (m, 2H), 2.81–2.90 (m, 2H), 4.15–4.22 (m, 4H), 4.96–5.00 (m, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, $J_{(C,P)} = 3.1$ Hz), 15.8 (d, $J_{(C,P)} = 3.0$ Hz), 30.1, 35.6 (d, $J_{(C,P)} = 5.1$ Hz), 63.9 (d, $J_{(C,P)} = 6.3$ Hz), 64.5 (d, $J_{(C,P)} = 6.1$ Hz), 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 116.5 (d, $J_{(C,P)} = 4.1$ Hz), 120.5, 128.2, 128.5, 138.8; ^{31}P NMR ($CDCl_3$) δ −1.86; LRMS (ESI, methanol) m/z 320 [M+Na$^+$]; HRMS (FAB) m/z 298.1210 [M+H$^+$] calcd for $C_{14}H_{21}NO_4P = 298.1203$; $[\alpha]_D^{23.6} = +7.4$ (c 1.2, $CHCl_3$); HPLC DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 14.7 min (minor)/18.1 min (major).

4.3.7. 1-Cyano-2-methylpropyl diethyl phosphate 6g. Colorless oil; IR (neat) ν 1274, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, $J = 7.0$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.36–1.40 (m, 6H), 2.16–2.23 (m, 1H), 4.14–4.23 (m, 4H), 4.83 (dd, $J = 5.5$, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.8, 15.9, 16.8, 17.2, 32.5 (d, $J_{(C,P)} = 6.3$ Hz), 64.5 (d, $J_{(C,P)} = 4.1$ Hz), 64.6 (d, $J_{(C,P)} = 4.1$ Hz), 69.9 (d, $J_{(C,P)} = 6.3$ Hz), 115.8 (d, $J_{(C,P)} = 3.1$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.58; LRMS (ESI, methanol) m/z 258 [M+Na$^+$]; HRMS (FAB) m/z 236.1044 [M+H$^+$] calcd for $C_9H_{19}NO_4P = 236.1046$; $[\alpha]_D^{23.0} = +23.9$ (c 1.4, $CHCl_3$); GC, initial temp 90 °C, initial time 5 min, program rate 0.5 °C/min, final temp 120 °C, final time 10 min, injection temp 200 °C, detection temp 250 °C, retention time 43.7 min (minor)/44.7 min (major).

4.3.8. 1-Cyano-1-cyclohexylmethyl diethyl phosphate 6h. Colorless oil; IR (neat) ν 1273, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08–1.27 (m, 6H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.33 (t, $J = 6.7$ Hz, 3H), 1.65–1.88 (m, 6H), 4.09–4.16 (m, 4H), 4.75 (dd, $J = 6.1$, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, $J_{(C,P)} = 2.0$ Hz), 15.9 (d, $J_{(C,P)} = 3.1$ Hz), 25.1, 25.1, 25.6, 27.3, 27.6, 41.4 (d, $J_{(C,P)} = 5.3$ Hz), 64.5 (d, $J_{(C,P)} = 6.1$ Hz), 64.5 (d, $J_{(C,P)} = 6.1$ Hz), 69.2 (d, $J_{(C,P)} = 6.3$ Hz), 116.0 (d, $J_{(C,P)} = 3.1$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.45; LRMS (ESI, methanol) m/z 298 [M+Na$^+$]; HRMS (FAB) m/z 276.1362 [M+H$^+$] calcd for $C_{12}H_{23}NO_4P = 276.1359$; $[\alpha]_D^{23.0} = +15.0$ (c 1.2, $CHCl_3$); GC, initial temp 140 °C, initial time 10 min, program rate 0.7 °C/min, final temp 160 °C, final time 20 min, injection temp 250 °C, detection temp 250 °C, retention time 36.3 min (minor)/37.1 min (major).

4.3.9. 1-Cyano-2,2-dimethyl-3-phenylpropyl diethyl phosphate 6i. Colorless oil; IR (neat) ν 1276, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.07 (s, 3H), 1.38 (t, $J = 7.0$ Hz, 6H), 2.74 (s, 2H), 4.17–4.25 (m, 4H), 4.69 (d, $J_{(H,P)} = 7.7$ Hz, 1H), 7.17 (d, $J_{(H,P)} = 7.3$ Hz, 2H), 7.24–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, $J_{(C,P)} = 6.1$ Hz), 15.9 (d, $J_{(C,P)} = 6.1$ Hz), 22.0, 22.3, 39.3 (d, $J_{(C,P)} = 6.3$ Hz), 43.2, 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 72.5 (d, $J_{(C,P)} = 7.3$ Hz), 116.0, 126.7, 128.1, 130.5, 136.0; ^{31}P NMR ($CDCl_3$) δ −1.54; LRMS (ESI, methanol) m/z 348 [M+Na$^+$]; HRMS (FAB) m/z 326.1521 [M+H$^+$] calcd for $C_{16}H_{25}NO_4P = 326.1516$;

$[\alpha]_D^{23.5} = +8.7$ (*c* 1.6, $CHCl_3$); HPLC DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 11.1 min (major)/12.7 min (minor).

4.3.10. 1-Cyano-3-phenyl-2-propen-1-yl diethyl phosphate 6j. Colorless oil; IR (neat) *v* 1272, 1030, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, $J = 7.1$ Hz, 3H), 1.37 (t, $J = 7.0$ Hz, 3H), 4.12–4.21 (m, 4H), 5.65–5.68 (m, 1H), 6.23 (dd, $J = 6.7$, 15.6 Hz, 1H), 6.95 (d, $J = 15.6$ Hz, 1H), 7.31–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.8 (d, $J_{(C,P)} = 4.1$ Hz), 15.9 (d, $J_{(C,P)} = 4.0$ Hz), 64.6 (d, $J_{(C,P)} = 6.3$ Hz), 64.7 (d, $J_{(C,P)} = 5.1$ Hz), 65.0 (d, $J_{(C,P)} = 4.1$ Hz), 115.4 (d, $J_{(C,P)} = 6.1$ Hz), 119.1 (d, $J_{(C,P)} = 5.1$ Hz), 127.1, 128.7, 129.4, 134.1, 137.5; ^{31}P NMR ($CDCl_3$) δ −1.73; LRMS (ESI, methanol) *m/z* 318 [M+Na^+]; HRMS (FAB) *m/z* 296.1045 [M+H^+] calcd for $C_{14}H_{19}NO_4P = 296.1046$; $[\alpha]_D^{22.2} = -6.6$ (*c* 1.1, $CHCl_3$); HPLC DAICEL CHIRALPAK OD-H, hexane/2-propanol = 9:1, flow rate = 1.0 mL/min, retention time 13.3 min (minor)/18.9 min (major).

Acknowledgments

The work was supported by Grant-in-Aid for Specially Promoted Research and Grand-in-Aid for Encouragement for Young Scientists (B) (for SM) from JSPS and MEXT.

References

1. For recent reviews on catalytic asymmetric cyanation of carbonyl compounds, see: (a) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; (b) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147; (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491; (d) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246; (e) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3949.
2. Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.
3. (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636; (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021; (c) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413.
4. (a) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197; For other related enantioselective reactions using benzoyl cyanide as the cyanide source, (b) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385.
5. (a) Belokon', Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505; (b) Belokon', Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433, and references cited therein; For other related enantioselective reactions to afford cyanohydrin *O*-acetates, see: (c) Belokon', Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244, and references cited therein; (d) Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763, and references cited therein.
6. Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592, Synthesis of cyanohydrin *O*-acetates is also described in their report.
7. For other asymmetric reactions using anhydrous YLB **1**, see: (a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178; (b) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4493; (c) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419.
8. For the preparation and structural determination of YLB complex, see: (a) Aspinall, H. C.; Dwyer, J. L.; Greeves, N.; Steiner, A. *Organometallics* **1999**, *18*, 1366; (b) Aspinall, H. C.; Bickley, J. F. B.; Dwyer, L. M.; Greeves, N.; Kelly, R. V.; Steiner, A. *Organometallics* **2000**, *19*, 5416.
9. For reviews on rare earth metal–alkali metal heterobimetallic asymmetric catalysis, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187; (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1236.
10. Hodakowski, J. E.; Mohammed, A. H. Eur. Pat. Appl., 1981, EP 44, 214.
11. (a) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1983**, *31*, 2932; Review: (b) Kurihara, T.; Harusawa, S.; Yoneda, R. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 1164; For a review of **4** as a coupling reagent: (c) Shioiri, T. *J. Synth. Org. Chem. Jpn.* **1979**, *37*, 856; For other methods to synthesize cyanohydrin *O*-phosphates, see: Micó, I.; Nájera, C. *Tetrahedron* **1993**, *49*, 4327, and references cited therein.
12. (a) Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143; (b) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Chem. Eur. J.* **2005**, 3849.
13. A part of this work was communicated previously. Abiko, Y.; Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *Synlett* **2004**, 2434.
14. Guzmán, A.; Díaz, E. *Synth. Commun.* **1997**, *27*, 3035, and references cited therein.
15. Coordination of one molecule of H_2O to a rare earth metal center was observed when Pr, Nd, Eu metals were used. See Ref. 9. On the other hand, Salvadori et al. reported that coordination number of Yb metal center in a related heterobimetallic Yb–Li–BINOL complex is six, and that H_2O does not coordinate with Yb metal center. In case of YLB **1**, NMR analysis implied the coordination of H_2O with Y metal center. For analysis of heterobimetallic Y complex, see Refs. 3c and 7c. For analysis of heterobimetallic Yb complex, see: (a) Bari, L. D.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549; (b) Bari, L. D.; Lelli, M.; Salvadori, P. *Chem. Eur. J.* **2004**, *10*, 4594.
16. Phosphine oxides **3** were synthesized from the corresponding phosphines: Kim, R. D.; Stevens, C. H. *Polyhedron* **1994**, *13*, 727.
17. We assumed that Lewis basic phosphine oxide **3a** would coordinate to lithium cation and increase electron density of cyanide anion, thus increasing the nucleophilicity of cyanide anion. For a related discussion, see Ref. 1c. Use of phosphine oxide to increase nucleophilicity of cyanide species generated from TMSCN in the catalytic asymmetric cyanosilylation reaction of aldehyde, see: Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106, and references cited therein.
18. For the preparation of LiCN, see: Livinghouse, T. *Org. Synth.* **1984**, *60*, 126. Although LiH was used to generate LiCN from acetone cyanohydrin in the original report, we used LiHMDS instead of LiH to obtain LiCN with high purity. [Procedure: *Caution! LiCN is highly toxic*]: To a stirred solution of acetone cyanohydrin in THF at 0 °C was added 1 equiv of LiHMDS. The mixture was stirred at 0 °C for 30 min, then solvent was evaporated

under reduced pressure to afford colorless powder in quantitative yield. Because LiCN is highly hygroscopic, LiCN was handled under Ar and immediately used after preparation.
19. As the intensity of the carbonyl absorbance of **5h** was much weaker than that of **5a**, signal/noise ratio in Figure 4b is not good. The *Y*-axis scale in Figure 4b is different from that in Figure 4a.
20. Kinetic dynamic resolution pathway was proposed by Deng et al. when using chiral Lewis base catalyst in asymmetric cyano-ethoxycarbonylation of ketones at −12 °C or −24 °C. See Ref. 2.