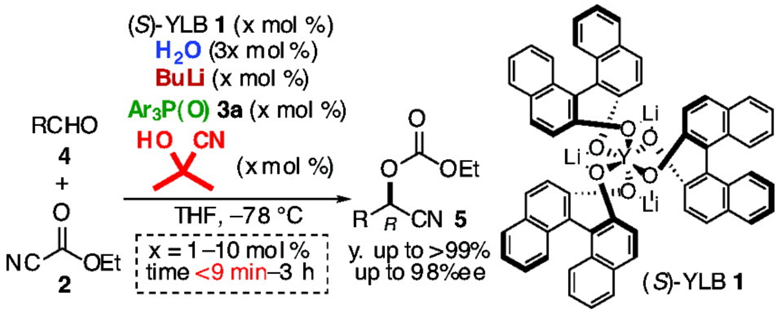
Article

Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction of Aldehydes using a YLiTris(binaphthoxide) (YLB) Complex: Mechanism and Roles of Achiral Additives

Noriyuki Yamagiwa, Jun Tian, Shigeki Matsunaga, and Masakatsu Shibasaki

J. Am. Chem. Soc., **2005**, 127 (10), 3413-3422• DOI: 10.1021/ja042887v • Publication Date (Web): 18 February 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
ARTICLES

Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction of Aldehydes using a YLi$_3$Tris(binaphthoxide) (YLB) Complex: Mechanism and Roles of Achiral Additives

Noriyuki Yamagiwa, Jun Tian, Shigeki Matsunaga,* and Masakatsu Shibasaki*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received November 25, 2004; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Abstract: Full details of a catalytic asymmetric cyano-ethoxycarbonylation reaction promoted by a heterobimetallic YLi$_3$tris(binaphthoxide) complex (YLB **1**), especially mechanistic studies, are described. In the cyanation reaction of aldehydes with ethyl cyanoformate, three achiral additives, H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide (**3a**), and BuLi, were required to achieve high reactivity and enantioselectivity (up to $>$99% yield and up to 98% ee). The roles of achiral additives and the reaction pathway were investigated in detail. In situ IR analysis revealed that the initiation step to generate LiCN from H_2O, BuLi, and ethyl cyanoformate is rather slow. On the basis of mechanistic studies of the initiation step to generate an active nucleophilic species, reaction conditions were optimized by using a catalytic amount of acetone cyanohydrin as an initiator. Under the optimized conditions, the induction period decreased and the reaction completed within 9 min using 5 mol % YLB at −78 °C. Catalyst loading was successfully reduced to 1 mol %. Kinetic experiments and evaluation of the substituent effects of phosphine oxide revealed that phosphine oxide had beneficial effects on both the reaction rate and the enantioselectivity. The putative active species as well as the catalytic cycle of the reaction are also discussed.

Introduction

The catalytic asymmetric cyanation reaction of carbonyl compounds is one of the most powerful tools available to supply useful chiral building blocks. Various catalyst systems have been developed over the last two decades;[1] $(CH_3)_3SiCN$ and/or HCN are most often used as 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. To avoid the problems, one-pot catalytic asymmetric cyanation-*O*-protection reaction with a robust protecting group was investigated recently by Deng,[2] Belokon and North,[3,4] our group,[5] and Nájera and Saá.[6] Either ethyl cyanoformate or diethyl cyanophosphonate was used as a cyanide source, affording corresponding cyanohydrin *O*-carbonate or *O*-phosphate. Although excellent enantioselectivity and chemical yield were achieved in those catalytic asymmetric reactions,[2−6] there is only limited information on the reaction mechanisms based on detailed studies of asymmetric catalysis.[4] Understanding the reaction mechanisms of the new variant in asymmetric cyanation reactions, including the generation of active species and catalytic cycle, is necessary for further rational improvement of the reaction. In our preliminary report,[5a] a heterobimetallic YLi$_3$tris(binaphthoxide) complex[7] (YLB **1**, Figure 1) effectively promoted the reaction with the aid of three achiral additives: H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide (**3a**), and BuLi. Cyanohydrin *O*-carbonates were obtained in high yield (up to $>$99% yield) and enantiomeric excess (up to 98% ee) (Scheme 1). In most asymmetric reactions using rare earth−alkali metal heterobimetallic complexes reported by our group, the Lewis acid−Brønsted base cooperative function

---

(1) For recent reviews on asymmetric cyanation reaction, see: (a) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752. (b) North, M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 147. (c) Gröger, H. *Chem.−Eur. J.* **2001**, *7*, 5246. (d) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3949.

(2) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.

(3) (a) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505. For related reactions, see also: (b) 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. (c) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301. Same Ti−salen catalyst was applicable in asymmetric cyanation reactions with $(CH_3)_3SiCN$: (d) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moskalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968 and references therein.

(4) During preparation of this manuscript, North and Belokon reported mechanistic studies concerning the structure of chiral Ti−salen catalyst in solution using various cyanide sources: Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433.

(5) (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. With diethyl cyanophosphonate as a cyanide source: (c) Abiko, Y.; Yamagiwa, N.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. *Synlett* **2004**, 2434.

(6) (a) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 197. With diethyl cyanophosphonate as a cyanide source: (b) Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143. Same Al catalyst was applicable in asymmetric cyanation reactions with $(CH_3)_3SiCN$: (c) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589.

(7) For reviews of asymmetric catalysis using rare earth−alkali metal heterobimetallic complexes, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. For the preparation of YLB **1** complex and X-ray structure, see: (c) Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; Steiner, A. *Organometallics* **1999**, *18*, 1366. (d) Aspinall, H. C.; Bickley, J. F. B.; Dwyer, L. M.; Greeves, N.; Kelly, R. V.; Steiner, A. *Organometallics* **2000**, *19*, 5416.

10.1021/ja042887v CCC: $30.25 © 2005 American Chemical Society

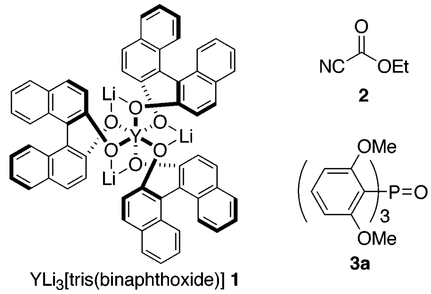
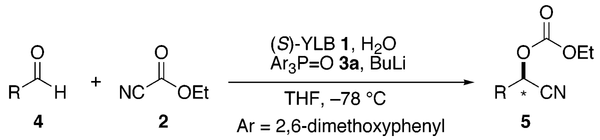


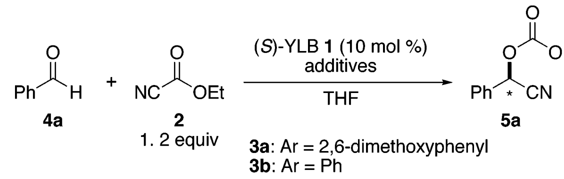
Figure 1. Structures of YLi$_3$tris(binaphthoxide) (YLB **1**), ethyl cyanoformate (**2**), and tris(2,6-dimethoxyphenyl)phosphine oxide **3a**.

Scheme 1. Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction Promoted by a Mixture of YLB **1**, H_2O, BuLi, and $Ar_3P(O)$ **3a**



had a key role in promoting the reactions.[7a,b] The active proton of the nucleophiles is deprotonated by a Brønsted basic moiety of the complex to form metalated nucleophiles. In the present cyanation reaction, however, there is no active proton in the cyanide source. The reaction mechanism, especially generation of the active nucleophilic species, should be different from that in previous reactions with heterobimetallic complexes. Moreover, in striking contrast to a catalytic asymmetric 1,4-addition reaction of methoxylamine promoted by the same YLB **1** complex under strictly anhydrous conditions using desiccant,[8] the asymmetric cyano-ethoxycarbonylation reaction required H_2O to achieve both high reactivity and enantioselectivity. In our preliminary report,[5a] the roles of H_2O and phosphine oxide in the reaction were not clear. In a related catalytic asymmetric cyanosilylation reaction, we reported the efficacy of Lewis acid−Lewis base cooperative catalysts,[9] which contained a phosphine oxide unit in the chiral ligands as a Lewis basic moiety to activate and control the orientation of the $(CH_3)_3SiCN$ nucleophile. Interaction of phosphine oxide with the Si of $(CH_3)_3SiCN$ was proposed.[9,10] Because a silyl reagent is not involved in the asymmetric cyano-ethoxycarbonylation reaction, the role of phosphine oxide should be different. In this article, we report the full details of a catalytic asymmetric cyano-ethoxycarbonylation reaction with YLB **1**. Mechanistic studies of the reaction are the main topic of this paper. The role of achiral additives was investigated in detail. Both the initiation step and the catalytic cycle of the reaction are discussed. On the basis of information about the initiation step, reaction conditions were improved by adding a catalytic amount of acetone cyanohydrin as an initiator.

Table 1. Optimization of Reaction Conditions with Achiral Additives



	additives						
entry	H_2O (mol %)	$Ar_3P{=}O$ (mol %)	BuLi (mol %)	T(°C)	time (h)	% yield	% ee
1	10	0	0	−60	9	84	58
2	0	0	0	−60	7.5	0	ND
3	0	**3b** 10	0	−60	8.5	93	64
4	10	**3b** 10	0	−60	2.5	88	83
5	20	**3b** 10	0	−60	2.5	74	88
6	30	**3b** 10	0	−60	2.5	54	89
7	30	**3a** 10	0	−60	1.5	97	92
8	30	**3a** 10	0	−78	2	76	90
9	30	**3a** 10	10	−78	2	96	94

Results and Discussion

A. Development of a Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction. Initial screening of both cyanide and metal sources revealed that commercially available ethyl cyanoformate **2** and (*S*)-YLB **1** prepared from $Y(HMDS)_3$, (*S*)-BINOL, and BuLi were promising candidates.[11] With YLB **1** (10 mol %), H_2O (10 mol %), and **2**, cyanation of aldehyde **4a** proceeded at −60 °C to afford **5a** in 84% yield and 58% ee (Table 1, entry 1). Interestingly, the reaction did not proceed without the addition of H_2O (entry 2). To fine tune the chiral environment, various achiral additives were surveyed and triarylphosphine oxide, $Ar_3P(O)$ **3**, was determined to be optimal.[12] Addition of both H_2O and $Ph_3P(O)$ **3b** (10 mol %) significantly improved both the reaction rate and the enantioselectivity (entry 4). The highest selectivity was obtained by adding 30 mol % H_2O (entry 6). $Ar_3P(O)$ **3** was optimized, and tris(2,6-dimethoxyphenyl)phosphine oxide **3a**[13] had the highest reactivity and selectivity (entry 7). Moreover, by adding 10 mol % BuLi, the reaction proceeded smoothly at −78 °C to afford **5a** in 94% ee (entry 9). In the absence of BuLi, the reaction rate was not sufficient at −78 °C (entry 8). The optimized reaction conditions for cyanation, YLB **1** (10 mol %), H_2O (30 mol %), BuLi (10 mol %), $Ar_3P(O)$ **3a** (10 mol %), and **2** (1.2 equiv), were applicable to various aldehydes (Table 2). In all cases, good yield and enantiomeric excess (87−98% ee) were achieved using aromatic aldehydes (entries 1 and 2), α,β-unsaturated aldehydes (entries 3−5), α-unsubstituted (entries 6 and 7), α-monosubstituted (entries 8 and 9), and α,α-disubstituted aliphatic aldehydes (entry 10). The short reaction time (<3 h) for all aldehydes as well as broad substrate generality is noteworthy.

---

(8) (a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178. For discussion of the reaction mechanism using anhydrous YLB as a catalyst, see: (b) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4493.

(9) (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641. For reviews, see also: (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (c) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.

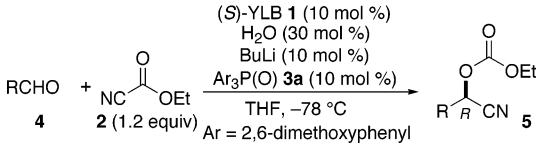
(10) For use of phosphine oxide to increase nucleophilicity of cyanide species generated from TMSCN in the catalytic asymmetric cyanosilylation reaction of aldehyde, see: Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106 and references therein.

(11) Catalyst screening was performed without phosphine oxide and BuLi. Other rare earth−alkali metal heterobimetallic complexes gave less satisfactory results in terms of reaction rate and enantioselectivity. For example: Dy−Li−BINOL, 4 h, y. quant, 45% ee; Yb−Li−BINOL, 4 h, y. quant, 31% ee; Sc−Li−BINOL, 1 h, y. quant, 9% ee; Y−Na−BINOL, 0.5 h, y. quant, 0% ee; Y−K−BINOL, 5.5 h, y. quant, 8% ee.

(12) Screening of achiral additives was performed at −60 °C using aldehyde **4a** and 10 mol % YLB **1**. Other Lewis basic achiral additives gave less satisfactory results. For example, $(n\text{-Bu})_3P(O)$: 63% ee, $(c\text{-hexyl})_3P(O)$: 69% ee, $(t\text{-Bu})_3P(O)$: 63% ee, $Ph_3As(O)$: 78% ee, $(PhO)_3P(O)$: 70% ee, NMO: 69% ee, $Ph_2P(O)CH_2CH_2P(O)Ph_2$: 82% ee, Ph_3P: 71% ee.

(13) For the preparation of phosphine oxides, see: Kim, R. D.; Stevens, C. H. *Polyhedron* **1994**, *13*, 727. For the procedure, see Supporting Information.

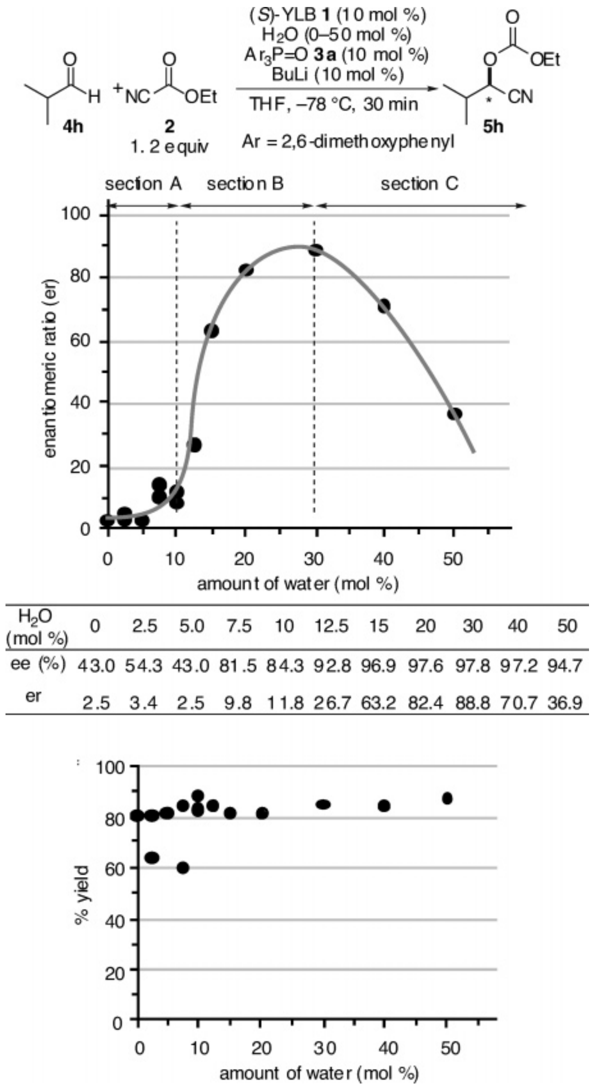
Table 2. Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction of Various Aldehydes



entry		aldehyde (R)	product	time (h)	% yield	% ee
1	**4a**	Ph	**5a**	2	96	94
2	**4b**	1-naphthyl	**5b**	2	97	90
3	**4c**	(*E*)-$CH_3(CH_2)_2CH{=}CH$	**5c**	3	>99	92
4	**4d**	(*E*)-*cyclo*-C_6H_{11}-$CH{=}CH$	**5d**	3	98	93
5	**4e**	(*E*)-$PhCH{=}CH$	**5e**	3	>99	91
6	**4f**	$CH_3(CH_2)_4$	**5f**	3	93	94
7	**4g**	CH_3CH_2	**5g**	2	79[a]	92
8	**4h**	$(CH_3)_2CH$	**5h**	2	88[a]	98
9	**4i**	*cyclo*-C_6H_{11}	**5i**	2	97	96
10	**4j**	$(CH_3)_3C$	**5j**	3	93	87

[a] Product was volatile.

Under the optimized conditions, YLB required three achiral additives, H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide **3a**, and BuLi, to achieve the best enantioselectivity and reaction rate. The detailed catalytic cycle, mechanisms for the generation of an active nucleophilic species, and the roles of the achiral additives, however, were not clear. The following sections describe mechanistic investigations to clarify these points.



H_2O (mol %)	0	2.5	5.0	7.5	10	12.5	15	20	30	40	50
ee (%)	43.0	54.3	43.0	81.5	84.3	92.8	96.9	97.6	97.8	97.2	94.7
er	2.5	3.4	2.5	9.8	11.8	26.7	63.2	82.4	88.8	70.7	36.9

Figure 2. Water effects on enantioselectivity and chemical yield in the catalytic asymmetric cyano-ethoxycarbonylation reaction of aldehyde **4h**.

B. Effects of H_2O. Effects of the amount of H_2O on reactivity and enantioselectivity were examined using 10 mol % YLB **1**, 10 mol % **3a**, and 10 mol % BuLi in THF at −78 °C (Figure 2). Aldehyde **4h** was used instead of **4a** because enantioselectivity with aldehyde **4h** was more sensitive to the amount of H_2O compared with that of **4a**. To clearly compare the difference in enantioselectivity, both enantiomeric ratio (er: *R*-enantiomer/*S*-enantiomer) and enantiomeric excess (ee: *R*-enantiomer − *S*-enantiomer/*R*-enantiomer + *S*-enantiomer) are presented in Figure 2. The enantiomeric ratio and chemical yield after 30 min were plotted against the amount of H_2O (0−50 mol %). A rather unexpected curve was observed for the enantiomeric ratio, while the chemical yield was not affected (80−90% yield). To explain the effects of H_2O, the curve in Figure 2 was separated into three sections (A, H_2O, 0−10 mol %; B, H_2O, 10−30 mol %; and C, H_2O, 30−50 mol %). In section A (H_2O, 0−10 mol %), the enantiomeric ratio was generally low, ranging from 2.5 to 11.8 (43−84% ee). The enantiomeric ratio increased gradually depending on the amount of H_2O in section B (H_2O, 10−30 mol %), and the highest enantiomeric ratio was obtained with 20−30 mol % H_2O. In section C (H_2O, 30−50 mol %), too much H_2O had adverse effects on enantioselectivity. We assumed that the effects of H_2O were as follows. In section A, all H_2O was consumed by BuLi (10 mol %) to generate LiOH. LiOH reacts with ethyl cyanoformate, and essentially no free H_2O remained in the reaction mixture. In sections B and C, an excess amount of H_2O remained in the reaction mixture and coordinated with YLB, thereby affecting the chiral environment. NMR spectroscopy revealed a reversible interaction between YLB and H_2O in solution. As shown in Figure 3a, NMR spectra of anhydrous YLB in THF at −20 °C showed six sharp signals, implying that the YLB complex has C_3-symmetry in solution. The signals gradually broadened, however, by adding H_2O to YLB (Figure 3b,c).[14] In Figure 3d, Drierite ($CaSO_4$), a neutral desiccant, was added to the mixture of YLB and 3 equiv of H_2O. The sharp signals of YLB **1** were observed again. These observations suggested that there is rapid equilibrium between anhydrous YLB and the YLB−H_2O complex (Figure 4). On the other hand, Aspinall et al. reported the X-ray crystallographic structure of both $[Li(Et_2O)]_3[Eu(binol)_3]$ (anhydrous EuLB) and $[Li(Et_2O)]_3[Eu(binol)_3(H_2O)]$ (aqueous EuLB).[7c,d] The anhydrous EuLB had nearly D_3-symmetry, while aqueous EuLB had bent C_3-symmetry due to coordination of H_2O with the europium center. Aspinall et al. insisted that H_2O would be effective for finely tuning the chiral environment and enantioselectivity of the catalyst. We assumed H_2O would coordinate with the yttrium center in solution and have effects similar to those observed with the europium complex. Considering 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 center.[16] We speculated that a slightly excess amount of H_2O to YLB has beneficial effects to make the equilibrium between YLB−H_2O

---

(14) Free H_2O in THF was not observed by ^1H NMR, probably due to rapid equilibrium between anhydrous YLB and the YLB−H_2O complex.

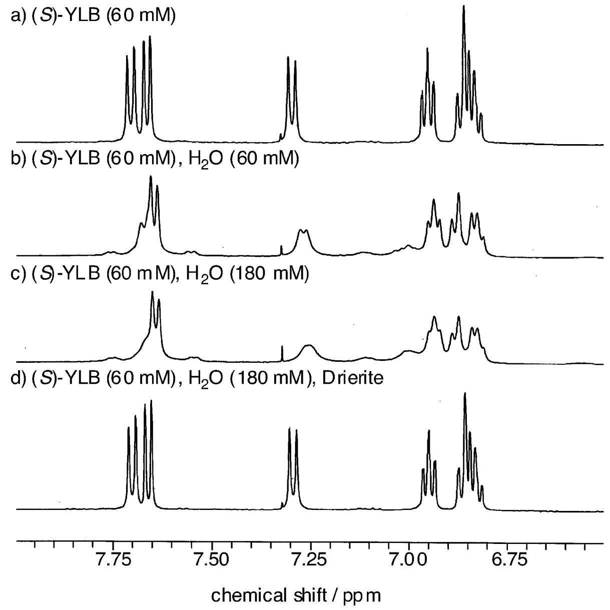


Figure 3. NMR spectra of (*S*)-YLB (60 mM in d_8-tetrahydrofuran) at −20 °C (a) without H_2O, (b) with 60 mM H_2O, (c) with 180 mM H_2O, (d) with 180 mM H_2O, and Drierite ($CaSO_4$: 200 mg/mL of d_8-tetrahydrofuran).

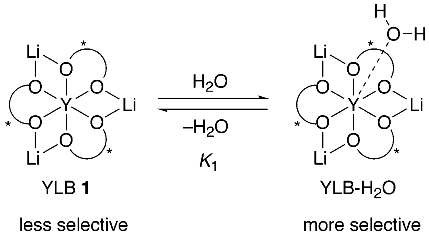
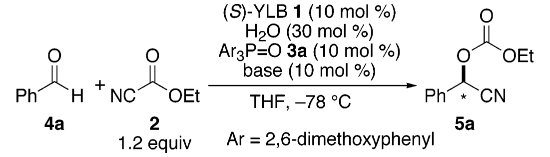


Figure 4. Supposed reversible interaction between YLB **1** and H_2O in solution.

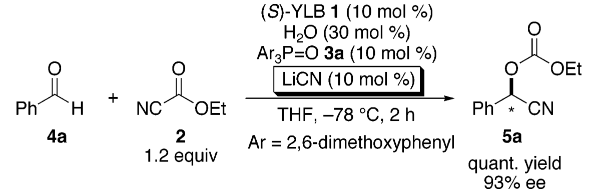
and anhydrous YLB more favorable to the YLB−H_2O complex; 30 mol % H_2O gave the best result (Figure 4). In section C, too much H_2O slightly decreased enantioselectivity (with 50 mol % H_2O, er = 36.9 and 94.7% ee), probably because too much H_2O promoted the racemic reaction pathway without YLB **1**.

Table 3. Base Effects on Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction



entry	base	time (h)	% yield	% ee
1	none	0.5	17	94
2	none	2	76	90
3	BuLi	0.5	95	96
4	BuLi	2	96	94
5	LiHMDS	2	94	93
6	NaHMDS	2	92	90
7	KHMDS	2	69	83

Scheme 2. Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction using LiCN as an Additive



C. Effects of BuLi. BuLi affected reaction time rather than enantioselectivity. As summarized in Table 3, the chemical yield after 30 min in the absence of BuLi was only 17% (entry 1), although the enantiomeric excess was high. The reaction did not complete even after 2 h (entry 2, 76%). With BuLi, the reaction completed within 30 min at −78 °C (entry 3). Similar reactivity and enantioselectivity were obtained with LiHMDS (entry 5), suggesting that the same active species was generated with LiHMDS. Alkali metal affected both the enantioselectivity and the reaction rate. Lithium gave better results than sodium and potassium, as shown in entries 4−7, implying that lithium metal was integrated into the active chiral species.

We hypothesized that the LiCN generated from LiOH and ethyl cyanoformate was a key nucleophilic species. In the racemic reaction using ethyl cyanoformate as a cyanide source, the cyanide anion itself was proposed to be the key intermediate.[17] In the catalytic asymmetric reaction, generated LiCN should self-assemble with the chiral catalyst, otherwise a racemic reaction would proceed. To examine our hypothesis, LiCN prepared by a known procedure[18] was added to the mixture of YLB, H_2O, and phosphine oxide **3a** in the absence of BuLi. As expected, the reaction proceeded smoothly, and the product was obtained in 93% ee and quantitative yield (Scheme 2).[19] The similar enantioselectivity suggested that the same active species was generated using LiCN instead of BuLi. On the other hand, there was a difference in the reaction profile when reactions (a) without BuLi, (b) with BuLi, and (c) with LiCN instead of BuLi were monitored using in situ IR (Figure 5a−c). Aldehyde **4a** was added to a mixture of YLB, H_2O, $Ar_3P{=}O$ **3a**, and

---

(15) Although rare earth metal complexes with a coordination number higher than eight are well-known, maximum coordination number of rare earth metals in rare earth−alkali metal−BINOL (1:3:3) heterobimetallic complexes reported so far is seven, according to crystal structure analysis of various complexes. See refs 7, 16 and references therein. See, also: Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807.

(16) Coordination of one molecule of H_2O to a rare earth metal center was observed when Pr, Nd, and Eu metals were used. See, ref 7. On the other hand, in a related heterobimetallic Yb−Li−BINOL complex, Salvadori et al. reported that the coordination number of the Yb metal center is six, and that H_2O does not coordinate with the Yb metal center. In the case of YLB **1**, the NMR experiment in Figure 3 implied the coordination of H_2O with the Y metal center. For analysis of the 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.

(17) For examples of racemic reactions, see: (a) Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229 and references therein. (b) Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188. (c) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995. For related racemic reaction using diethyl cyanophosphonate as a cyanide source, see: (d) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1983**, *31*, 2932. (e) Kurihara, T.; Harusawa, S.; Yoneda, R. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 1164 and references therein.

(18) 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) The beneficial effects of H_2O on enantioselectivity were reconfirmed by the control experiments excluding H_2O. When the cyanation was performed in the absence of H_2O, enantiomeric excess decreased significantly. With LiCN (10 mol %) in the absence of H_2O (control experiment for Scheme 2), the results were 65% ee, 96% yield, after 2 h; with acetone cyanohydrin (10 mol %) in the absence of H_2O (control experiment for Scheme 3), the results were 63% ee, 99% yield, after 2 h.

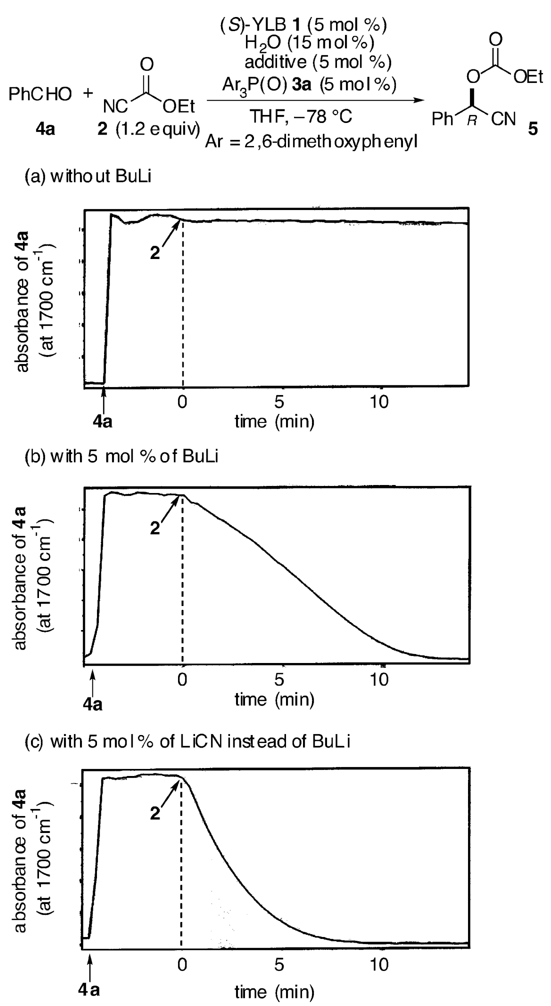


Figure 5. Reaction profiles (a) without BuLi, (b) with BuLi, and (c) with LiCN instead of BuLi.

additive (BuLi or LiCN), and the mixture was stirred for 5 min. Then, ethyl cyanoformate **2** was added, and the carbonyl peak of aldehyde **4a** (1700 cm^{-1}) was monitored (0−15 min). The reaction proceeded smoothly with LiCN instead of BuLi (Figure 5c), while the initiation period was observed in Figure 5b. The reaction profile had a sigmoid curve in Figure 5b. The initial reaction rate at −78 °C was very slow in Figure 5a. The results suggested that generation of the active species was very slow in the absence of BuLi at −78 °C and was moderate even in the presence of BuLi.

To investigate the generation of LiCN from LiOH and ethyl cyanoformate in more detail, we performed in situ IR experiments using a stoichiometric amount of the catalyst species and ethyl cyanoformate. When 1 molar equiv of ethyl cyanoformate **2** was treated with a mixture of YLB (1 molar equiv), H_2O (3 molar equiv), $Ar_3P{=}O$ **3a** (1 molar equiv), and BuLi (1 molar equiv) at −78 °C, the absorption of the carbonyl group of ethyl cyanoformate ($\nu = 1750$ cm^{-1}) gradually shifted to a new peak ($\nu = 1740$ cm^{-1}) (Figure 6). Because the two peaks (1740 and 1750 cm^{-1}) overlapped, the profiles of the two peaks were separated mathematically (Figure 6a).[20] Unexpectedly, ethyl cyanoformate was not completely consumed, although just 1 equiv of the cyanide source was used (Figure 6b). The result implied a side reaction that consumed the LiOH. We assumed that LiOH reacted with ethyl cyanoformate to generate LiCN and ethyl hydrogen carbonate **6**. Because **6** has an acidic proton, **6** would immediately react with LiOH to generate H_2O and lithium ethyl carbonate **7**; **7** would be stable enough at −78 °C in THF to avoid decomposition into CO_2 and LiOEt, which would react with H_2O to regenerate LiOH. Thus, only one-half of the LiOH would react with ethyl cyanoformate to generate LiCN, and the other half would be consumed to generate lithium salt **7**. In fact, the absorption of **2** ($\nu = 1750$ cm^{-1}) disappeared completely within 15 min when an additional 1 molar equiv of BuLi was added to the reaction mixture (Figure 6c, at 50 min).

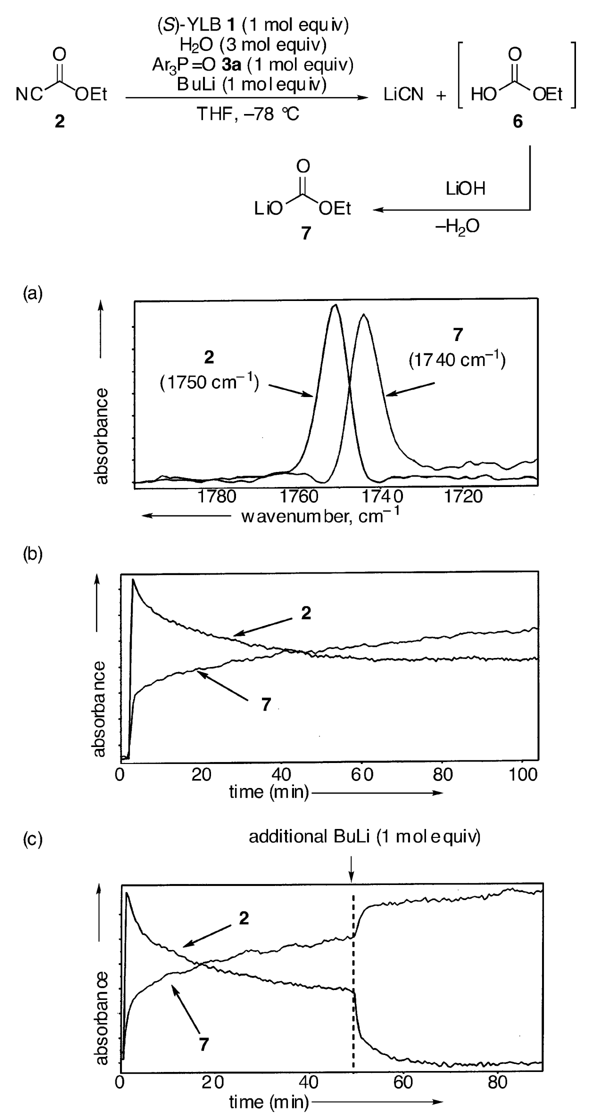


Figure 6. Reaction profiles using a stoichiometric amount of catalyst.

The experiment shown in Figure 7 supported our assumption. In Figure 7, 1 molar equiv of ethyl cyanoformate **2** was treated with 50 mol % YLB, 150 mol % H_2O, 50 mol % $Ar_3P{=}O$ **3a**, and 50 mol % BuLi at −78 °C for 1 h, followed by the addition of 1 molar equiv of aldehyde **4h**. The reaction was monitored by gas chromatography. Chemical yield reached approximately 75%. The results suggested that only 25% of the ethyl cyanoformate reacted to generate LiCN, and approximately 75% of the ethyl cyanoformate remained when using 50 mol % LiOH. If **7** decomposed smoothly at −78 °C to CO_2 and LiOEt, the chemical yield of product **5h** should be less than 50% under

---

[20] *ConcIRT AF*, version 3.5.0.4 software (METTLER TOLEDO Autochem), was used for mathematical treatment of IR spectra.

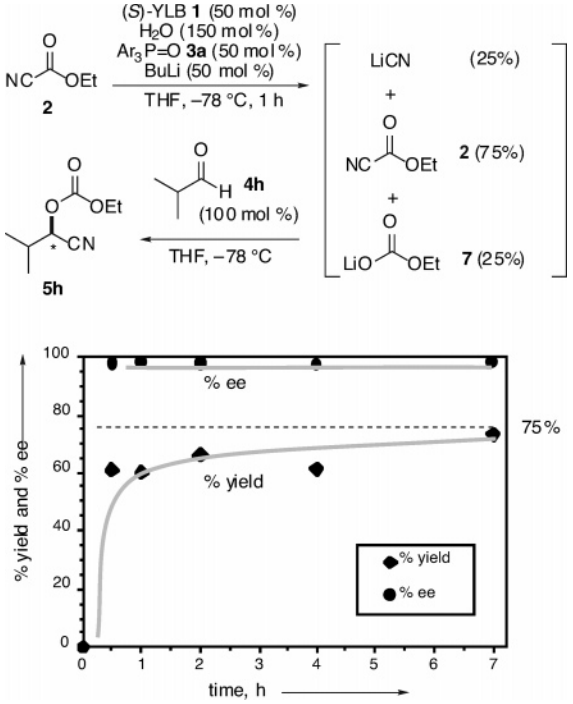


Figure 7. Reaction profile using 50 mol % YLB, 150 mol % H_2O, 50 mol % $Ar_3P{=}O$ **3a**, and 50 mol % BuLi.

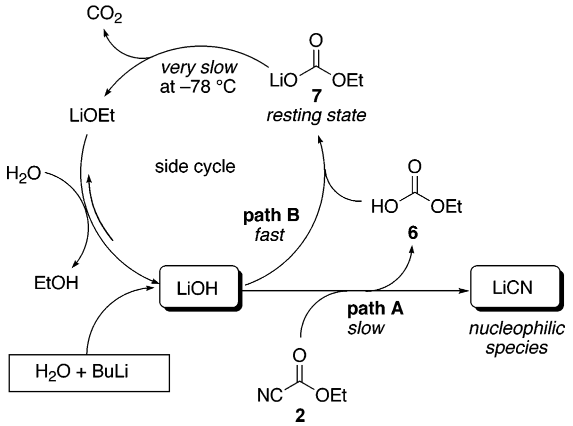
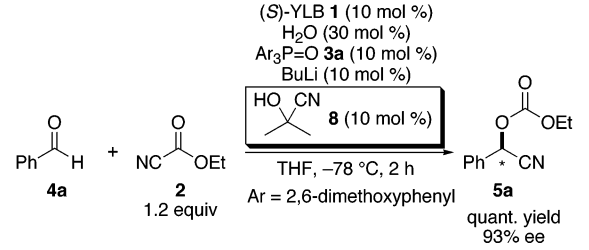


Figure 8. Supposed initiation step to generate LiCN.

the conditions in Figure 7. The postulated initiation step to generate LiCN is summarized in Figure 8. LiOH generated from H_2O and BuLi reacted with ethyl cyanoformate to afford LiCN.[21] The reaction of LiOH with ethyl cyanoformate was rather slow at −78 °C as detected by in situ IR (Figure 6). Approximately one-half of the LiOH was consumed by the reaction with **6**, and decomposition of **7** was slow at −78 °C. Thus, only one-half of the BuLi generated the active nucleophilic species.

D. Optimization of Reaction Conditions. As shown in the in situ IR spectra in Figure 5a−c, the addition of a catalytic amount of LiCN instead of BuLi was effective to avoid the slow initiation step and to accelerate the reaction. Moreover, by adding LiCN directly to the catalyst mixture, the undesired pathway consuming LiOH was excluded, thus increasing the amount of the active species. Use of LiCN itself is, however, not suitable from a practical point of view due to its high toxicity and hygroscopic properties. Acetone cyanohydrin is a suitable precursor of LiCN, as shown in Scheme 3 and Figure 9. With 10 mol % acetone cyanohydrin **8** as an initiator, the reaction proceeded smoothly, and the product was obtained in the same enantiomeric excess (93%) and yield (>99%) as that obtained by using LiCN directly (Scheme 3).[19] Because the reaction proceeded too fast to evaluate the reaction rate with 10 mol % catalyst loading, the reaction profile was monitored with 5 mol % catalyst loading pretreated with 5 mol % acetone cyanohydrin **8**. The reaction completed within 9 min at −78 °C (Figure 9). In this case, the reaction profile did not have a sigmoid curve and was similar to that observed with LiCN (see also Figure 5b,c).

Scheme 3. Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction using Acetone Cyanohydrin as a Precursor of LiCN



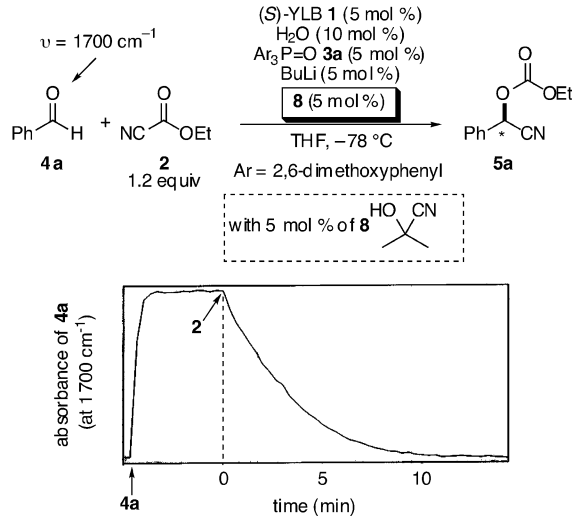


Figure 9. Reaction profile of catalytic asymmetric cyano-ethoxycarbonylation reaction with acetone cyanohydrin as an initiator.

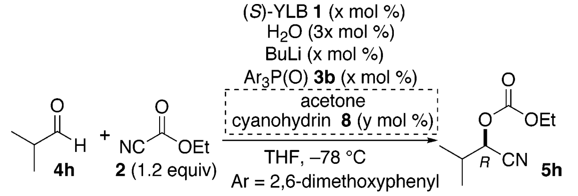
Trials to reduce catalyst loading are summarized in Table 4. In the absence of acetone cyanohydrin **8**, the reaction with 1 mol % catalyst resulted in a less satisfactory reaction rate and enantioselectivity compared with 10 mol % (entry 1) and 5 mol % catalyst loading (entry 2). As shown in entries 3 and 4, the reaction did not complete after 2 h (entry 3, 79% yield), and product **5h** was obtained in 96% yield after 9 h, but in only 90% ee (entry 4). On the other hand, in the presence of 1 mol % **8**, 1 mol % catalyst was sufficient to complete the reaction within 2 h; **5h** was obtained in 93% yield and 95% ee (entry 5).

E. Effects of Phosphine Oxide. Triarylphosphine oxide was essential to achieve high reactivity and enantioselectivity in the present reaction.[12] To evaluate substituent effects of the aromatic ring, various triarylphosphine oxides (Figure 10) were synthe-

---

(21) In Table 1, entry 3, reaction proceeded without adding H_2O at −60 °C. We speculated that a part of lithium binaphthoxide of YLB might react slowly with ethyl cyanoformate to produce active species. In the case without BuLi, H_2O would slowly attack **2** to generate LiCN (Table 1, entries 4−8).

Table 4. Trials to Reduce Catalyst Loading



entry	catalyst (x mol %)	**8** (x mol %)	time (h)	% yield	% ee
1	10	0	2	88	98
2	5	0	2	82	96
3	1	0	2	79	91
4	1	0	9	96	90
5	1	1	2	93	95

sized[13] and used in an asymmetric cyano-ethoxycarbonylation reaction of aldehyde **4h**. The enantiomeric ratios with various phosphine oxides are summarized in Figure 11. In the absence of phosphine oxide, enantioselectivity was modest (er = 8.7 and 79.0% ee). With **3a**, the enantiomeric ratio was highest (er = 88.8 and 97.8% ee). Phosphine oxides **3b**−**3e** gave enantioselectivity much lower than that of **3a**. The results with **3b**−**3e** suggested that electronic effects of substituents are not very important. High enantioselectivity (er >50) was achieved when using **3f**, **3h**, **3j**, and **3k**. Even one or two methoxy groups at the ortho position were sufficient to achieve a high enantiomeric ratio (**3j**, er = 73.5; **3k**, er = 61.6). On the other hand, **3g** and **3i** with *ortho*-alkyl substituents were not effective, indicating that the bulkiness of the substituents is not important. These results suggested that chelating coordination with one of the methoxy groups and phosphine oxide is important.

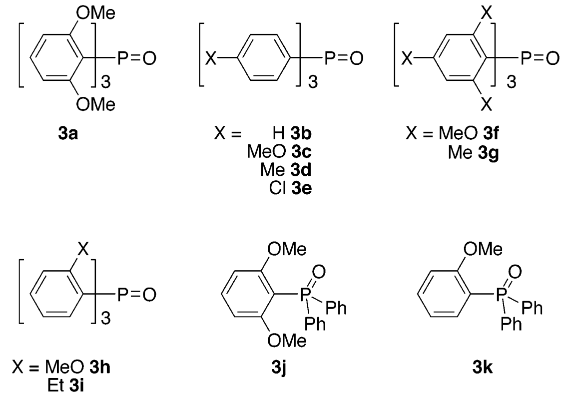


Figure 10. Various substituted phosphine oxides.

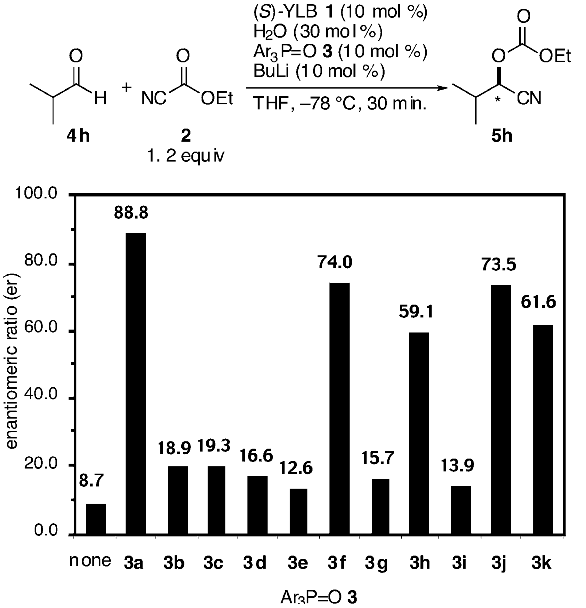


Figure 11. Effects of substituents on aromatic ring of phosphine oxides.

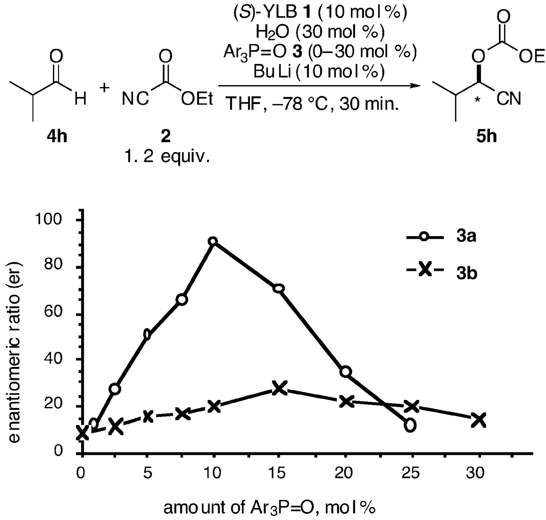


Figure 12. Effects of amount of phosphine oxides **3a** and **3b** on enantiomeric ratio.

The ratio of phosphine oxide to the YLB complex was also important to achieve optimal enantioselectivity (Figure 12). When using **3a**, just 1 equiv of **3a** to YLB **1** produced optimal enantioselectivity. Too much **3a** gradually decreased enantioselectivity, probably due to acceleration of the undesired racemic pathway without YLB. In the presence of excess **3a**, **3a** would strongly coordinate with LiCN, and LiCN might dissociate from YLB. On the other hand, the enantiomeric ratio of the product was not significantly dependent on the amount of unsubstituted phosphine oxide **3b**, the coordination ability of which would be weaker than chelating **3a**.

To obtain further insight into the role of phosphine oxide, initial rate kinetics were investigated using in situ IR. The results are summarized in Figure 13a−f.[22] In the presence of phosphine oxide, there was first-order dependency on the catalyst mixture (YLB:H_2O:$Ar_3P{=}O$:BuLi = 1:3:1:1) (Figure 13a), zero-order dependency on aldehyde (Figure 13b), and first-order dependency on ethyl cyanoformate (Figure 13c). On the other hand, in the absence of phosphine oxide, there was first-order dependency on the catalyst mixture (YLB:H_2O:BuLi = 1:3:1) (Figure 13d), zero-order dependency on the aldehyde (Figure 13e), and zero-order dependency on ethyl cyanoformate (Figure 13f). Phosphine oxide **3a** changed the rate-determining step of the reaction. In other words, phosphine oxide **3a** accelerated a step that was rate-determining without **3a**, and another step in the catalytic cycle became the new rate-determining step.

F. Active Catalyst Species and Catalytic Cycle. On the basis of experimental results and discussion in sections B, C, and E concerning H_2O, BuLi, generation of LiCN, and phosphine

---

(22) In Figure 13, initial reaction rate is shown as relative rate. Rate with the lowest concentration of variable factor is defined as standard (relative rate = 1), and other rates are shown relative to the standard. In Figure 13a,c, kinetics were measured without adding acetone cyanohydrin **8**. For detailed results of initial rate kinetics, see Supporting Information.

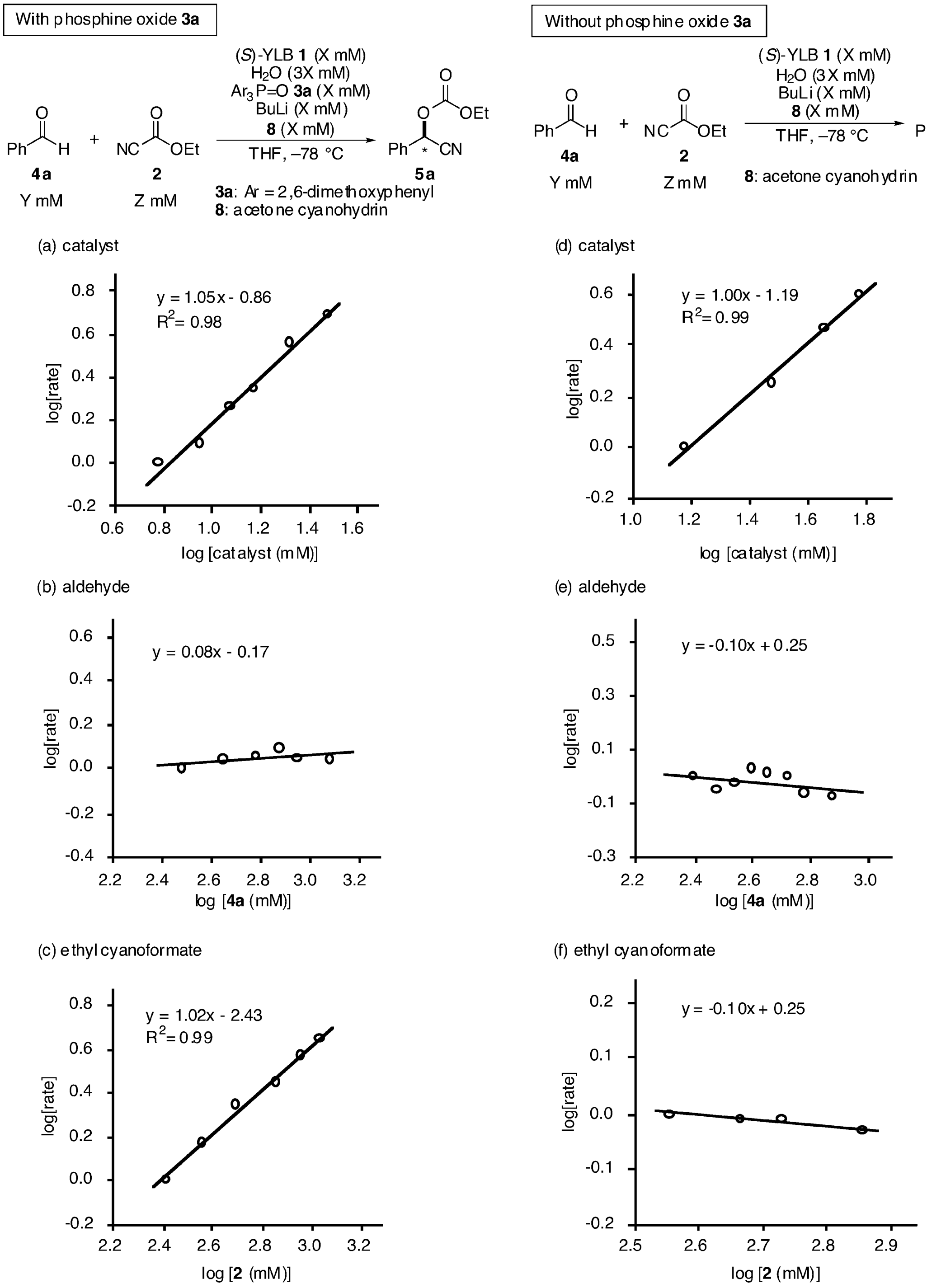


Figure 13. Initial rate kinetics (a−c) with phosphine oxide **3a**, and (d−f) without **3a**.

oxide, we hypothesize that YLB:H_2O:LiCN:phosphine oxide **3a** = 1:1:1:1 would be an active catalyst species. The structure of the proposed active catalyst species is shown in Figure 14a. H_2O would coordinate to the yttrium center and modify the chiral environment of YLB. Phosphine oxide would coordinate to the lithium cation of LiCN in a bidentate manner, thus increasing the nucleophilicity of the cyanide anion[23] as well as affecting the enantioselectivity. Both LiCN and phosphine oxide **3a** self-assembled with YLB, thus, 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. ESI-MS spectra of YLB **1** alone showed four major peaks: *m/z* = 969.3 (YLB + Li^+) as a base peak, *m/z* = 1267.9 (YLB + BINOL-Li_2 + Li^+), *m/z* = 671.4 (YLi(binaphthoxide)$_2$ + Li^+), and *m/z* = 305.3 (BINOL-Li_2 + Li^+). In the presence of phosphine oxide **3a**, H_2O, BuLi, and ethyl cyanoformate, a new peak corresponding to YLB with two **3a** and lithium, *m/z* = 1886.0 [YLB + (Ar_3P=O **3a**)$_2$ + Li^+],

---

[23] We assumed that Lewis basic phosphine oxide **3a** would coordinate to the lithium cation and increase electron density of the cyanide anion, thus increasing nucleophilicity of the cyanide anion.

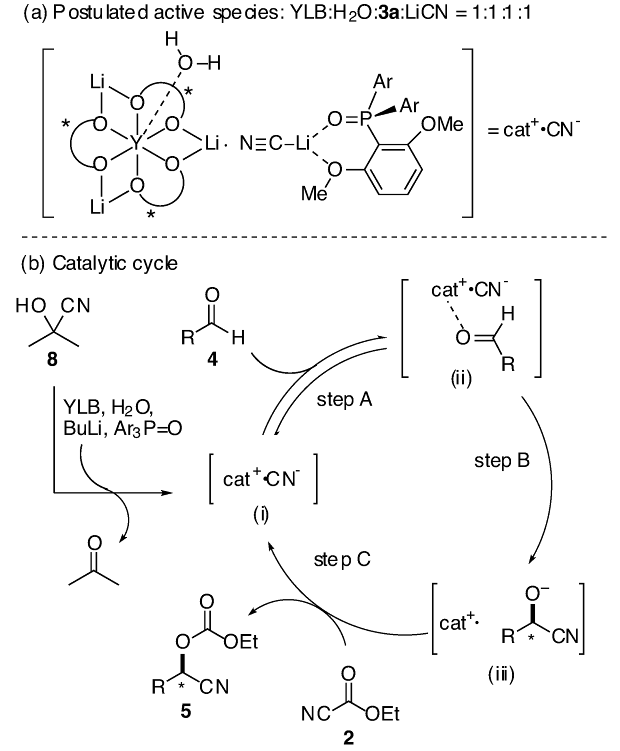


Figure 14. (a) Structure of postulated active species, and (b) proposed catalytic cycle of asymmetric cyano-ethoxycarbonylation reaction.

appeared and the peak corresponding to YLB (m/z = 969.3) disappeared.[24] Although a peak corresponding to YLB:**3a**:Li^+ = 1:1:1 was not observed under ESI-MS analysis conditions, we thought the active species would contain only one **3a** on the basis of the experiments shown in Figure 12. On the other hand, there was no peak corresponding to (Y + Li + 2 binaphtholate units). Although ESI-MS analysis does not necessarily support the structure of an active species in the catalytic cycle,[25] the results at least suggested that self-assembly of YLB with phosphine oxide **3a** and LiCN occurred, and that the framework of YLB (Y:Li:BINOL = 1:3:3) would remain unchanged in the reaction mixture with additives.[26] Because the coordination number of yttrium in YLB is assumed to be, at most, 7, the coordination site of yttrium of YLB is occupied with H_2O and three BINOLs. Aldehyde would not coordinate with the yttrium center. Aldehyde would coordinate with either lithium metal or a proton of H_2O coordinated with the yttrium center, although it is difficult to determine the exact coordination site of aldehyde through spectroscopic analysis.

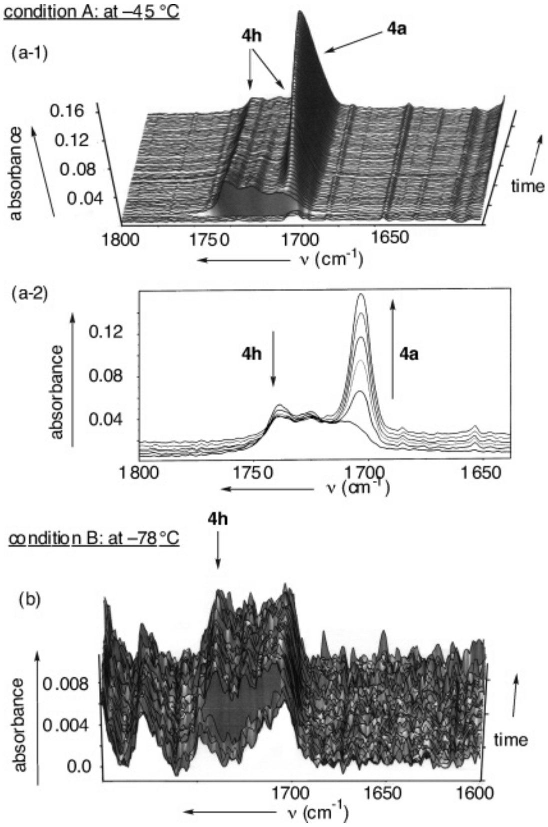
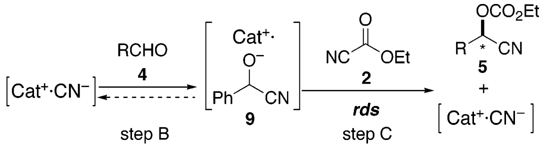


Figure 15. Profiles of IR spectra at −45 °C (condition A: a-1 and a-2) and at −78 °C (condition B: b) after addition of aldehyde **4h** to **9a**.

Scheme 4. Two Possibilities to Induce Chirality[a]



[a] Case 1: enantioselective addition of CN^- to Aldehyde **4**. Case 2: dynamic kinetic resolution of *rac*-**9**.

The postulated catalytic cycle of the reaction is shown in Figure 14b. To explain the results of the initial rate kinetics in Figure 13, the catalytic cycle should be constructed in three steps (A−C in Figure 14b). Step A: aldehyde coordinates with the active species (i) to afford (ii). Step B: cyanide attacks aldehyde activated by the catalyst, affording the cyanohydrin−catalyst complex (iii). Step C: cyanohydrin−catalyst complex (iii) reacts with ethyl cyanoformate to afford the product and to regenerate (i). In the absence of phosphine oxide **3a**, the reaction had zero-order dependency on the concentration of aldehyde and ethyl cyanoformate and first-order dependency on the catalyst mixture. Therefore, the rate-determining step without **3a** is thought to be step B. Phosphine oxide **3a** increased nucleophilicity of the cyanide anion, accelerating the rate of step B. Thus, the rate-determining step with **3a** changed to step C.

In the catalytic cycle in Figure 14b, there are two possibilities to transfer chirality from the chiral catalyst to the product, as shown in Scheme 4. One possibility is irreversible formation of the chiral cyanohydrin intermediate **9**, where enantioselective addition of cyanide to aldehyde in step B would determine the

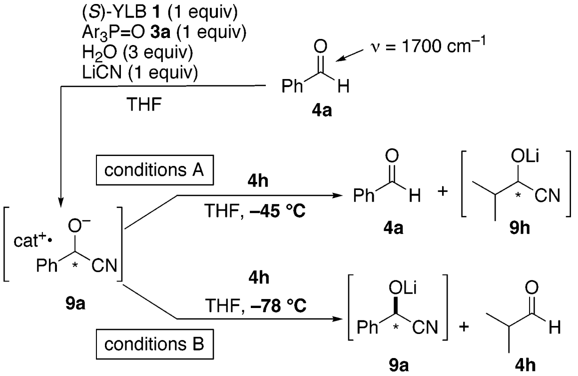
---

(24) For ESI-MS spectra of YLB **1** under various conditions, see Supporting Information.

(25) In the mechanistic studies of catalytic asymmetric reactions, the observed predominant species is not always an active species. For example, see: Landis, C.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

(26) There is a controversy whether active species of rare earth−alkali metal heterobimetallic complexes have two or three binaphtholates. Trials to unequivocally determine the structures of active species of heterobimetallic complexes in various asymmetric reactions are still ongoing. Structures of active species would change depending on the metal and nucleophile used. For a preliminary report from our group, see ref 8b. For other opinions, see ref 16. In the present cyanation reaction, $Y(HMDS)_3$:BuLi:BINOL = 1:3:3 complex (YLB **1**) provided product **5a** in 95% yield and 96% ee within 30 min at −78 °C (Table 3, entry 3), while reaction rate with $Y(HMDS)_3$:BuLi:BINOL = 1:1:2 mixture was very slow. Product was obtained in only 20% yield after 2 h, albeit in high enantiomeric excess (93%). On the other hand, $Y(HMDS)_3$:BuLi:BINOL = 0:2:1 mixture promoted the cyanation reaction of **4a** smoothly, and **5a** was obtained in 93% yield after 2 h at −78 °C, but in only 2% ee. Thus, we speculate that dissociation of Y:Li:BINOL = 1:3:3 complex into Y:Li:BINOL = 1:1:2 complex and Y:Li:BINOL = 0:2:1 complex is less likely, and that Y:Li:BINOL = 1:3:3 would be the more probable framework of active species in the present reaction. Further quantitative analysis to unequivocally determine the structure of active species will be discussed elsewhere.

Scheme 5. Evaluation of Reversibility of Cyanide Addition to Aldehyde at −45 and −78 °C



enantiomeric excess of the products. The other possibility is dynamic kinetic resolution of racemic cyanohydrin intermediate **9**. Because the reaction conditions are supposed to be somewhat basic, step B in Figure 14b might be reversible. In this case, enantioselectivity is induced during the reaction of the racemic cyanohydrin−catalyst complex with ethyl cyanoformate (step C). To determine the actual reaction pathway and enantiomer-recognizing step of the reaction, reversibility of step B in Figure 14b was examined using in situ IR analysis. The experiments are summarized in Scheme 5, and the results of in situ IR analysis are summarized in Figure 15. When benzaldehyde **4a** was treated with 1 molar equiv of YLB, 3 molar equiv of H_2O, 1 molar equiv of **3a**, and 1 molar equiv of LiCN, IR absorption of aldehyde **4a** ($\nu = 1700$ cm^{-1}) immediately disappeared, suggesting generation of cyanohydrin intermediate **9a**. Then, 1 molar equiv of aldehyde **4h** was added to the reaction mixture. The mixture was stirred at either −45 °C (condition A in Scheme 5, Figure 15a-1,a-2) or −78 °C (condition B in Scheme 5 and Figure 15b), and the IR spectra profile was monitored. As shown in Figure 15a, absorption of **4a** ($\nu = 1700$ cm^{-1}) was gradually regenerated at −45 °C, suggesting that the cyanide group was reversibly transferred from **9a** to **4h**, affording **9h**. On the other hand, at −78 °C, the peak corresponding to **4a** was not detected (Figure 15b).[27] These results indicated that cyanide 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.[28] In the present asymmetric catalysis, the catalyst recognized the enantioface of aldehydes in the cyanide addition step (step B in Figure 14b and Scheme 4).

In summary, we developed a catalytic enantioselective cyano-ethoxycarbonylation reaction of aldehydes with ethyl cyano-formate **2** using a heterobimetallic YLB **1** complex. Under optimized conditions, achiral additives, H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide **3a**, and BuLi had key roles in achieving high reactivity and enantioselectivity (up to >99% yield and up to 98% ee). The mechanism of the present reaction for generating the active nucleophilic species was different from that in previously reported reactions using related heterobimetallic complexes.[7a,b] Detailed mechanistic studies revealed that the initiation step to generate the active nucleophilic species is rather slow under the preliminary optimized conditions. To accelerate the initiation step, a catalytic amount of acetone cyanohydrin **8** was effective as an initiator. In the presence of **8**, the reaction completed within 9 min using 5 mol % catalyst at −78 °C. With **8** as an initiator, catalyst loading was successfully reduced to 1 mol %. The high reaction rate of the present catalysis is noteworthy. Roles of achiral additives and catalytic cycle of the reaction were also clarified through in situ IR analysis, initial rate kinetics, and other mechanistic experiments.

Acknowledgment. We thank Grant-in-Aid for Specially Promoted Research, Grant-in-Aid for Encouragements for Young Scientists (B) (for S.M.) from JSPS and MEXT for financial support.

Supporting Information Available: Experimental procedures, detail data for kinetic studies, and ESI-MS. This material is available free of charge via the Internet at http://pubs.acs.org.

JA042887V

---

(27) Because intensity of carbonyl absorbance of **4h** was much weaker than that of **4a**, the *y*-axis scale in Figure 15b is different from that in Figure 15a.

(28) Kinetic dynamic resolution pathway was proposed by Deng et al. when using chiral Lewis base catalyst in asymmetric cyano-ethoxycarbonylation of ketones at −12 or −24 °C. See ref 2.