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Asymmetric cyano-ethoxycarbonylation of aldehydes catalyzed by self-assembled titanium catalyst

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Abstract—A new self-assembled catalyst based on titanium complex has been developed for the effective enantioselective cyano-ethoxycarbonylation of aldehydes. The self-assembled catalyst was readily prepared from (*R*)-3,3′-bis((methyl((*S*)-1-phenylethyl)amino)methyl)-1,1′-binaphthyl-2,2′-diol (**1h**), *N*-((*1S*,*2R*)-2-hydroxy-1,2-diphenylethyl)acetamide (**2b**), and tetraisopropyl titanate (Ti(O*i*Pr)$_4$). A variety of aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes were found to be suitable substrates in the presence of the self-assembled titanium catalyst (5 mol % **1h**, 5 mol % **2b**, and 5 mol % Ti(O*i*Pr)$_4$). The desired cyanohydrin ethyl carbonates were afforded with high isolated yields (up to 95%) and moderate to good enantioselectivities (up to 92% ee) under mild conditions (at −15 °C). A possible catalytic cycle based on the experimental observation was proposed.
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1. Introduction

The asymmetric cyanation of carbonyl compounds is a useful synthetic method to prepare optically active cyanohydrins, which are versatile building blocks for the synthesis of natural products and biologically active compounds.[1] However, in contrast to the cyanation of aldehydes and ketones employing trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN) as the cyanide source in which considerable progress has been made,[2,3] the one-pot catalytic asymmetric cyanation-O-protection reaction is still less developed. Recently, several successful catalyst systems employing cyanoformate (ROCOCN), acetyl cyanide or diethyl cyanophosphonate have been studied.[4–7] Among these precedents, Deng reported a dimeric cinchona alkaloid derivative for the one-pot enantioselective cyanation of aliphatic ketones.[4] Shibasaki and Sansano et al. reported heterobimetallic complex {YLi$_3$[tris(binaphthoxide)]} and BINOLAM–Al or –Ti(IV) complex for the addition of cyanoformate (ROCOCN) to aldehydes.[5] Belokon', North, and Moberg developed a bimetallic titanium complex, and obtained the desired *O*-alkoxycarbonyl cyanohydrins with excellent results.[6] Very recently, our group investigated multicomponent titanium complex, *N*,*N*-dioxide titanium complex, mononuclear salen titanium, and heterobimetallic aluminum lithium bis(binaphthoxide) in cyano-ethoxycarbonylation of aldehydes, with good yields and enantioselectivities.[7]

In a different reaction, Mikami and Chan et al. reported self-assembly of two different chiral ligand components into a highly enantioselective titanium catalyst for carbonyl-ene reaction and addition of alkynylzinc to aldehydes.[8] Inspired by this method, we continued to search for a new highly efficient catalyst system using BINOL derivatives in combination with amino alcohol to achieve structural diversity. Thus, a set of BINOL derivatives **1a–i** and some chiral amino alcohol ligands **2a–i** were investigated (synthesis for ligands: see Section 4 for details). Herein, we wish to report these ligands that engender a more effective catalyst by self-assembly for the cyano-ethoxycarbonylation of aldehydes.

2. Results and discussion

2.1. Catalyst precursor screening

In the preliminary studies, 10 mol % complexes of **1**-Ti(O*i*Pr)$_4$ were evaluated for the addition of ethyl cyanoformate to benzaldehyde in dry CH_2Cl_2 at −15 °C (Table 1, entries 1–10). It was found that the complex of **1h**-Ti(O*i*Pr)$_4$ gave the best result (55% ee and 96% yield after 24 h, Table 1, entry 8). The reaction with complex of **1g**-Ti(O*i*Pr)$_4$ was slower, although it showed comparable enantioselectivity with **1h**-Ti(O*i*Pr)$_4$ (Table 1, entry 7). In contrast, the titanium complexes of binol (**1a**), phosphorus-containing **1b** or

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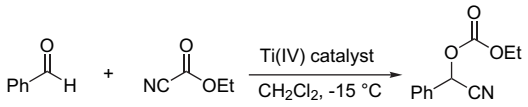
Table 1. Catalyst precursor screening



3a **4** **5a**

Entry[a]	Ti(O*i*Pr)$_4$ (mol %)	**1a–i** (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	10	**1a** (10)	48	0	—
2	10	**1b** (10)	48	0	—
3	10	**1c** (10)	48	0	—
4	10	**1d** (10)	48	0	—
5	10	**1e** (10)	48	0	—
6	10	**1f** (10)	48	85	14(*S*)
7	10	**1g** (10)	48	95	53(*S*)
8	10	**1h** (10)	24	96	55(*S*)
9	10	**1i** (10)	40	87	27(*S*)
10	5	**1h** (5)	48	87	87(*S*)

[a] Concentration of benzaldehyde: 0.5 M; EtOCOCN: 1.5 equiv.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 5a).

silicon-containing **1c**, nitrogen-containing BINOL derivatives **1d** and **1e**, did not catalyze the reaction under same reaction conditions (Table 1, entries 1–5). Gratifyingly, when the loading of **1h**-Ti(O*i*Pr)$_4$ complex was decreased from 10 to 5 mol %, higher enantioselectivity was achieved, although longer reaction time was required (87% ee after 48 h, Table 1, entry 10) (Fig. 1).

2.2. Chiral activator screening

To gain higher reactivity, some chiral activators[8a,b] **2a–i** were investigated fixing 5 mol % **1h**-Ti(O*i*Pr)$_4$ complex as the catalyst precursor (Table 2, entries 2 and 3, and 5–11). To our delight, when 5 mol % chiral acetamide **2b** was added together with 5 mol % **1h**-Ti(O*i*Pr)$_4$ complex, higher enantioselectivity was obtained and the reactivity was increased dramatically (Table 2, entry 3 vs 1), which might be attributed to the hydrogen bonding between the N–H moiety of acetamide with the oxygen atom of ethyl cyanoformate. Other combinations of chiral ligand with **1h**-Ti(O*i*Pr)$_4$ complex gave lower ee's, although higher reactivity was observed (Table 2, entries 2, 5–11). The combination of titanium binol complex with acetamide **2b** was also tested, but no product was detected (Table 2, entry 4). Therefore, **2b** was selected as the best chiral activator in the self-assembled catalytic system (Fig. 2).

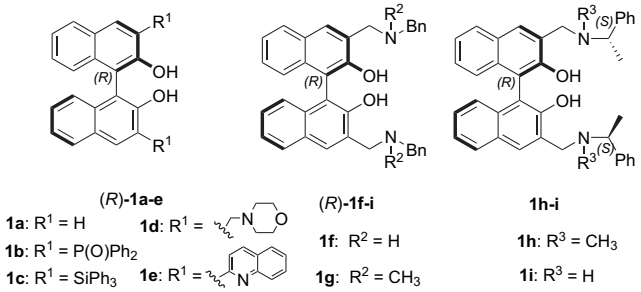


Figure 1. Structures of the ligands evaluated in this study.

Table 2. Chiral activator screening

3a **4** **5a**

Entry[a]	**1h** or **1a** (5 mol %)	**2a–i** (5 mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1h**	None	48	87	87(*S*)
2	**1h**	**2a**	20	99	17(*S*)
3	**1h**	**2b**	24	88	91(*S*)
4	**1a**	**2b**	48	0	—
5	**1h**	**2c**	24	97	60(*S*)
6	**1h**	**2d**	24	99	65(*S*)
7	**1h**	**2e**	30	99	63(*S*)
8	**1h**	**2f**	15	99	7(*S*)
9	**1h**	**2g**	20	90	15(*S*)
10	**1h**	**2h**	15	99	26(*S*)
11	**1h**	**2i**	24	90	3(*S*)

[a] Concentration of benzaldehyde: 0.5 M; Ti(O*i*Pr)$_4$: 5 mol %, EtOCOCN: 1.5 equiv.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 5a).

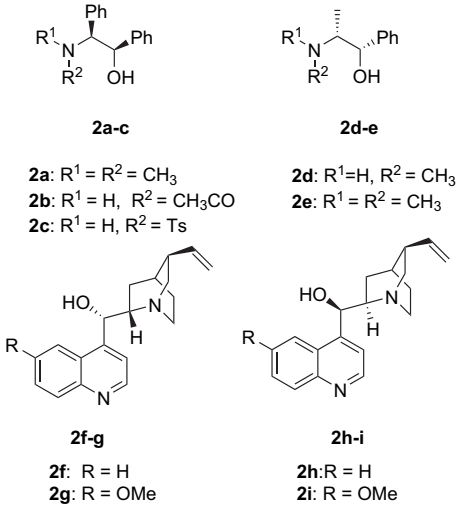


Figure 2. Structures of the chiral activators evaluated in this study.

2.3. Catalyst system optimization

In the further studies, we found that the optimum ratio of chiral ligands (**1h** and **2b**) to Ti(O*i*Pr)$_4$ was 5/5/5 (Table 3, entry 1 vs entries 2–8). Other ratios gave moderate enantioselectivity and reactivity (Table 3, entries 3 and 4, and 6–8). Changing the ratio of chiral ligands **1h**, **2b**, and Ti(O*i*Pr)$_4$ to 2.5/5/2.5 greatly decreased the reactivity (Table 3, entry 5). We also found that the desired product could not be obtained when titanium chiral acetamide **2b** was used as the catalyst (Table 3, entry 2).

Reaction solvent and other metal reagents were also examined (Table 4, entries 1–10). Among the investigated solvents, ether solvents (THF or Et$_2$O) were found to afford the product in very low yields (Table 4, entries 2 and 3). Toluene gave moderate enantioselectivity and reactivity

Table 3. Optimized ratios of chiral ligands **1h**, **2b**, and Ti(O*i*Pr)$_4$

Entry[a]	Ti(O*i*Pr)$_4$ (mol %)	**1h** (mol %)	**2b** (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	5	**1h** (5)	**2b** (5)	24	88	91(*S*)
2[d]	5	None	**2b** (5)	48	0	—
3	2.5	**1h** (2.5)	**2b** (2.5)	72	77	81(*S*)
4	5	**1h** (5)	**2b** (10)	48	76	89(*S*)
5	2.5	**1h** (2.5)	**2b** (5)	150	Trace	—
6	5	**1h** (5)	**2b** (2.5)	48	83	85(*S*)
7	10	**1h** (5)	**2b** (5)	120	70	79(*S*)
8	2.5	**1h** (5)	**2b** (5)	20	91	77(*S*)

[a] Concentration of benzaldehyde: 0.5 M in CH_2Cl_2; EtOCOCN: 1.5 equiv.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 5a).
[d] No product was obtained when employing 5 mol % of **2c**-Ti(IV) complex after 48 h, for the outcome of titanium **2a** and titanium **2d–i**, see Ref. 7b.

Table 4. The effect of reaction solvent and Lewis acid

Entry[a]	Solvent	Metal	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	Ti(O*i*Pr)$_4$	24	88	91(*S*)
2	THF	Ti(O*i*Pr)$_4$	60	10	78(*S*)
3	Et_2O	Ti(O*i*Pr)$_4$	96	Trace	—
4	$PhCH_3$	Ti(O*i*Pr)$_4$	60	45	82(*S*)
5	CH_2Cl_2	Al(O*i*Pr)$_3$	48	12	54(*S*)
6	CH_2Cl_2	Zr(O*i*Pr)$_4$	48	10	85(*S*)
7	CH_2Cl_2	Sm(O*i*Pr)$_3$	48	0	—
8	CH_2Cl_2	Yb(TfO)$_2$	48	0	—
9	CH_2Cl_2	Cu(TfO)$_2$	48	0	—

[a] Concentration of benzaldehyde: 0.5 M; 5 mol % **1h**+5 mol % **2b**+5 mol % corresponding metal reagent; EtOCOCN: 1.5 equiv; −15 °C.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis.

(Table 4, entry 4). The best result was obtained with CH_2Cl_2 (Table 4, entry 1). When other metal reagents were employed in the reaction, such as Al(O*i*Pr)$_3$, Zr(O*i*Pr)$_4$, Sm(O*i*Pr)$_3$, Yb(TfO)$_2$, and Cu(TfO)$_2$, dissatisfactory results were obtained (Table 4, entries 5–9).

Lowering the concentration of benzaldehyde from 0.5 to 0.25 resulted in lower yield and enantioselectivity (Table 5, entry 2). In contrast, the higher yields were obtained when the concentration of benzaldehyde was increased from 0.5 to 0.75 or 1.0, but the enantioselectivity was slightly decreased (Table 5, entries 3 and 4). Increasing the reaction temperature to 0 °C had little effect on the reactivity, but the enantioselectivity suffered (Table 5, entry 5). No product was observed after 48 h when the reaction temperature was lowered to −45 °C (Table 5, entry 6).

Table 5. The effect of concentration of benzaldehyde and reaction temperature

Entry[a]	Solvent	Concentration (M)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	0.5	−15	24	88	91(*S*)
2	CH_2Cl_2	0.25	−15	48	83	84(*S*)
3	CH_2Cl_2	0.75	−15	20	91	88(*S*)
4	CH_2Cl_2	1.0	−15	18	95	85(*S*)
5	CH_2Cl_2	0.5	0	18	93	78(*S*)
6	CH_2Cl_2	0.5	−45	48	Trace	—

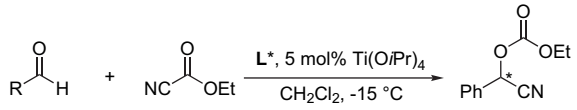
[a] Conditions: 5 mol % **1h**+5 mol % **2b**+5 mol % **Ti**(IV); EtOCOCN: 1.5 equiv.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis.

2.4. Substrate generality

To probe the generality of the self-assembled titanium catalyst in the one-pot catalytic asymmetric cyano-ethoxycarbonylation of aldehydes, a variety of aldehydes were tested under the optimal conditions (5 mol % **1h**, 5 mol % **2b**, and 5 mol % Ti(O*i*Pr)$_4$, concentration of aldehydes: 0.5 M in CH_2Cl_2, −15 °C), and the results are summarized in Table 6.

Moderate to good ee's were obtained in each case. 4-Methyl substituted benzaldehyde gave lower ee (Table 6, entry 2 vs 1), while methoxy or phenoxy substituted benzaldehyde was highly reactive and gave good ee (Table 6, entries 3–6). The product of 3-phenoxybenzaldehyde **5f** has been employed as a key intermediate in the synthesis of the insecticide fenvalerate Aa.[1e] 4-Fluorobenzaldehyde gave 92% ee after 48 h (Table 6, entry 8). 2-Naphthaldehyde gave lower ee value (Table 6, entry 7), which might be attributed to the steric hindrance. The *trans*-cinnamaldehyde gave 91% ee after 48 h (Table 6, entry 9). It was noteworthy that the enantioselectivity of hexanal was greatly increased from 45[7b] to 78% ee employing this self-assembled catalyst (Table 6, entry 10). When the temperature was lowered to −45 °C, better enantioselectivity of hexanal was afforded, but longer reaction time was required (Table 6, entry 11). Cyclohexanecarbaldehyde and propionaldehyde gave 75% ee and 76% ee after

Table 6. Asymmetric cyano-ethoxycarbonylation of aldehydes catalyzed by self-assembled titanium complex



3a-n **4** **5a-n**

L* = 5 mol % **1h** + 5 mol % **2b**

Entry[a]	Aldehydes	Time (h)	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde (**3a**)	24	88	91(*S*)
2	4-Methylbenzaldehyde (**3b**)	96	76	83(*S*)
3	2-Methoxybenzaldehyde (**3c**)	48	82	92(*S*)
4	3-Methoxybenzaldehyde (**3d**)	48	84	90(*S*)
5	4-Methoxybenzaldehyde (**3e**)	60	81	91(*S*)
6	3-Phenoxybenzaldehyde (**3f**)	24	95	89
7	2-Naphthaldehyde (**3g**)	24	91	81
8	4-Fluorobenzaldehyde (**3h**)	48	81	92
9	(*E*)-Cinnamaldehyde (**3i**)	48	83	91(*S*)
10	Hexanal (**3j**)	24	88	78(*S*)[d]
11[e]	Hexanal (**3j**)	96	64	85(*S*)[d]
12	Cyclohexanecarbaldehyde (**3k**)	24	86	75(*S*)[d]
13	Propionaldehyde (**3l**)	24	84	76(*S*)[d]
14	Isobutyraldehyde (**3m**)	24	81	62(*S*)[d]
15	Pivalaldehyde (**3n**)	24	83	74(*S*)[d]

[a] Concentration of aldehyde: 0.5 M; EtOCOCN: 1.5 equiv.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Refs. 5a and 6b).
[d] Determined by GC analysis.
[e] The reaction performed at −45 °C.

Table 7. Asymmetric cyano-ethoxycarbonylation of aldehydes catalyzed by **1h**-Ti(IV) complex

Entry[a]	Aldehydes	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-Methylbenzaldehyde (**3b**)	168	68	75(*S*)
2	2-Methoxybenzaldehyde (**3c**)	96	71	87(*S*)
3	3-Methoxybenzaldehyde (**3d**)	96	70	83(*S*)
4	4-Methoxybenzaldehyde (**3e**)	120	65	84(*S*)
5	3-Phenoxybenzaldehyde (**3f**)	48	77	81
6	2-Naphthaldehyde (**3g**)	48	78	76
7	4-Fluorobenzaldehyde (**3h**)	90	73	83
8	(*E*)-Cinnamaldehyde (**3i**)	96	70	84(*S*)
9	Hexanal (**3j**)	48	76	67(*S*)[d]
10	Cyclohexanecarbaldehyde (**3k**)	48	79	70(*S*)[d]
11	Propionaldehyde (**3l**)	48	74	61(*S*)[d]
12	Isobutyraldehyde (**3m**)	48	70	58(*S*)[d]
13	Pivalaldehyde (**3n**)	48	76	69(*S*)[d]

[a] Concentration of aldehyde: 0.5 M; 5 mol % **1h**-Ti(IV), EtOCOCN: 1.5 equiv, −15 °C.
[b] Isolated yield.
[c] Determined by HPLC on Chiral OD-H column, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Refs. 5a and 6b).
[d] Determined by GC analysis.

24 h, respectively (Table 6, entries 12 and 13). Isobutyraldehyde and pivalaldehyde gave the corresponding products with 62% ee and 74% ee after 24 h (Table 6, entries 14 and 15).

We also investigated the corresponding aldehydes with **1h**-Ti(O*i*Pr)$_4$ complex as catalyst under the same conditions (see Table 7, entries 1–10). It was found that the reaction time was longer compared with the self-assembled system (48–168 h). And the enantioselectivities were lower than the self-assembled catalyst system (58–87% ee; Table 7, entries 1–13). These results revealed that the self-assembled titanium catalyst was effective for the addition of ethyl cyanoformate to aldehydes.

2.5. Catalytic cycle considerations

According to the previous work in the field of cyano-ethoxycarbonylation of aldehyde and ketone,[4–6] the self-assembled titanium catalyst might play a multifunctional role in this reaction (see Fig. 3). The metal moiety of complex **I** might act as Lewis acid to activate the aldehyde and engender the species **II**. On the other hand, the tertiary amine moiety of complex **I** might act as Lewis base to activate the ethyl cyanoformate (EtOCOCN),[4,5c,d] and the hydrogen of acetamide (**2b**) might coordinate weakly to the oxygen atom of ethyl cyanoformate, simultaneously. Then, the activated ethyl cyanoformate transfer the cyanide to the activated aldehyde and afford the corresponding product. At the same time, a catalytic cycle was completed.

3. Conclusions

In conclusion, a new enantioselective catalyst for the synthesis of optically active cyanohydrins via ethyl cyanoformate addition to aldehydes has been developed. This study showed that a combination of two kinds of chiral ligands such as nitrogen-containing BINOL derivatives (**1h**) and acetamide (**2b**) with Ti(O*i*Pr)$_4$ generated an effective enantioselective catalyst. Compared with the multicomponent titanium catalyst, which we previously developed, the most remarkable features of this catalyst system include: (a) low amount of catalyst loading, (b) more effective for aliphatic aldehydes, (c) the mild reaction conditions, and (d) providing a different enantiomer of the cyanohydrin ethyl

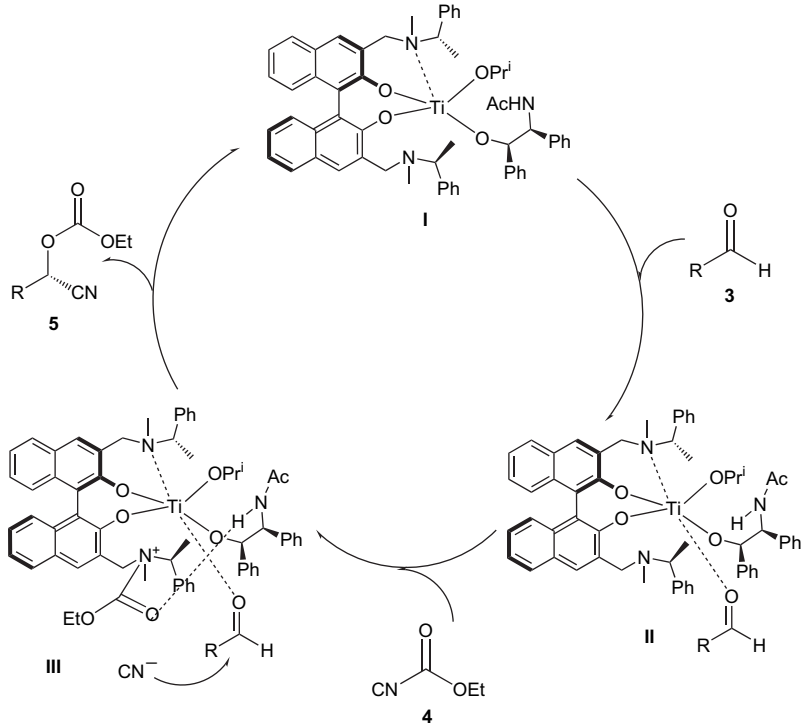


Figure 3. The proposed catalytic cycle.

carbonates. The applications of the self-assembled titanium catalyst system in other asymmetric catalytic reactions are currently underway.

4. Experimental section

4.1. General methods

^{1}H NMR spectra were recorded with 300 MHz spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ=7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s-singlet, d-doublet, t-triplet, and m-multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectroscopic data were collected with a 75 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ=77.0 ppm). Enantiomeric excesses were determined by chiral HPLC analysis on a Daicel Chiralcel OD-H column or chiral GC analysis on a Varian Chirasil DEX CB instrument in comparison with authentic racemates. Optical rotations were recorded as follows: $[\alpha]_D^T$ (*c*, g/100 mL in solvent). HRMS was recorded with ESI source (in CH_3OH).

4.2. Materials

All liquid aldehydes were used after distilled; EtOCOCN was used directly without further purification. Solvents were purified by the usual methods. Binol and ligands **2d–i** were commercially available. Ligands **1b–c**,[9] **1d**,[3e] **1e**,[10] (**1f** and **1i**),[11] and **2a–c**[12] were synthesized according to the literature procedure. Other reagents were commercially available (Scheme 1).

4.2.1. Synthesis of ligands 1f–h.

4.2.1.1. Typical procedure for the preparation of 1g and 1h. To a solution of 25 mmol formic acid (HCOOH) was slowly added 5.0 mmol of **2** (**1f** or **1i**)[11] at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1.0 h. Then the solution was refluxed for 10 h under N_2 atmosphere after 5.0 mmol of HCHO (37% aqueous) was added. The mixture was cooled to room temperature, and adjusted to pH 9–10 with K_2CO_3. The resulting mixture was extracted by CH_2Cl_2 (3×20 mL) and the combined organic phases were dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate (3/1, v/v) as an eluent to give BINOL derivatives **1g** and **1h**.

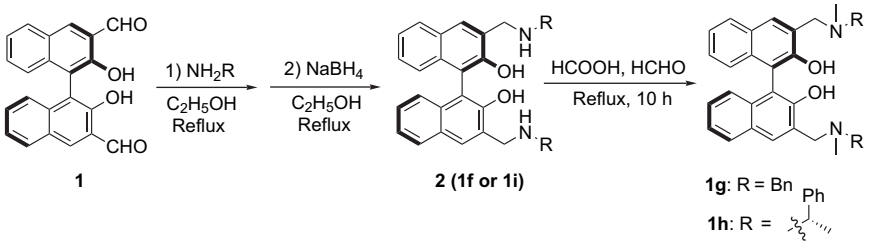
*4.2.1.1.1. (R)-3,3′-Bis((benzyl(methyl)amino)methyl)-1,1′-binaphthyl-2,2′-diol (**1g**).* Yield 87%; lightly yellow solid, mp 128–130 °C, $[\alpha]_D^{23}$ +50.52 (*c* 2.0 in $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ=2.28 (s, 6H), 3.60 (d, *J*=12.9 Hz, 2H), 3.72 (d, *J*=13.1 Hz, 2H), 3.94 (d, *J*=13.7 Hz, 2H), 4.12–4.22 (m, 2H), 5.06 (s, 2H), 7.17–7.29 (m, 16H), 7.96 (s, 2H), 7.80 (d, *J*=8.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$), 41.02, 61.30, 61.75, 116.72, 122.93, 124.66, 124.85, 126.03, 127.52, 127.65, 127.89, 128.28, 128.43, 129.61, 133.96, 136.62, 153.62. HRMS (ESI, CH_3OH) calcd for $C_{38}H_{36}N_2O_2$ $(M)^+$: requires 552.2777, found: 552.2709.

*4.2.1.1.2. (R)-3,3′-Bis((methyl((S)-1-phenylethyl)amino)methyl)-1,1′-binaphthyl-2,2′-diol (**1h**).* Yield 89%; lightly yellow solid, mp 244–246 °C, $[\alpha]_D^{23}$ +17.86 (*c* 2.0 in $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ=1.50 (d, *J*=6.9 Hz, 6H), 2.24 (s, 6H), 3.83–3.91 (m, 4H), 4.13 (d, *J*=13.9 Hz, 2H), 5.23 (s, 2H), 7.18–7.34 (m, 16H), 7.62 (s, 2H), 7.77 (d, *J*=7.9 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$), 17.40, 29.69, 37.02, 58.76, 62.22, 116.51, 122.82, 124.75, 125.90, 127.56, 127.73, 128.26, 128.40, 129.61, 133.79, 139.94, 153.93. HRMS (ESI, CH_3OH) calcd for $C_{40}H_{40}N_2O_2$ $(M)^+$: requires 580.3156, found: 580.3090.

4.2.1.2. Typical procedure for optically active cyanohydrin ethyl carbonates. $Ti(OiPr)_4$ (1.0 M in toluene, 12.5 μL, 0.0125 mmol) was added to a solution of **1h** (7.25 mg, 0.0125 mmol) and **2b** (3.18 mg, 0.0125 mmol) in CH_2Cl_2, and the mixture was stirred at 30 °C for 1.0 h under N_2. Followed by the addition of the corresponding aldehyde (0.25 mmol, Table 6, entries 1–15) and EtOCOCN at −15 °C after 30 min, the contents were stirred for the indicated time in tables, and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether, 10/1, v/v) to afford the corresponding cyanohydrin carbonates.

*4.2.1.2.1. 2-Ethoxycarbonyl (S)-2-hydroxy-2-phenyl-acetonitrile (**5a**).* Yield 88%; colorless oil, $[\alpha]_D^{23}$ −17.8 (*c* 2.0 in $CHCl_3$) (91% ee). HPLC (OD-H column), 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R (minor)= 8.9 min and t_R (major)=10.6 min. {Lit.[5a] $[\alpha]_D^{21.7}$ +16.2 (*c* 2.8 in $CHCl_3$) for *R* enantiomer in 94% ee}. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.34 (t, *J*=7.1 Hz, 3H), 4.26–4.32 (m, 2H), 6.27 (s, 1H), 7.45–7.49 (m, 3H), 7.53–7.56 (m, 2H) ppm.

*4.2.1.2.2. 2-Ethoxycarbonyl (S)-2-hydroxy-2-(4-methylphenyl)-acetonitrile (**5b**).* Yield 76%; colorless oil, $[\alpha]_D^{23}$ −4.5 (*c* 2.0 in $CHCl_3$) (83% ee). HPLC (OD-H column), 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=8.26 min and t_R (major)=9.24 min. {Lit.[6b] $[\alpha]_D^{16}$ −5.1(*c* 2.0 in $CHCl_3$) for *S* enantiomer in



Scheme 1. The route for preparation of **1f–i**.

94% ee}. ^{1}H NMR ($CDCl_3$), δ=1.33 (t, J=7.1 Hz, 3H), 2.39 (s, 3H), 4.22–4.33 (m, 2H), 6.22 (s, 1H), 7.25 (d, J=7.9 Hz, 2H), 7.43 (d, J=8.1 Hz, 2H) ppm.

*4.2.1.2.3. 2-Ethoxycarbonyl (S)-2-hydroxy-2-(2-methoxylphenyl)-acetonitrile (**5c**).* Yield 82%; colorless oil, $[\alpha]_D^{23}$ +51.7 (c 2.0 in $CHCl_3$) (92% ee). HPLC (OD-H column), 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=6.3 min and t_R (major)=8.8 min. {Lit.[6b] $[\alpha]_D^{20}$ +57.0 (c 1.4 in $CHCl_3$) for S enantiomer in 98% ee}. ^{1}H NMR ($CDCl_3$), δ=1.30 (t, J=7.1 Hz, 3H), 3.87 (s, 3H), 4.24–4.32 (m, 2H), 6.58 (s, 1H), 6.93 (dd, J=8.3, 1.6 Hz, 1H), 7.05 (dt, J=8.2, 1.6 Hz, 1H), 7.42 (dt, J=8.2, 1.6 Hz, 1H), 7.58 (dd, J=8.2, 1.6 Hz, 1H) ppm.

*4.2.1.2.4. 2-Ethoxycarbonyl (S)-2-hydroxy-2-(3-methoxylphenyl)-acetonitrile (**5d**).* Yield 84%; colorless oil, $[\alpha]_D^{23}$ −10.4 (c 2.0 in $CHCl_3$) (90% ee). HPLC (OD-H column), 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=11.92 min and t_R (major)=15.77 min. Lit.[6b] $[\alpha]_D^{20}$ −11.3 (c 1.2 in $CHCl_3$) for S enantiomer in 99% ee. ^{1}H NMR ($CDCl_3$), δ=1.33 (t, J=7.1 Hz, 3H), 3.81 (s, 3H), 4.23–4.31 (m, 2H), 6.22 (s, 1H), 6.96–7.11 (m, 3H), 7.31–7.34 (t, J=7.9 Hz, 1H) ppm.

*4.2.1.2.5. 2-Ethoxycarbonyl (S)-2-hydroxy-2-(4-methoxylphenyl)-acetonitrile (**5e**).* Yield 81%; colorless oil, $[\alpha]_D^{23}$ +2.2 (c 2.0 in $CHCl_3$) (91% ee). HPLC (OD-H column), 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=13.5 min and t_R (major)=16.9 min. {Lit.[6b] $[\alpha]_D^{20}$ +1.8 (c 1.8 in $CHCl_3$) for S enantiomer in 95% ee}. ^{1}H NMR ($CDCl_3$), δ=1.30 (t, J=7.2 Hz, 3H), 3.81 (s, 3H), 4.19–4.30 (m, 2H), 6.19 (s, 1H), 6.93 (d, J=8.8 Hz, 2H), 7.46 (d, J=8.8 Hz, 2H) ppm.

*4.2.1.2.6. 2-Ethoxycarbonyl 2-hydroxy-2-(3-phenoxyphenyl)-acetonitrile (**5f**).*[7b] Yield 95%; colorless oil, $[\alpha]_D^{23}$ −2.9 (c 2.0 in $CHCl_3$) (89% ee). HPLC (OD-H column), 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R (major)=7.8 min and t_R (minor)=9.8 min. ^{1}H NMR ($CDCl_3$), δ=1.34 (t, J=7.1 Hz, 3H), 4.24–4.35 (m, 2H), 6.22 (s, 1H), 7.02–7.05 (m, 1H), 7.17–7.19 (m, 2H), 7.28–7.35 (m, 3H), 7.38 (m, 3H) ppm.

*4.2.1.2.7. 2-Ethoxycarbonyl (S)-2-hydroxy-2-(2-naphthyl)-acetonitrile (**5g**).*[7b] Yield 91%; white solid, $[\alpha]_D^{23}$ +6.1(c 2.0 in $CHCl_3$) (81% ee). HPLC (OD-H column), 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=9.6 min and t_R (major)=10.3 min. ^{1}H NMR ($CDCl_3$), δ=1.35 (t, J=7.1 Hz, 3H), 4.25–4.37 (m, 2H), 6.44 (s, 1H), 7.55–7.61 (m, 3H), 7.89–8.05 (m, 3H), 8.04–8.05 (m, 1H) ppm.

*4.2.1.2.8. 2-Ethoxycarbonyl 2-hydroxy-2-(4-fluorophenyl)-acetonitrile (**5h**).*[7b] Yield 81%; colorless oil, $[\alpha]_D^{23}$ −20.1 (c 2.0 in $CHCl_3$) (92% ee). HPLC (OD-H column), 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R (minor)=10.0 min and t_R (major)=11.8 min. ^{1}H NMR ($CDCl_3$), δ=1.33 (t, J=7.2 Hz, 3H), 4.24–4.33 (m, 2H), 6.24 (s, 1H), 7.11–7.17 (m, 2H; Ar–*H*), 7.52–7.57 (m, 2H) ppm.

*4.2.1.2.9. 2-Ethoxycarbonyl (S)-2-hydroxy-4-phenyl-but-3-enonitrile (**5i**).* Yield 83%; colorless oil, $[\alpha]_D^{23}$ +24.0 (c 2.0 in $CHCl_3$) (91% ee). HPLC (OD-H column), 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R (major)=11.93 min and t_R (minor)=12.15 min {Lit.[5a] $[\alpha]_D^{20}$ −17.2 (c 0.9 in $CHCl_3$) for R enantiomer in 88% ee}. ^{1}H NMR ($CDCl_3$), δ=1.36 (t, J=7.1 Hz, 3H), 4.27–4.34 (m, 2H), 5.89 (d, J=6.8 Hz, 1H), 6.26 (dd, J=15.8, 6.8 Hz, 1H), 7.02 (d, J=15.8 Hz, 1H), 7.34–7.45 (m, 5H) ppm.

*4.2.1.2.10. (S)-2-Ethoxycarboxyheptanenitrile (**5j**).* Yield 88%; colorless oil, $[\alpha]_D^{23}$ −53.6 (c 2.0 in $CHCl_3$) (78% ee). GC [Varian Chirasil DEXCB (0.25 mm×25 m), detection temp 110 °C; initial column temp 230 °C; injection temp 250 °C; t_R (minor)=30.4 min and t_R (major)=32.2 min. {Lit.[5b] $[\alpha]_D^{23}$ +61.7 (c 2.21 in $CHCl_3$) for R enantiomer in 94% ee}. ^{1}H NMR ($CDCl_3$), δ=0.87–0.90 (m, 3H), 1.31–1.32 (m, 7H), 1.46–1.54 (m, 2H), 1.89–1.94 (m, 2H), 4.23–4.32 (m, 2H), 5.19 (t, J=6.7 Hz, 1H) ppm.

*4.2.1.2.11. 2-Ethoxycarbonyl (S)-2-hydroxy-2-cyclohexylethanonitrile (**5k**).* Yield 86%; colorless oil, $[\alpha]_D^{23}$ −49.7 (c 2.0 in $CHCl_3$) (75% ee). GC [Varian Chirasil DEXCB (0.25 mm×25 m), detection temp 130 °C; initial column temp 250 °C; injection temp 250 °C; t_R (minor)=29.1 min and t_R (major)=29.7 min. {Lit.[5b] $[\alpha]_D^{27.4}$ +53.4 (c 2.21, $CHCl_3$) for R enantiomer in 96% ee}. ^{1}H NMR ($CDCl_3$), δ=1.21–1.32 (m, 6H), 1.33 (t, J=7.2 Hz, 3H), 1.73–2.05 (m, 5H), 4.21–4.33 (m, 2H), 5.14 (d, J=5.8 Hz, 1H) ppm.

*4.2.1.2.12. 2-Ethoxycarbonyl (S)-2-hydroxy-butanitrile (**5l**).* Yield 76%, $[\alpha]_D^{25}$ −77.1 (c 2.0 in $CHCl_3$) (76% ee). GC [Varian Chirasil DEXCB (0.25 mm×25 m), detection temp 80 °C; initial column temp 200 °C; injection temp 250 °C; t_R (minor)=20.01 min and t_R (major)=24.17 min. {Lit.[5b] $[\alpha]_D^{23}$ +87.0 (c 1.0 in $CHCl_3$) for R enantiomer in 92% ee}. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.12 (dd, J=7.2 Hz, 3H), 1.34 (dd, J=7.1 Hz, 3H), 1.90–2.10 (m, 2H), 4.25–4.30 (m, 2H), 5.14 (dd, J=6.7 Hz, 1H) ppm.

*4.2.1.2.13. 2-Ethoxycarbonyl (S)-3-methylbutanenitrile (**5m**).* Yield 81%, $[\alpha]_D^{25}$ −50.2 (c 2.0 in $CHCl_3$) (62% ee). GC [Varian Chirasil DEXCB (0.25 mm×25 m), detection temp 80 °C; initial column temp 200 °C; injection temp 250 °C; t_R (minor)=24.973 min and t_R (major)=28.307 min. {Lit.[6b] $[\alpha]_D^{20}$ −59.8 (c 1.0 in $CHCl_3$) for S enantiomer in 79% ee}. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.1–1.2 (m, 6H), 1.34 (t, J=7.1 Hz, 3H), 2.1–2.2 (m, 1H), 4.3–4.4 (m, 2H), 5.1 (d, J=5.8 Hz, 1H) ppm.

*4.2.1.2.14. 2-Ethoxycarbonyl (S)-3,3′-dimethylbutanenitrile (**5n**).* Yield 83%, $[\alpha]_D^{25}$ −49.7 (c 2.0 in $CHCl_3$) (74% ee). GC [Varian Chirasil DEXCB (0.25 mm×25 m), detection temp 80 °C; initial column temp 200 °C; injection temp 250 °C; t_R (minor)=30.798 min and t_R (major)=32.798 min. {Lit.[6b] $[\alpha]_D^{20}$ −48.5 (c 1.0 in $CHCl_3$) for S enantiomer in 73% ee}. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.08 (s, 9H), 1.32 (dd, J=7.2 Hz, 3H), 4.25 (m, 2H), 4.89 (s, 1H) ppm.

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References and notes

1. For reviews on the syntheses and applications of cyanohydrins, see: (a) North, M. *Science of Synthesis*; Murahashi, S.-I., Ed.; Thieme: Stuttgart, 2004; Vol. 19, pp 235–284; (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989–1999; (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, NY, 2001; pp 1239–1240; (d) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley: New York, NY, 2000; pp 235–284; (e) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (f) Mori, A.; Inoue, S. Cyanation of Carbonyl and Amino Groups. In *Comprehensive Asymmetric Synthesis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 983–992; (g) Effenberger, F. *Angew. Chem.* **1994**, *106*, 1609–1619.
2. For recent reviews on cyanation reactions, see: (a) Chen, F. X.; Feng, X. M. *Curr. Org. Synth.* **2006**, *3*, 77–97; (b) Thierry, R. J. A.; Lisa, A. C.; North, M. *Synlett* **2005**, 1828–1847; (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491–1508; (d) Chen, F. X.; Feng, X. M. *Synlett* **2005**, 892–899; (e) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752–2778; (f) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (g) Gröger, H. *Chem.—Eur. J.* **2001**, *7*, 5246–5251.
3. For selected recent examples, see: (a) Liu, X. H.; Qin, B.; Zhou, X.; He, B.; Feng, X. M. *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225; (b) Ryu, H.-D.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384–5387; (c) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; (d) Wen, Y. H.; Huang, X.; Hang, J. L.; Xiong, Y.; Qin, B.; Feng, X. M. *Synlett* **2005**, 2445–2447; (e) Qin, Y. C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381–2383; (f) Li, Y.; He, B.; Qin, B.; Feng, X. M.; Zhang, G. L. *J. Org. Chem.* **2004**, *69*, 7910–7913; (g) Tian, S. K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; (h) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589–2592; (i) Chen, F. X.; Zhou, H.; Liu, X. H.; Qin, B.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Chem.—Eur. J.* **2004**, *10*, 4790–4797.
4. Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.
5. (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636–3638; (b) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413–3422; (c) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385–2389; (d) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197–200; (e) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143–3146; (f) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Chem.—Eur. J.* **2005**, *11*, 3849–3862; (g) Baeza, A.; Casas, J.; Nájera, C.; Sansano, J.; Saá, J. M. *Eur. J. Org. Chem.* **2006**, 1949–1958.
6. (a) Belokon', Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505–4508; (b) Belokon', Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433–10447; (c) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593.
7. (a) Li, Q. H.; Chang, L.; Liu, X. H.; Feng, X. M. *Synlett* **2006**, 1675–1678; (b) Gou, S. H.; Chen, X. H.; Xiong, Y.; Feng, X. M. *J. Org. Chem.* **2006**, *71*, 5732–5736; (c) Chen, S. K.; Peng, D.; Zhou, H.; Wang, L. W.; Chen, F. X.; Feng, X. M. *Eur. J. Org. Chem.* **2006**, 639–644; (d) Gou, S. H.; Wang, J.; Liu, X. H.; Wang, W. T.; Chen, F. X.; Feng, X. M. *Adv. Synth. Catal.* **2007**, *349*, 343–349.
8. (a) Mikami, K.; Matasukawa, S.; Volk, T.; Terada, M. *Angew. Chem.* **1997**, *109*, 2936–2939; (b) Mikami, K.; Terada, M.; Korenage, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532–3556; (c) Li, X. S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637.
9. (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *Adv. Synth. Catal.* **2005**, *347*, 1561–1568; (b) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975–2976.
10. Guo, S. Q.; Lu, N. Y.; Liu, B.; Xiao, J.; Li, J. S. *J. Organomet. Chem.* **2006**, *691*, 1282–1287.
11. Lin, J.; Rajaram, A. R.; Pu, L. *Tetrahedron* **2004**, *60*, 11277–11281.
12. (a) Jiang, Y. Z.; Mi, A. Q.; Wang, Z. Y.; Li, S. J. *Chin. J. Org. Chem.* **1994**, *14*, 68–73; (b) Jiang, Y. Z.; Qin, Y.; Mi, A. Q.; Li, Z.; Chen, X. Z.; Yang, D. G. *Chin. J. Org. Chem.* **1996**, *16*, 29–33.