Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction of Aldehydes Using a Novel C_2-Symmetric Chiral *N*,*N*′-Dioxide Titanium Complex

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Received 1 April 2006

Abstract: The asymmetric addition of ethyl cyanoformate to a range of aldehydes was efficiently catalyzed by a easily prepared C_2-symmetric chiral *N*,*N*′-dioxide–Ti(IV) complex in high yields with up to 90% ee under mild conditions. A linear effect between the enantiopurity of the ligand and the enantiopurity of the product was observed.

Key words: C_2-symmetric chiral *N*,*N*′-dioxide ligand, ethyl cyanoformate, aldehydes, enantioselectivity, organotitanium

Cyanoformate esters (ROCOCN) are known to react with aldehydes and ketones, leading directly to cyanohydrin carbonates.[1] Recently, asymmetric catalysts for this reaction have been reported. While, the majority of chiral catalysts used for this goal are cinchona alkaloid derivatives, oxynitrilase enzyme and chiral metal complexes.[2] In recent years, chiral *N*-oxides have been used in several asymmetric procedures, such as the allylation of aldehydes,[3] the addition of Et_2Zn to aldehydes,[4] the reduction of ketones,[5] the epoxide openings,[6] the aldol reaction[7] and the cyanosilylation of carbonyl compounds.[8] Herein, we wish to repot the results on the asymmetric cyano-ethoxycarbonylation reaction of aldehydes using a novel, easily prepared C_2-symmetric chiral *N*,*N*′-dioxide (Figure 1) titanium complexes.

For the initial studies, the addition of ethyl cyanoformate to benzaldehyde catalyzed by chiral *N*,*N*′-dioxide ligands **1a**–**h** (Figure 1) with titanium complexes were investigated at –20 °C. As illustrated in Table 1, ligand **1a** afforded cyanohydrin ethyl carbonates with 90% yield and 38% ee (Table 1, entry 1). Based on the successful ligand **1a** skeleton, we then modified the prolinamide parts and prepared a series of chiral *N*,*N*′-dioxide derivatives **1b**–**h** (Figure 1).[9] It was found that the amide substituent played an important role on the enantioselectivity. Ligand **1c**,[10] which contained a 2-*tert*-butylphenyl group, gave good enantioselectivity (Table 1, entry 3 vs. entries 1, 2, 4–8). Increasing the size of the prolinamide parts resulted in efficiency with lower enantioselectivities than **1c** (Table 1, entries 5, 6).

Then the N-terminal effect of the catalyst was investigated, a variety of proline-based *N*,*N*′-dioxides, bearing the optimal 2-*tert*-butylphenylamine terminus, were prepared and examined (Table 1, entries 7, 8). Lower enantioselectivity than **1c** was observed when the size of the N-terminal substituents was increased (Table 1, entry 7). Ligands bearing electron-poor substituents (**1h**) also led to low reactivity and enantioselectivity (Table 1, entry 8). In addition, in order to compare with catalyst **1c**–Ti(O*i*-Pr)$_4$, complex **3**–Ti(O*i*-Pr)$_4$ was also examined in this reaction under the same conditions, but it was less efficient than **1c**–Ti(O*i*-Pr)$_4$ (Table 1, entry 10). While the alternative diastereomer **2**–Ti(O*i*-Pr)$_4$ promoted the same selective transformation to afford the alternative product antipode (Table 1, entry 9). Thus **1c** was identified as the most effective catalyst (Table 1, entry 3).

We then further optimized the reaction conditions by exploring the use of other Lewis acids. The results were summarized in Table 1. Ti(O*i*-Pr)$_4$ gave more promising enantioselectivity (63% ee) than other Lewis acids

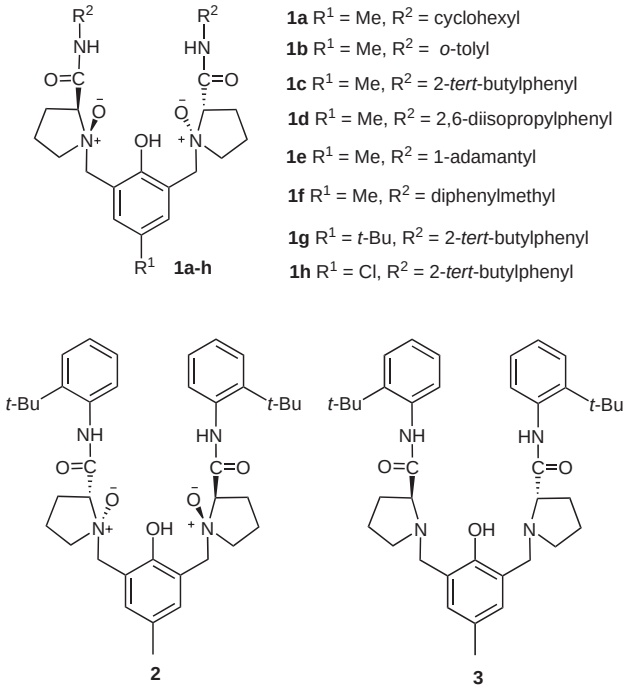
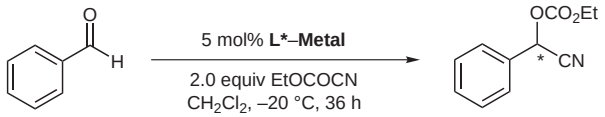


Figure 1 Ligands evaluated for asymmetric addition of ethyl cyanoformate to benzaldehyde.

SYNLETT 2006, No. 11, pp 1675–1678
Advanced online publication: 04.07.2006
DOI: 10.1055/s-2006-947322; Art ID: W06906ST

Table 1 Asymmetric Addition of Ethyl Cyanoformate to Benzaldehyde by Different C_2-Symmetric Chiral *N*,*N*′-Dioxide Ligand–Titanium Complexes[a]



Entry	Ligand[f]	Metal	Yield (%)[b]	ee (%)[c]
1	**1a**	Ti(O*i*-Pr)$_4$	90	38
2	**1b**	Ti(O*i*-Pr)$_4$	91	39
3	**1c**	Ti(O*i*-Pr)$_4$	86	63
4	**1d**	Ti(O*i*-Pr)$_4$	64	37
5	**1e**	Ti(O*i*-Pr)$_4$	80	36
6	**1f**	Ti(O*i*-Pr)$_4$	84	36
7	**1g**	Ti(O*i*-Pr)$_4$	86	44
8	**1h**	Ti(O*i*-Pr)$_4$	76	38
9	**2**	Ti(O*i*-Pr)$_4$	83	63[g]
10	**3**	Ti(O*i*-Pr)$_4$	75	27
11	**1c**	$AlEt_3$	40	23
12	**1c**	Ti(O*i*-Pr)$_4$	–	–
13[d]	**1c**	Ti(O*i*-Pr)$_4$	10	36
14[e]	**1c**	Ti(O*i*-Pr)$_4$	17	43

[a] Reactions were carried out on a 0.25 mmol scale of benzaldehyde in 1.0 mL of CH_2Cl_2; ligand:metal (5 mol%) = 1:1; EtOCOCN (2.0 equiv).
[b] Isolated yield of the cyanohydrin carbonates.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] Ratio **1c**:Ti(O*i*-Pr)$_4$ (5 mol%) = 1:2.
[e] Ratio **1c**:Ti(O*i*-Pr)$_4$ (5 mol%) = 1.25:1.
[f] Structural identity of all ligands were determined by ^{1}H NMR, ^{13}C NMR and HRMS.
[g] The configurations was *S*, determined by comparison of optical rotation with reported in the literature, and the others were *R*.[2b]

(Table 1, entries 11, 12). Changing the molar ratio between Ti(O*i*-Pr)$_4$:**1c** led to low yields and enantioselectivities (Table 1, entries 13, 14 vs. entry 3). Therefore, the complex **1c**–Ti(O*i*-Pr)$_4$ (1:1) was employed in screening other conditions.

Firstly, a series of solvents including toluene, Et_2O, CH_2Cl_2 were screened (Table 2, entries 1–3). The best solvent was found to be CH_2Cl_2 (Table 2, entry 1). Further studies indicated that the concentration of benzaldehyde had a slight influence upon the enantioselectivity (Table 2, entries 4–6). The optimum concentration of benzaldehyde was 0.5 M (Table 2, entry 4). Both the yield and enantioselectivity were dramatically influenced by catalyst loading. The most favorable catalyst loading was found to be 10 mol% (Table 2, entry 7). The effect of additives showed that 4 Å MS was most promising in this catalytic system (Table 2, entry 10). Temperature clearly

Table 2 Optimization of the Addition of Ethyl Cyanoformate to Benzaldehyde in the Presence of **1c**–Ti(IV) Complex[a]

Entry	**1c** (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	5	CH_2Cl_2	–20	36	86	63
2[d]	5	Toluene	–20	36	34	33
3[d]	5	Et_2O	–20	36	30	27
4	5	CH_2Cl_2	–20	36	92	65
5[e]	5	CH_2Cl_2	–20	36	54	57
6[f]	5	CH_2Cl_2	–20	36	94	54
7	10	CH_2Cl_2	–20	36	97	72
8	15	CH_2Cl_2	–20	30	98	69
9	30	CH_2Cl_2	–20	30	98	65
10[g]	10	CH_2Cl_2	–20	30	93	78
11[g]	10	CH_2Cl_2	0	8	85	66
12[g]	10	CH_2Cl_2	–45	48	85	86
13[g]	10	CH_2Cl_2	–78	48	53	86

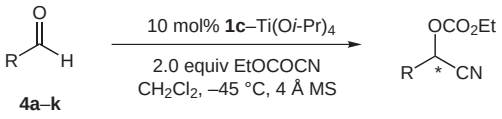
[a] Unless otherwise specified, reactions were carried out on a 0.25 mmol scale of benzaldehyde in 0.5 mL of solvent; EtOCOCN (2.0 equiv); **1c**: Ti(O*i*-Pr)$_4$ (10 mol%) = 1:1.
[b] Isolated yield of cyanohydrin carbonates.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] [Benzaldehyde] = 0.25 M.
[e] [Benzaldehyde] = 0.125 M.
[f] [Benzaldehyde] = 1.0 M.
[g] In the presence of 4 Å MS (20 mg).

affected the yield and the enantioselectivity. The satisfying temperature was –45 °C (Table 2, entry 12). Increasing the temperature caused a drop in enantioselectivity (Table 2, entry 11). Further decreasing the temperature led to a dramatic decrease in reactivity without any improvement in enantioselectivity (Table 2, entry 13).

Extensive screening showed that the optimized catalytic system was 10 mol% **1c**–Ti(O*i*-Pr)$_4$ (1:1), 0.5 M benzaldehyde, 2.0 equivalents EtOCOCN in 0.5 mL of CH_2Cl_2 in the presence of 4 Å MS (20 mg) at –45 °C (Table 2, entry 13).

Encouraged by the result obtained for the benzaldehyde, the addition of ethyl cyanoformate to other aldehydes was then investigated under the optimized conditions,[11] and the results were shown in Table 3. The asymmetric cyanosilylation of aromatic, α,β-unsaturated and aliphatic aldehydes proceeded smoothly to provide the corresponding cyanohydrin carbonates in high yields with moderate to good enantioselectivities (Table 3). Electron-rich or electron-withdrawing aromatic aldehydes were found to be good substrates for this reaction, giving enantioselectivities of cyanohydrin carbonates similar to those obtained with benzaldehyde (Table 3, entries 2–8). β-Naphthaldehyde was found to be excellent substrate

Table 3 Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by **1c**–Ti(IV) Complex[a]



4a–k

Entry	Aldehydes	Yield (%)[b]	ee (%)[c] (Config)[d]
1	Benzaldehyde (**4a**)	88	86 (*R*)
2	4-Methylbenzaldehyde (**4b**)	86	84 (*R*)
3	2-Methylbenzaldehyde (**4c**)	92	86
4	4-Methoxybenzaldehyde (**4d**)	83	82 (*R*)
5	3-Methoxybenzaldehyde (**4e**)	93	80 (*R*)
6	2-Methoxybenzaldehyde (**4f**)	91	86 (*R*)
7	3-Phenoxybenzaldehyde (**4g**)	92	88
8	4-Fluorobenzaldehyde (**4h**)	88	83
9	β-Naphthaldehyde (**4i**)	82	90 (*R*)
10	(*E*)-Cinnamaldehyde (**4j**)	83	62 (*R*)
11	Cyclohexanecarbaldehyde (**4k**)	81	68 (*R*)

[a] See ref. 11 for a general procedure of the reaction; EtOCOCN (2.0 equiv), ratio **1c**:Ti(O*i*-Pr)$_4$ (10 mol%) = 1:1, 4 Å MS, –45 °C.
[b] Isolated yield of the cyanohydrin carbonates.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column) or GC on a Chirasil DEX CB.
[d] Absolute configurations were determined by comparison of optical rotations with those reported in the literature.[2b,f]

giving cyanohydrin carbonate with 90% enantiomeric excess, while (*E*)-cinnamaldehyde and cyclohexanecarbaldehyde only gave moderate enantioselectivities (Table 3, entries 13, 14).

Finally, in order to obtain the information on possible structure of the C_2-symmetric chiral *N*,*N*′-dioxide–Ti(IV) complex in solution, a series of experiments about the relationship between the enantiopurity of the ligand **1c** (Figure 1) and the enantioselectivity of the product were studied. A clear linear effect was observed in this reaction

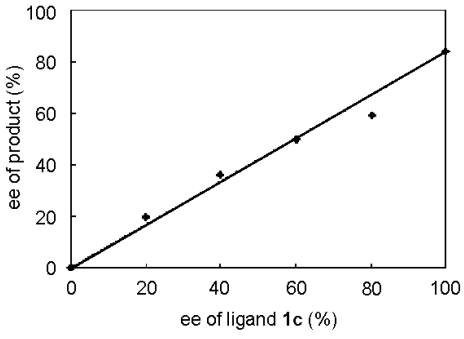


Figure 2 NLE in asymmetric addition of ethyl cyanoformate to benzaldehyde catalyzed by **1c**– Ti(O*i*-Pr)$_4$ (Figure 1).

(Figure 2). The result simply indicated that homochiral polymeric **1c**– Ti(O*i*-Pr)$_4$ (1:1) complexes are more stable than heterochiral polymers in the stereodiscriminating step of the reaction.[12]

In conclusion, asymmetric cyanation of aldehydes has been achieved using 10 mol% of the C_2-symmetric chiral *N*,*N*′-dioxide–Ti(IV) complex and good yields of the corresponding cyanohydrin carbonates are obtained with high enantioselectivities (up to 90% ee) under mild reaction conditions. Further investigations are planned to search for more effective chiral *N*-oxide ligands and provide additional information with regard to the scope and precise mechanism.

Acknowledgment

The authors thank the National Natural Science Foundation of China (No. 20225206, 20390055, 20502019 and 20472056) and the Ministry of Education, China (Nos. 104209, 20030610021 and others) for financial support.

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(9) **General Procedure for the Preparation of *C*$_2$-Symmetric *N*,*N*′-Dioxide Ligands.**
(a) To a solution of (***S***)-1-(***tert***-butoxycarbonyl)pyrrolidine-2-carboxylic acid (2.3 g, 10.0 mmol) in CH_2Cl_2 was added Et_3N (4 mL), isobutyl carbonochloride (1.44 mL, 10.0 mmol) at 0 °C under stirring After 25 min, the amine (10.2 mmol) was added. It was allowed to warm to r.t. and stirred for 8 h. The mixture was washed with 1 M $KHSO_4$ (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated. The residue in CH_2Cl_2 (25 mL) was added TFA (10 mL) and stirred for 2 h. Then, the solvent was evaporated, and H_2O (20 mL) was added. The pH of the mixture was brought into the range of 8–10 by the addition of 2 M NaOH. The aqueous phase was extracted with CH_2Cl_2 (50 mL). The CH_2Cl_2 extracts were pooled, washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was used for next step directly.
(b) 2,6-Di(bromomethyl)-4-methylphenol (5.1 mmol) was added in one portion to a stirred and cooled solution of (***S***)-pyrrolidine-2-carboxamide (10.2 mmol) and K_2CO_3 (21 mmol) in dry DMF (8 mL). The ice bath was removed after the addition and the resulting solution was allowed to stir at r.t. for 12 h before it was diluted with H_2O (50 mL) and Et_2O (50 mL). The two phases were separated and the aqueous phase was extracted with Et_2O three times and the combined organic phases were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by silic gel column chromatography to give the foam product. Next, MCPBA (13 mmol) was added at –78 °C to a solution of the above product and anhyd K_2CO_3 in CH_2Cl_2. The resulting mixture was stirred at the same temperature and the reaction was monitored by TLC. After completion, the mixture was allowed to warm slowly to r.t. and filtered. The solvents were evaporated under reduced pressure. Purification of the residue by silica gel column chromatography (Et_2O–MeOH, 10:1 and Et_2O–MeOH, 6:1) to afford the corresponding (2***S***,2′***S***)-1,1′-[(2-hydroxy-5-methyl-1,3-phenylene)di(methylene)]bis[***N***-(2-***tert***-butylphenyl)pyrrolidine-2-carboxamide]-***N***,***N***′-dioxide (**1c**).
(10) The following are the physical, NMR and HRMS data of **1c**: mp 127–129 °C; $[\alpha]_D^{25}$ –7.3 (*c* 2.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 2 H), 7.25–7.33 (m, 4 H,), 7.07–7.15 (m, 4 H), 6.82 (s, 2 H), 3.82–3.85 (d, *J* = 12 Hz, 2 H), 3.59–3.62 (d, *J* = 12 Hz, 2 H), 3.30–3.34 (m, 2 H), 2.95–3.00 (m, 2 H), 2.39–2.46 (m, 2 H), 2.19 (s, 3H), 1.99–2.05 (m, 4 H), 1.76–1.79 (m, 4 H), 1.44 (s, 18 H,). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 20.39, 24.01, 30.16, 30.56, 34.54, 53.83, 55.78, 67.42, 123.07, 125.89, 126.34, 126.58, 127.8, 129.74, 135.08, 142.76, 153.32, 172.28. HRMS: *m/z* calcd for $C_{38}H_{52}N_4O_5$: 657.4016 $[M + H]^+$; found: 657.4005 $[M + H]^+$.
(11) **General Procedure for Asymmetric Addition of Ethyl Cyanoformate to Aldehydes.**
To a solution of **1c** (16.4 mg, 0.025 mmol) and 4 Å MS (20 mg) in CH_2Cl_2 (0.5 mL) was added Ti(O*i*-Pr)$_4$ (1 M in toluene, 25 μL, 0.025 mmol) at r.t., then the mixture was stirred at 35 °C for 1 h under N_2 atmosphere. To this solution aldehyde (0.25 mmol) and EtOCOCN (50 μL, 0.5 mmol) were added at –45 °C under N_2 atmosphere. After the complete conversion of the aldehyde (monitored by TLC, 48–100 h), the crude product was purified by column chromatography on silica gel (PE–Et_2O, 10:1) to give the corresponding cyanohydrin carbonates for further analysis.
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