DOI: 10.1002/ejoc.200600795

Highly Enantioselective Cyanoformylation of Aldehydes Catalyzed by a Mononuclear Salen-Ti(O*i*Pr)$_4$ Complex Produced In Situ

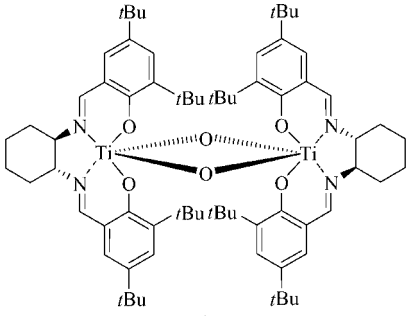
Shi-Kui Chen,[a] Dan Peng,[a] Hui Zhou,[a] Li-Wei Wang,[a] Fu-Xue Chen,[a] and Xiao-Ming Feng*[a,b]

Keywords: Asymmetric catalysis / Cyanohydrin / In situ preparation / Solvent effects / Titanium

An efficient enantioselective cyanoformylation of aldehydes with ethyl cyanoformate, catalyzed by a salen-Ti(O*i*Pr)$_4$ complex generated in situ, has been developed. Studies of nonlinear effects indicated that the mononuclear salen-titanium complex, and not a heterochiral complex, played a key role in the stereodiscriminating step of the reaction. During the preparation of the catalyst, the addition of isopropyl alcohol was shown to avoid the formation of a heterochiral complex. In the presence of 5 mol-% catalyst, the reaction can be carried out in excellent yields (up to 99%) and with high enantioselectivities (up to 91% *ee*). From preliminary studies, a transition state to explain the origin of the asymmetric induction has been proposed.

Introduction

Optically active cyanohydrins are of great interest for a series of chiral, nonracemic compounds, such as β-amino alcohols and α-hydroxy carbonyl compounds,[1] many of them serving as highly versatile building blocks in the synthesis of biologically active products and chiral medicinal agents. The last two decades have witnessed the study of a variety of chiral catalyst systems using hydrogen cyanide (HCN) or trimethylsilyl cyanide (TMSCN) as the cyanide source in reactions with carbonyl compounds.[2,3] Because of the volatile and hence hazardous natures of these reagents, however, cyanoformate esters (ROCOCN), acetyl cyanide, or diethyl cyanophosphonate have been investigated as alternatives, and several successful catalytic systems for the cyanation of aldehydes and ketones with the aid of these new cyanide sources have been developed. Deng's group found that a chiral tertiary amine catalyst gave excellent yields and good enantioselectivities for cyanations of ketones,[4] Belokon' and North's group developed salen-titanium bimetallic catalyst **1**, which was found to be efficient for additions of ethyl cyanoformate to aldehydes,[5] Moberg and coworkers described the crucial importance of dual Lewis acid/Lewis base activation in cyanations of aldehydes with acetyl cyanide and cyanoformate as cyanide sources,[6] Shibasaki's group demonstrated the utility of a {YLi$_3$[tris(binaphthoxide)]} single catalyst in asymmetric cyanoethoxycarbonylation reactions of aldehydes,[7] and Sansano et al. first reported the use of BINOLAM-Ti^{IV} complexes in asymmetric cyanobenzoylations of aldehydes at room temperature and without additives.[8] Very recently, our group has presented multicomponent titanium and *N*,*N*-dioxide titanium catalysts in cyanoformylations of aldehydes, with good yields and enantioselectivities being obtained,[9] while in our previous study the mononuclear salen-Ti(O*i*Pr)$_4$ complex was successfully utilized in cyanosilylations of carbonyl compounds.[10] Combining these precedents, we now wish to report the use of the salen-Ti(O*i*Pr)$_4$ mononuclear complex generated in situ in catalytic asymmetric additions of ethyl cyanoformate to aldehydes, providing very stable enantiomerically enriched O-protected cyanohydrins – very interesting from the general synthetic point of view – in only one step.



1

[a] Key Laboratory of Green Chemistry and Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University,
Chengdu 610064, China
Fax: +86-28-85418249
E-mail: xmfeng@scu.edu.cn
[b] State Key Laboratory of Biotherapy, West China Hospital, Sichuan University,
Chengdu 610041, China

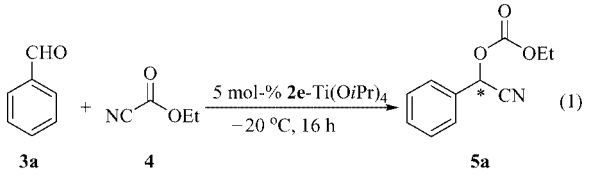
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

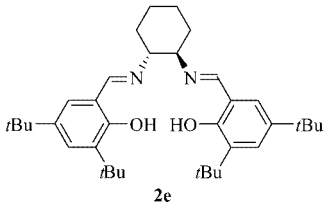
Results and Discussion

The Effect of Isopropyl Alcohol

In the preliminary study, (1*R*,2*R*)-**2e**-Ti(O*i*Pr)$_4$ complex was used as the catalyst and chloroform as the solvent to perform the asymmetric addition of ethyl cyanoformate (**4**) to benzaldehyde (**3a**) [Equation (1)], but only a 19% isolated yield and a 72% *ee* were obtained (Table 1, Entry 1), perhaps because of the formation of a multinuclear complex. With reference to Carreira's previous study,[11] we speculated that the addition of isopropyl alcohol might prevent multinuclear complex formation, so isopropyl alcohol was added to enhance the reactivity and enantioselectivity. As shown in Table 1, the enantioselectivity improved slightly as the molar ratio of isopropyl alcohol to benzaldehyde was increased from 10 to 100 mol-% (Entries 1–4).

Table 1. Effects of solvents in the asymmetric cyanoformylation of benzaldehyde with ethyl cyanoformate.[a]





2e

Entry	Solvent	*i*PrOH/Solvent[b]	Yield [%][d]	*ee* [%][e]
1	$CHCl_3$	–	19	72
2	$CHCl_3$	10 mol-%[c]	21	73
3	$CHCl_3$	50 mol-%[c]	22	76
4	$CHCl_3$	100 mol-%[c]	24	78
5	$CHCl_3$	1:9	77	88
6	$CHCl_3$	1:4	99	91
7	$CHCl_3$	3:7	99	89
8	$CHCl_3$	1:1	99	87
9	*i*PrOH	–	trace	–
10	CH_2Cl_2	1:4	99	89
11	toluene	1:4	20	84
12	THF	1:4	42	90
13	CH_2ClCH_2Cl	1:4	48	90
14	CH_3CN	1:4	99	84

[a] All reactions were performed with benzaldehyde (0.4 mmol) and **4** (0.6 mmol) in solvent (0.8 mL) at –20 °C over 16 h. Catalyst consisted of a 1:1 molar ratio of ligand **2e** to Ti(O*i*Pr)$_4$; catalyst loading was 5 mol-%. [b] The volume ratio relative to the solvent (0.8 mL in all), unless otherwise indicated. [c] The molar ratio relative to benzaldehyde. [d] Isolated yield. [e] The *ee* values were determined by HPLC with a Chiralcel OD-H column. The absolute configuration was (*S*), by comparison with the sign of the reported optical rotation value.[5a]

Encouraged by these results, we next studied the volume ratio of the isopropyl alcohol/chloroform mixture (Entries 5–8). The best ratio should be 1:4 (Entry 6, up to 91% *ee*). If the ratio is decreased to 1:9, the reaction proceeds slowly and affords the product in a lower isolated yield (Entry 5), whereas at a higher volume ratio (Entries 7 and 8) the yield and the enantioselectivity scarcely changed. If isopropyl alcohol is used as the solvent, however, no reaction was observed, which might be explained by the low solubility of ligand **2e** in it (Entry 9). The best result (99% yield, 91% *ee*, Entry 6) was obtained with the optimal ratio between *i*PrOH and $CHCl_3$ (1:4 v/v, 0.8 mL). If CH_2Cl_2 or CH_3CN mixed with isopropyl alcohol is used as the solvent, the enantioselectivity decreases appreciably (Entries 10, 14), whereas poor yields are obtained when toluene, THF, and CH_2ClCH_2Cl are employed (Entries 11–13).

To gain some insight into the effect of isopropyl alcohol, the nonlinear effect was studied. As shown in Figure 1, when a mixture of *i*PrOH/$CHCl_3$ (1:4 v/v, 0.8 mL) was used as the solvent, the *ee* values between ligand **2e** and product **5a** were perfectly linear (Figure 1, ▲), while without the addition of isopropyl alcohol a multishaped nonlinear effect was observed (Figure 1, ■), which indicated that a small quantity of heterochiral complex might be being formed: that is, that the presence of isopropyl alcohol did suppress the formation of heterochiral complex in the catalyst preparation step. It also demonstrated that homochiral complex **2e**-Ti(O*i*Pr)$_4$ (1:1) played a key role in the stereodiscriminating step of the reaction.[12]

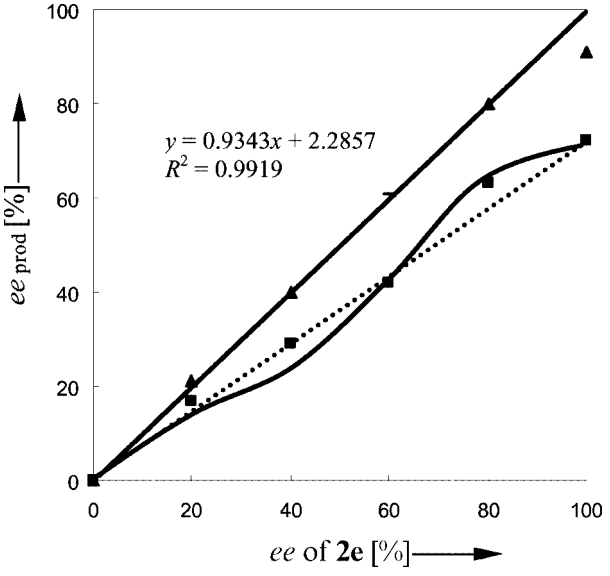
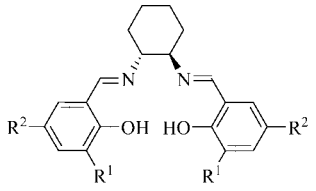


Figure 1. Studies of the nonlinear effect in the reaction between benzaldehyde and ethyl cyanoformate in an *i*PrOH/$CHCl_3$ mixture (1:4 v/v, 0.8 mL) as solvent (▲), and in chloroform as solvent (■).

Catalyst Optimization

To obtain higher enantioselectivities, some mono complexes of easily accessible ligands (as shown in Figure 2) with Ti(O*i*Pr)$_4$ were tested in the reaction between benzal-

dehyde and ethyl cyanoformate. These tests showed that the yield and enantiomeric excess of product **5a** were greatly affected by the substituents on the salen ligands: as shown in Table 2, the best ligand was **2e**, derived from the ligand bearing *t*Bu groups at the 3′- and the 5′-positions in the salicylidene phenolic rings (99% yield, 91% *ee*, Entry 5), whereas the presence of smaller substituents at the 3′- and 5′-positions decreased the enantioselectivity considerably (Entries 1–4). However, the presence of the much bulkier 1-adamantanyl group at the 3′-position resulted in the abolition of catalytic activity (Entry 6). In addition, ligands with electron-donating or -withdrawing substituents showed considerable decreases in both reactivity and enantioselectivity (Entries 7–9). A series of metals were then screened in combination with ligand **2e** (Entries 10–12), but, unfortunately, no adduct was detected when $TiCl_4$, $Al(OiPr)_4$, or $Zr(OiPr)_4$ were used as metal salts (Entries 10–12).



2a: R^1 = H, R^2 = *t*Bu
2b: R^1 = H, R^2 = Ph
2c: R^1 = Ph, R^2 = H
2d: R^1 = *t*Bu, R^2 = CH_3
2e: R^1 = *t*Bu, R^2 = *t*Bu
2f: R^1 = 1-Adamantanyl, R^2 = *t*Bu
2g: R^1 = H, R^2 = OMe
2h: R^1 = H, R^2 = Br
2i: R^1 = H, R^2 = Cl

Figure 2. Ligands assessed in this study.

Table 2. Effects of ligands and metal compounds in this catalysis.[a]

Entry	Ligand	Metal compound	Time [h]	Yield [%][b]	*ee* [%][d]
1	**2a**	$Ti(OiPr)_4$	22	99	57
2	**2b**	$Ti(OiPr)_4$	22	94	44
3	**2c**	$Ti(OiPr)_4$	20	92	46
4	**2d**	$Ti(OiPr)_4$	20	90	62
5	**2e**	$Ti(OiPr)_4$	16	99	91
6	**2f**	$Ti(OiPr)_4$	40	0	–
7	**2g**	$Ti(OiPr)_4$	40	99	50
8	**2h**	$Ti(OiPr)_4$	40	20	47
9	**2i**	$Ti(OiPr)_4$	40	43	46
10	**2e**	$TiCl_4$	40	N.D.[c]	–
11	**2e**	$Al(OiPr)_3$	40	N.D.[c]	–
12	**2e**	$Zr(OiPr)_4$	40	N.D.[c]	–

[a] All reactions were performed with benzaldehyde (0.4 mmol) and **4** (0.6 mmol) in an *i*PrOH/$CHCl_3$ (1:4 v/v, 0.8 mL) mixture at –20 °C. Catalyst consisted of a 1:1 molar ratio of ligands to $Ti(OiPr)_4$; catalyst loading was 5 mol-%. [b] Isolated yield. [c] N.D. = Not detected. [d] The *ee* values were determined by HPLC with a Chiralcel OD-H column. The absolute configuration was (*S*), by comparison with the sign of a reported optical rotation value.[5a]

Subsequently, the molar ratio of ligand **2e** to $Ti(OiPr)_4$ was surveyed, and, as shown in Table 3 (Entries 1–5), the enantioselectivity hardly varied with changes in this molar ratio, which might be an indication that with the addition of no isopropyl alcohol a multinuclear complex was formed in the reaction. Accordingly, the optimal molar ratio should be 1:1 (Entry 1). The effect of catalyst loading was also studied, but, unfortunately, when the catalyst loading was 2.5 mol-%, almost no adduct was detected (Entry 6) and the optimal catalyst loading should therefore be 5 mol-%.

Table 3. Effects of the ligand/metal ratio and the catalyst loading on the enantioselectivity.[a]

Entry	Ligand **2e** [mol-%]	$Ti(OiPr)_4$ [mol-%]	Yield [%][b]	*ee* [%][d]
1	5	5	99	91
2	6.25	5	99	90
3	7.5	5	99	88
4	5	6.25	99	89
5	5	7.5	99	88
6	2.5	2.5	N.D.[c]	–

[a] All reactions were performed with benzaldehyde (0.4 mmol) and **4** (0.6 mmol) in an *i*PrOH/$CHCl_3$ mixture (1:4 v/v, 0.8 mL) at –20 °C over 16 h. [b] Isolated yield. [c] N.D. = Not detected. [d] The *ee* values were determined by HPLC with a Chiralcel OD–H column. The absolute configuration was (*S*) by comparison with the sign of a reported optical rotation value.[5a]

Effect of the Amount of EtOCOCN

Furthermore, the effect of the amount of EtOCOCN was studied and, as shown in Table 4, the reactivity and enantioselectivity hardly changed with a variation of the amount of ethyl cyanoformate from 1.25 to 1.75 equiv. However, a decrease in the amount to 1.0 equiv. or an increase to 2.0 equiv. was capable of reducing the isolated yield dramatically, so the optimal conditions involved the use of ligand **2e** (5 mol-%) and $Ti(OiPr)_4$ (5 mol-%) as the catalyst, with ethyl cyanoformate (1.5 equiv.) and benzaldehyde (0.5 M) in an *i*PrOH/$CHCl_3$ mixture (1:4 v/v, 0.8 mL) at –20 °C.

Table 4. Effects of the amount of ethyl cyanoformate in this catalysis.[a]

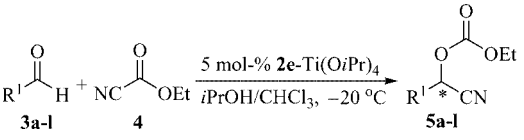
Entry	EtOCOCN [equiv.]	Yield [%][b]	*ee* [%][c]
1	1.0	50	90
2	1.25	96	87
3	1.5	99	91
4	1.75	89	89
5	2.0	82	89

[a] All reactions were performed with benzaldehyde (0.4 mmol) and **4** in an *i*PrOH/$CHCl_3$ mixture (1:4 v/v, 0.8 mL) at –20 °C over 16 h. Catalyst consisted of a 1:1 molar ratio of ligand **2e** to $Ti(OiPr)_4$; catalyst loading was 5 mol-%. [b] Isolated yield. [c] The *ee* values were determined by HPLC with a Chiralcel OD-H column. The absolute configuration was (*S*), by comparison with the sign of a reported optical rotation value.[5a]

Substrate Generality

Encouraged by the results obtained from benzaldehyde, we subjected a variety of aldehydes to cyanoformylation with ethyl cyanoformate under the optimized conditions. As shown in Table 5, good to excellent enantioselectivities of 76–91% *ee* and high to excellent isolated yields were obtained in the presence of 5 mol-% catalyst with aromatic, α,β-unsaturated, and aliphatic aldehydes.

Table 5. Asymmetric cyanoformylations of aldehydes with ethyl cyanoformate catalyzed by (1*R*,2*R*)-salen-Ti(O*i*Pr)$_4$ complex.[a]



Entry	Aldehydes **3a**–**l**	Time [h]	Yield [%][b]	*ee* [%][c]
1	Benzaldehyde	16	99	91 (*S*)[d]
2	3-Methylbenzaldehyde	40	99	91[e]
3	4-Methylbenzaldehyde	55	99	87 (*S*)[d]
4	4-Methoxybenzaldehyde	14	99	91 (*S*)[d]
5	4-Chlorobenzaldehyde	92	89	88 (*S*)[d]
6	2-Naphthaldehyde	16	91	90
7	3-Phenoxybenzaldehyde	10	90	90
8	(*E*)-Cinnamaldehyde	40	87	81 (*S*)[d]
9	4-Fluorobenzaldehyde	114	93	87 (*S*)[d]
10	Heliotropin	10	85	86
11	*n*-Hexanal	54	92	86[f]
12	2-Butyraldehyde	60	59	76 (*S*)[d,f]

[a] All reactions were performed with aldehydes (0.4 mmol) and **4** (0.6 mmol) in an *i*PrOH/CHCl$_3$ mixture (1:4 v/v, 0.8 mL) at –20 °C; catalyst consisted of a 1:1 molar ratio of ligand **2e** to Ti(O*i*Pr)$_4$; catalyst loading was 5 mol-%. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column (unless otherwise indicated). [d] The absolute configuration of the major product was determined by comparison with the sign of the reported optical rotation value.[5a,7c] [e] Determined by HPLC with a Chiralcel OD column. [f] Determined by GC with a Chirasil DEX CB column.

In these cases, the presence of 3- and 4-substituents on benzaldehyde had a slight effect on the enantioselectivities (Entries 1–3): 3-methylbenzaldehyde afforded the corresponding product with 91% *ee* (Entry 2), whereas 4-methylbenzaldehyde gave the adduct with 87% *ee* (Entry 3). In comparison, electron-rich aromatic aldehydes such as heliotropin yielded the cyanohydrin ethyl carbonate in 86% *ee* (Entry 10), 4-methoxybenzaldehyde gave the *O*-protected cyanohydrin with 91% *ee* (Entry 4), and 3-phenoxybenzaldehyde – the cyanohydrin ethyl carbonate, which might be applied in the synthesis of the insecticide fenvalerate Aα[1a] – provided the adduct with 90% *ee* (Entry 7). Among electron-withdrawing aromatic aldehydes, meanwhile, 4-chlorobenzaldehyde afforded the product in 88% *ee* (Entry 5) and 4-fluorobenzaldehyde gave its corresponding adduct in 87% *ee* (Entry 9). Significantly, α,β-unsaturated, aliphatic, and condensed cyclic aldehydes also provided their corresponding products with good to excellent enantioselectivities (Entries 6, 8, 11, 12).

Transition State Considerations

According to the X-ray structure of titanium complex **1**,[13] the potential transition state shown in Figure 3 was proposed. To minimize the interactions between benzaldehyde and the substituent on the phenyl ring of the ligand, transition state **A** versus **B** may be favored. It also results in an orientation in which the *re*-face of benzaldehyde is exposed to the cyanide group for the nucleophilic attack, producing the (*S*) enantiomer of the O-protected cyanohydrin.

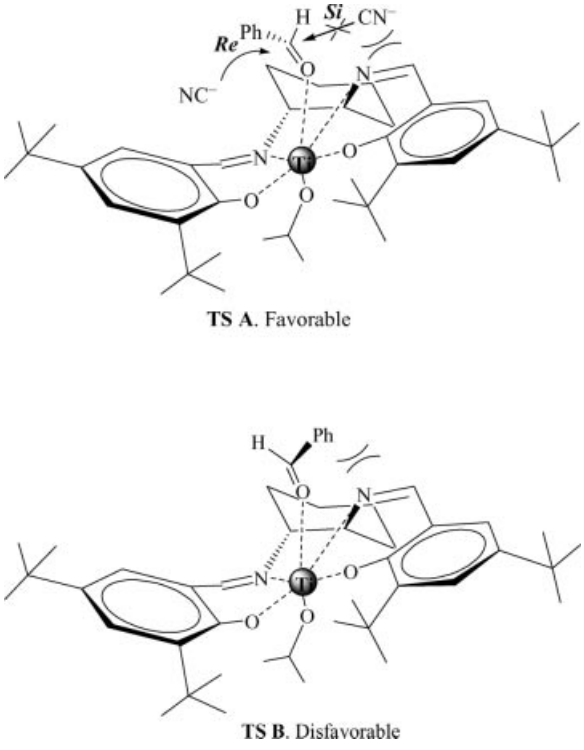


Figure 3. The potential transition states.

Conclusions

In conclusion, a mononuclear salen-Ti(O*i*Pr)$_4$ complex has been used to catalyze asymmetric cyanoformylations of aldehydes with ethyl cyanoformate. The addition of isopropyl alcohol to chloroform in the reaction has been demonstrated to avoid the formation of the multinuclear complex in the catalyst preparation step and optimal results were obtained with only 5 mol-% catalyst in an *i*PrOH/CHCl$_3$ mixture (1:4 v/v) at –20 °C, under which conditions a variety of aldehydes including aromatic, α,β-unsaturated, and aliphatic aldehydes were converted into the corresponding cyanohydrin ethyl carbonates in 76–91% enantiomeric excesses. A potential transition state based on the experimental results, which explains the origin of the asymmetric induction, has been presented. Meanwhile, since optically active salen is easily available on a large scale, this asymmetric cyanoformylation, catalyzed by the mononuclear salen-Ti(O*i*Pr)$_4$ complex, might be expected to have excellent po-

tential for practical applications. Further efforts might be devoted to application of this reaction in the pharmaceutical chemistry and other fields.

Experimental Section

General Methods: All reactions were carried out with anhydrous solvents and under a nitrogen atmosphere in oven-dried tubes. Toluene, CH_3CN, and THF were dried and distilled from sodium/benzophenone under a nitrogen atmosphere prior to use. CH_2Cl_2, $CHCl_3$, and CH_2ClCH_2Cl were dried with powdered CaH_2 and distilled under a nitrogen atmosphere prior to use. $(CH_3)_2CHOH$ was purchased from Fisher. $Ti(OiPr)_4$ (from Acros) was distilled and diluted to 1.0 M in toluene and stored under a nitrogen atmosphere. HG/T2354-92 silica gel (Qingdao Haiyang Chemical Co., Ltd.) was used for flash chromatography (FC). Enantiomeric excesses (*ee*'s) were determined by HPLC on the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with UV detection at 254 nm or GC. Specific optical rotations are reported as follows: $[a]_D^T$ (*c* g/100 mL, solvent).

Materials: The ligands were prepared as described in the literature.[14] All aldehydes, 1,2-diaminocyclohexane, and NCCOOEt were purchased from Acros or Aldrich and used directly without further purification.

Typical Procedure for the Asymmetric Synthesis of Optically Active Cyanohydrin Ethyl Carbonates. (*S*)-2-Ethoxycarbonyloxy-2-phenylacetonitrile (5a):[9b] $Ti(OiPr)_4$ (1.0 M in toluene, 20 μL, 0.02 mmol) was added under an N_2 atmosphere at room temperature to a solution of (1*R*,2*R*)-salen (10.9 mg, 0.02 mmol) in mixed solvents [$CHCl_3$/$(CH_3)_2CHOH$ 4:1, 0.8 mL], followed by the addition at –20 °C of benzaldehyde (0.4 mmol) and EtOCOCN (59.3 μL, 0.6 mmol). The contents were stirred for 16 h, and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether 10:1) to afford title compound **5a** as a colorless oil in 99% yield and with 91% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 8.4 min, t_r (major) = 9.9 min]. $[a]_D^{25}$ = –15.6 (*c* 0.109, $CHCl_3$); {ref.[5a] $[a]_D^{20}$ = –20.1 (*c* 1.8, $CHCl_3$) for the (*S*) enantiomer with 95% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.26–4.32 (m, 2 H, OCH_2), 6.27 (s, 1 H, O-C*H*-CN), 7.45–7.49 (m, 3 H, Ar-*H*), 7.53–7.56 (m, 2 H, Ar-*H*) ppm.

2-Ethoxycarbonyloxy-2-(3-methylphenyl)acetonitrile (5b):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5b** as a colorless oil in 99% yield and with 91% *ee* as determined by HPLC analysis with a Chiralcel OD column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 10.6 min, t_r (major) = 12.5 min]. $[a]_D^{25}$ = –14.43 (*c* 0.097, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.5 (s, 3 H, CH_3), 4.25–4.33 (m, 2 H, OCH_2), 6.39 (s, 1 H, O-C*H*-CN), 7.24–7.39 (m, 3 H, Ar-*H*), 7.58 (d, *J* = 6.4 Hz, 1 H, Ar-*H*) ppm.

(*S*)-2-Ethoxycarbonyloxy-2-(4-methylphenyl)acetonitrile (5c):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5c** as a colorless oil in 99% yield and with 87% *ee* as determined by HPLC analysis on a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 8.6 min, t_r (major) = 9.7 min]. $[a]_D^{25}$ = –6.19 (*c* 0.097, $CHCl_3$); {ref.[5a] $[a]_D^{20}$ = –5.1 (*c* 2.0, $CHCl_3$) for the (*S*) enantiomer with 94% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.39 (s, 3 H, CH_3), 4.22–4.33 (m, 2 H, OCH_2), 6.22 (s, 1 H, O-C*H*-CN), 7.25 (d, *J* = 7.9 Hz, 2 H, Ar-*H*), 7.43 (d, *J* = 8.1 Hz, 2 H, Ar-*H*) ppm.

(*S*)-2-Ethoxycarbonyloxy-2-(4-methoxylphenyl)acetonitrile (5d):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5d** as a colorless oil in 99% yield and with 91% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 13.8 min, t_r (major) = 17.7 min]. $[a]_D^{25}$ = +3.00 (*c* 0.100, $CHCl_3$); {ref.[5a] $[a]_D^{20}$ = +1.8 (*c* 1.8, $CHCl_3$) for the (*S*) enantiomer with 95% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 3.81 (s, 3 H, OCH_3), 4.19–4.30 (m, 2 H, OCH_2), 6.19 (s, 1 H, O-C*H*-CN), 6.93 (d, *J* = 8.8 Hz, 2 H, Ar-*H*), 7.46 (d, *J* = 8.8 Hz, 2 H, Ar-*H*) ppm.

(*S*)-2-Ethoxycarbonyloxy-2-(4-chlorophenyl)acetonitrile (5e):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5e** as a colorless oil in 89% yield and with 88% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 11.248 min, t_r (major) = 14.553 min]. $[a]_D^{25}$ = –4.95 (*c* 0.101, $CHCl_3$); {ref.[5a] $[a]_D^{20}$ = –2.9 (*c* 1.3, $CHCl_3$) for the (*S*) enantiomer with 94% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 4.23–4.34 (m, 2 H, OCH_2), 6.23 (s, 1 H, O-C*H*-CN), 7.41–7.51 (m, 4 H, Ar-*H*) ppm.

2-Ethoxycarbonyloxy-2-(2-naphthyl)acetonitrile (5f):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5f** as a white solid in 91% yield and with 90% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 90:10, 1.0 mL min^{-1}, t_r (minor) = 10.3 min, t_r (major) = 11.0 min]. $[a]_D^{25}$ = +6.25 (*c* 0.096, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.25–4.37 (m, 2 H, OCH_2), 6.44 (s, 1 H, O-C*H*-CN), 7.55–7.61 (m, 3 H, Ar-*H*), 7.89–8.05 (m, 3 H, Ar-*H*), 8.04–8.05 (m, 1 H; Ar-*H*) ppm.

2-Ethoxycarbonyloxy-2-(3-phenoxyphenyl)acetonitrile (5g):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5g** as a colorless oil in 90% yield and with 90% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (major) = 17.1 min, t_r (minor) = 26.3 min]. $[a]_D^{25}$ = –2.75 (*c* 0.109, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.24–4.35 (m, 2 H, OCH_2), 6.22 (s, 1 H, O-C*H*-CN), 7.02–7.05 (m, 1 H, Ar-*H*), 7.17–7.19 (m, 2 H, Ar-*H*), 7.28–7.35 (m, 3 H, Ar-*H*), 7.38 (m, 3 H, Ar-*H*) ppm.

(*S*)-2-Ethoxycarbonyloxy-4-phenylbut-3-enonitrile (5h):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5h** as a colorless oil in 87% yield and with 81% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 90:10, 1.0 mL min^{-1}, t_r (major) = 11.8 min, t_r (minor) = 13.2 min]. $[a]_D^{25}$ = +10.78 (*c* 0.102, $CHCl_3$); {ref.[7c] $[a]_D^{20}$ = –17.2 (*c* 1.9, $CHCl_3$) for the (*R*) enantiomer with 88% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.27–4.34 (m, 2 H, OCH_2), 5.89 (d, *J* = 6.8 Hz, 1 H, O-C*H*-CN), 6.26 (dd, *J* = 15.8, 6.8, Hz, 1 H, =C*H*), 7.02 (d, *J* = 15.8 Hz, 1 H, Ph-C*H*=), 7.34–7.45 (m, 5 H, Ar-*H*) ppm.

2-Ethoxycarbonyloxy-2-(4-fluorophenyl)acetonitrile (5i):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5i** as a colorless oil in 93% yield and with 87% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 99:1, 1.0 mL min^{-1}, t_r (minor) = 10.4 min, t_r (major) = 12.4 min]. $[a]_D^{25}$ = –19.35 (*c* 0.062, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H,

OCH_2CH_3), 4.24–4.33 (m, 2 H, OCH_2), 6.24 (s, 1 H, O-C*H*-CN), 7.11–7.17 (m, 2 H, Ar-*H*), 7.52–7.57 (m, 2 H, Ar-*H*) ppm.

2-Ethoxycarbonyloxy-2-(benzo[*d*][1,3]dioxol-5-yl)acetonitrile (5j):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5j** as a colorless oil in 85% yield and with 86% *ee* as determined by HPLC analysis with a Chiralcel OD-H column [hexane/2-propanol 90:10, 1.0 mL min^{-1}, t_r (minor) = 8.9 min, t_r (major) = 12.5 min]. $[\alpha]_D^{25}$ = +2.17 (*c* 0.092, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 4.22–4.33 (m, 2 H, OCH_2), 6.02 (s, 2 H, O-CH_2-O), 6.16 (s, 1 H, O-C*H*-CN), 6.82–6.85 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 6.99–7.04 (m, 2 H, Ar-*H*) ppm.

2-Ethoxycarboxyheptanenitrile (5k):[9b] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5k** as a colorless oil in 92% yield and with 86% *ee* as determined by GC analysis with a Varian Chirasil DEXCB column (0.25 mm × 25 m) [column temp. 130 °C; inject temp. 250 °C; detection temp. 250 °C; inlet pressure 8 psi; t_r (minor) = 12.5 min, t_r (major) = 13.0 min]. $[\alpha]_D^{25}$ = –55.65 (*c* 0.115, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.90 (m, 3 H, CH_3), 1.31–1.32 (m, 7 H, CH_2CH_2, OCH_2CH_3), 1.46–1.54 (m, 2 H, CH_2CH_3), 1.89–1.94 (m, 2 H, CH_2CH), 4.23–4.32 (m, 2 H, OCH_2), 5.19 (t, *J* = 6.7 Hz, 1 H, O-C*H*-CN) ppm.

(*S*)-2-Ethoxycarbonyloxy-3-methylbutyronitrile (5l):[5a] This compound was purified by FC with silica gel (petroleum/Et_2O 10:1) to afford title compound **5l** as a colorless oil in 59% yield and with 76% *ee* as determined by GC analysis with a Varian Chirasil DEXCB column (0.25 mm × 25 m), [column temp. 130 °C; inject temp. 200 °C; detection temp. 250 °C; inlet pressure 8 psi; t_r (minor) = 24.9 min, t_r (major) = 28.4 min]. $[\alpha]_D^{25}$ = –82.76 (*c* 0.058, $CHCl_3$); {ref.[5a] $[\alpha]_D^{20}$ = –59.8 (*c* 1.2, $CHCl_3$) for the (*S*) enantiomer with 79% *ee*}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.15 (m, 6 H, CH_3, CH_3), 1.34–1.37 (m, 3 H, OCH_2CH_3), 2.18–2.24 (m, 1 H, C*H*), 4.25–4.31 (m, 2 H, OCH_2), 5.04 (t, *J* = 5.6 Hz, 1 H, O-C*H*-CN) ppm.

Supporting Information (see footnote on the first page of this article): Details of the HPLC and GC analyses.

Acknowledgments

The authors thank the National Natural Science Foundation of China(20390055, 20225206, 20502019) and the Ministry of Education, P. R. China (104209, 20030610021 for financial support.

[1] For reviews on the synthesis and applications of cyanohydrins, see: a) F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609–1619; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564; b) A. Mori, S. Inoue "Cyanation of Carbonyl and Amino Groups" in *Comprehensive Asymmetric Synthesis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 983–992; c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682; d) I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*, John Wiley & Sons, Chichester, **2000**, pp. 235–284; e) M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th ed., John Wiley & Sons, New York, **2001**, pp. 1239–1240; f) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999; g) M. North, in *Science of Synthesis* (Ed.: S. I. Murahashi), Thieme, Stuttgart, **2004**, vol. 19, pp. 235–284.

[2] For reviews on cyanation reactions, see: a) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682; b) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; c) J. M. Brunel, I. P. Holmes, *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778; d) F.-X. Chen, X.-M. Feng, *Synlett* **2005**, 892–899; e) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491–1508; f) T. R. J. Achard, L. A. Clutterbuck, M. North, *Synlett* **2005**, 1828–1847; g) F.-X. Chen, X.-M. Feng, *Curr. Org. Synth.* **2006**, *3*, 77–97.

[3] a) S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; b) Y. Li, B. He, B. Qin, X.-M. Feng, G.-L. Zhang, *J. Org. Chem.* **2004**, *69*, 7910–7913; c) Y.-H. Wen, X. Huang, J.-L. Hang, Y. Xiong, B. Qin, X.-M. Feng, *Synlett* **2005**, 2445–2448; d) Y.-C. Qin, L. Liu, L. Pu, *Org. Lett.* **2005**, *7*, 2381–2383; e) D.-H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 5384–5387; f) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; g) X.-H. Liu, B. Qin, X. Zhou, B. He, X.-M. Feng, *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225; h) Y. Xiong, X. Huang, S.-H. Gou, J.-L. Huang, Y.-H. Wen, X.-M. Feng, *Adv. Synth. Catal.* **2006**, *348*, 538–544.

[4] S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.

[5] a) Y. N. Belokon', A. J. Blacker, L. A. Clutterbuck, M. North, *Org. Lett.* **2003**, *5*, 4505–4507; b) Y. N. Belokon', A. J. Blacker, P. Carta, L. A. Clutterbuck, M. North, *Tetrahedron* **2004**, *60*, 10433–10447.

[6] S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593.

[7] a) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2002**, *41*, 3636–3638; b) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3021–3024; c) N. Yamagiwa, J. Tian, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 3413–3422.

[8] a) J. Casas, A. Baeza, J. M. Sansano, C. Nájera, J. M. Saá, *Tetrahedron: Asymmetry* **2003**, *14*, 197–200; b) A. Baeza, J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Angew. Chem. Int. Ed.* **2003**, *42*, 3143–3146; c) A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá, *Tetrahedron: Asymmetry* **2005**, *16*, 2385–2389; d) A. Baeza, J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Eur. J. Org. Chem.* **2006**, 1949–1958.

[9] a) Q.-H. Li, L. Chang, X.-H. Liu, X.-M. Feng, *Synlett* **2006**, 1675–1678; b) S.-H. Gou, X.-H. Chen, Y. Xiong, X.-M. Feng, *J. Org. Chem.* **2006**, *71*, 5732–5736.

[10] a) F.-X. Chen, X.-M. Feng, B. Qin, G.-L. Zhang, Y.-Z. Jiang, *Synlett* **2003**, 558–560; b) B. He, F.-X. Chen, Y. Li, X.-M. Feng, G.-L. Zhang, *Eur. J. Org. Chem.* **2004**, 4657–4666; c) F.-X. Chen, H. Zhou, X.-H. Liu, B. Qin, X.-M. Feng, G.-L. Zhang, Y.-Z. Jiang, *Chem. Eur. J.* **2004**, *10*, 4790–4797; d) B. He, F.-X. Chen, Y. Li, X.-M. Feng, G.-L. Zhang, *Tetrahedron Lett.* **2004**, *45*, 5465–5467; e) F.-X. Chen, B. Qin, X.-M. Feng, G.-L. Zhang, Y.-Z. Jiang, *Tetrahedron* **2004**, *60*, 10449–10460.

[11] a) E. M. Carreira, R. A. Singer, W. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 8837–8838; b) E. M. Carreira, W. Lee, R. A. Singer, *J. Am. Chem. Soc.* **1995**, *117*, 3649–3650; c) R. A. Singer, E. M. Carreira, *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361.

[12] a) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402–411; c) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16–17.

[13] a) Y. N. Belokon', S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973; b) Y. N. Belokon', B. Green, N. S. Ikonnikov, V. S. Larichev, B. V. Lokshin, M. A. Moscalenko, M. North, C. Orizu, A. S. Peregudov, G. I. Timofeeva, *Eur. J. Org. Chem.* **2000**, 2655–2661.

[14] Y.-Z. Jiang, L.-Z. Gong, X.-M. Feng, W.-H. Hu, W.-D. Pan, Z. Li, A.-Q. Mi, *Tetrahedron* **1997**, *53*, 14327–14338.

Received: September 13, 2006
Published Online: November 27, 2006

