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Highly Enantioselective Cyanation of Aldehydes Catalyzed by a Multicomponent Titanium Complex

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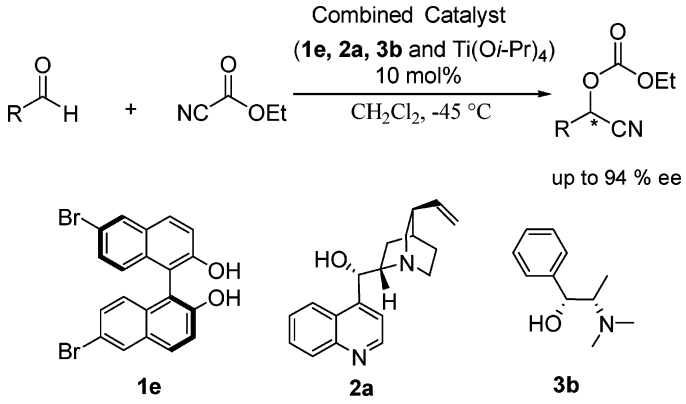

A new multicomponent bifunctional catalytic system based on a titanium complex was used for the efficient enantioselective cyanation of aldehydes. The catalyst was readily prepared from tetraisopropyl titanate (Ti(O*i*-Pr)$_4$), (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol (**1e**), cinchonine (**2a**), and (1*R*,2*S*)-(−)-*N*-methylephedrine (**3b**). It was revealed that the combination of **1e**, **2a**, **3b**, and Ti(IV) was essential in this cyanation. The reaction proceeded smoothly in the presence of a catalytic amount of the multicomponent catalyst to afford the desired cyanohydrins ethyl carbonates in moderate to excellent isolated yields (up to 95%) with high enantioselectivities (up to 94% ee). A catalytic cycle based on experimental phenomena was proposed to explain the origin of the asymmetric induction.

Introduction

Optically active cyanohydrins serve as important precursors for many useful organic intermediates and chiral starting materials for synthesis of several natural products.[1] Various types of catalyst systems have been applied to prepare these compounds using trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN) as the cyanide source to react with carbonyl compounds over the last two decades.[2,3] Recently, asymmetric cyanations employing cyanoformate ester (ROCOCN), acetyl

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cyanide, diethyl cyanophosphonate, or benzoyl cyanide as the cyanide source to afford corresponding functionalized cyanohydrins have been reported by Deng,[4] Shibasaki,[5] Sansano, Nájera and Saá,[6] Belokon and North,[7] and Moberg.[8] Among these precedents, a number of bifunctional chiral catalysts that are based on BINOL and natural glucose have been successfully applied in many asymmetric reactions.[3f,g,6,9] Triggered by the bifunctional catalysts' methods, we wish to explore whether the combination of BINOL derivatives **1** with chiral amine **2** and **3** would improve enantioselectivity and reactivity. We assume that the metallic reagent (titanium) would work as a Lewis acid to activate the substrates (carbonyl group), meanwhile the nitrogen atom of the amine would work as a Lewis base to activate the nucleophile (EtOCOCN).[4,5,9f] We report herein an efficient multicomponent bifunctional catalyst (the combination of **1e**, **2a**, **3b**, and Ti(IV)) for the cyanation of aldehydes with ethyl cyanoformate, and each component of the catalyst is commercially available or easily prepared.

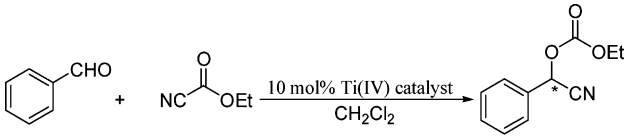
Results and Discussion

Initially, we wish to promote the reaction of benzaldehyde with ethyl cyanoformate (EtOCOCN) in dichloromethane at −20 °C in the presence of 10 mol % mono-ligand with Ti(IV) complexes (Table 1). The data indicated that the BINOL derivatives **1f,g**, chiral amine **2** and **3** complexes with Ti(IV) were able to catalyze the reaction in excellent yields (Table 1, entries 6−14) except for BINOL derivatives **1a**−**e** (Table 1, entries 1−5, no reactions were observed); however, the highest enantioselectivity was only 27% (Table 1, entry 7). Herein, we assumed that the nitrogen atoms of these ligands (chiral amine **2** and **3**, BINOL derivatives **1f,g**) might act as a Lewis base to activate the EtOCOCN in the reaction (Table 1, entries 6−14).[4,6,8,9]

On the basis of bifunctional conception,[6,8,9] we expected that bifunctional catalysts could be realized by the complexes of BINOL derivative **1** with a metallic reagent as Lewis acid moieties to activate the carbonyl group, while chiral amine **2** or **3** acts as Lewis base moieties to activate EtOCOCN simultaneously through a combination approach. Then, some combinations of BINOL derivatives **1** with chiral amine **2** or **3** were investigated (Table 2, entries 1−16).

The data indicated that the combination of **1e** (6,6′-Br_2−BINOL), **2a**, and Ti(IV) was the best one (Table 2, entry 5). Other combinations could catalyze the reaction in excellent yields with 12−68% ee (Table 2, entries 1−4, 8−16). Moreover, the absolute configuration of BINOL, its derivatives, and chiral tertiary amines could affect the face selectivity of the reactions. When fixing tertiary amine **2a**, BINOL derivatives **1e** (*S*) and **1h** (*R*) led to *Si* face and *Re* face attack, respectively (Table 2,

TABLE 1. Asymmetric Cyanation of Benzaldehyde Catalyzed by the Combination of Mono-Ligand and Ti(IV)



4a **5** **6a**

entry[a]	ligand	time (h)	yield (%)[b]	ee (%)[c,d]
1	**1a**	96	0	
2	**1b**	96	0	
3	**1c**	96	0	
4	**1d**	96	0	
5	**1e**	96	0	
6	**1f**	48	85	14(*R*)
7	**1g**	40	87	27(*R*)
8	**2a**	24	99	11(*R*)
9	**2b**	24	99	10(*R*)
10	**2c**	24	99	9(*S*)
11	**2d**	24	99	10(*S*)
12	**3a**	24	99	4(*R*)
13	**3b**	24	99	8(*R*)
14	**3c**	24	99	3(*R*)

[a] Conditions: 1igand/Ti(IV) = 1/1, concentration of benzaldehyde: 0.25 M, EtOCOCN: 1.2 equiv, −20 °C. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column. [d] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation (ref 5a).

TABLE 2. Asymmetric Cyanation of Benzaldehyde Catalyzed by the Combination of Double-Ligand and Ti(IV)

entry[a]	combined ligands		yield (%)[b]	ee (%)[c,d]
1	**1a**	**2a**	99	42(*R*)
2	**1b**	**2a**	99	13(*R*)
3	**1c**	**2a**	95	12(*R*)
4	**1d**	**2a**	99	46(*R*)
5	**1e**	**2a**	99	69(*R*)
6	**1e**	**2a**	60	59(*R*)[e]
7	**1e**	**2a**	48	52(*R*)[f]
8	**1f**	**2a**	99	13(*R*)
9	**1g**	**2a**	99	26(*R*)
10	**1h**	**2a**	99	31(*S*)
11	**1e**	**2b**	93	68(*R*)
12	**1e**	**2c**	94	40(*S*)
13	**1e**	**2d**	95	20(*R*)
14	**1e**	**3a**	90	20(*R*)
15	**1e**	**3b**	80	37(*R*)
16	**1e**	**3c**	90	12(*R*)

[a] Conditions: 10 mol % of catalyst (**1**/Ti(IV)/**2** or **3** = 1/1/1), concentration of benzaldehyde: 0.25 M in CH_2Cl_2, −20 °C, 48 h, EtOCOCN: 1.2 equiv. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column. [d] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation (ref 5a). [e] Add **2a** to the complex of **1e** with Ti(IV), 168 h. [f] At −45 °C, for 96 h.

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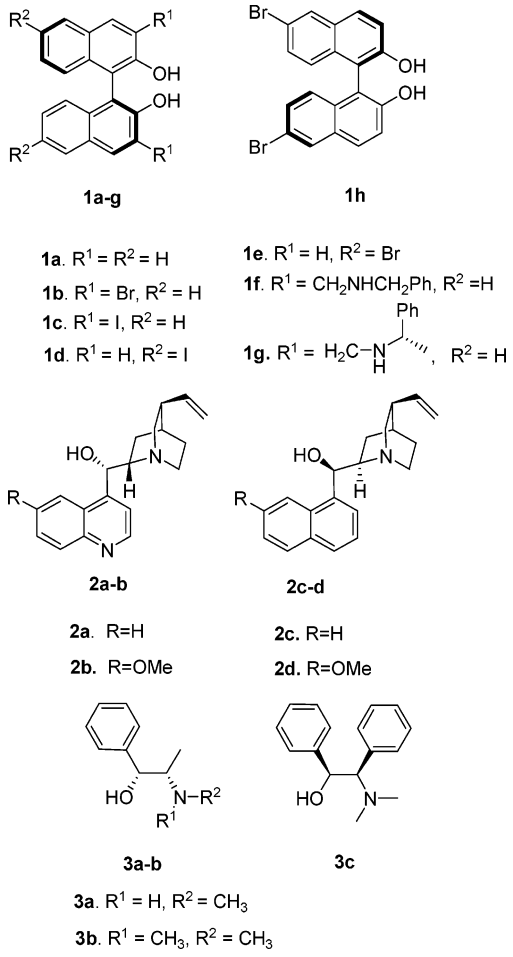


FIGURE 1. The screened ligands.

entry 5 vs 10), and vice versa (Table 2, entry 12 vs 5). Notably, when the procedure of preparing the catalyst was changed, **2a** was added to the complex of **1e** with Ti(IV), and the reactivity and enantioselectivity were dramatically decreased (Table 2, entry 6).

Then, we selected the combination of **1e**, **2a**, and Ti(IV) to investigate other parameters. However, the enantioselectivity was not further improved. When the reaction temperature was decreased to −45 °C, the reactivity and enantioselectivity were decreased to 48% yield and 52% ee, respectively (Table 2, entry 7).

So, we tried to introduce a third component which might coordinate with the titanium to improve the ability of chiral induction (Table 3, entries 2−7). Fortunately, when **3b** was additionally combined in the reaction system, with the time shortened, yield remained and higher enantioselectivity was obtained than that only using **1e**, **2a**, and Ti(IV) (Table 3, entry 5 vs 1). Under the same conditions, the combination of **1e**, **2a**, **3b**, and Ti(IV) afforded better results than other combinations (Table 3, entries 2−4, 7). It was noteworthy that, when **3b** was added to the complex of **1e**, **2a**, and Ti(IV), the reactivity and enantioselectivity were slightly decreased (Table 3, entry 6 vs 5).

Then, other reaction factors were examined. It was found that benzaldehyde could not be converted into the corresponding product when Ti(O*i*-Pr)$_4$ was replaced by Zn(OTf)$_2$ (Table 4, entry 3). Although the combination of **1e**, **2a**, **3b**, and Al(O*i*-Pr)$_3$ or **1e**, **2a**, **3b**, and Zr(O*i*-Pr)$_4$ had excellent reactivity, the enantioselectivities were very unsatisfactory (Table 4, entries 2 and 4). Among the solvent examination, ether solvents (THF or Et$_2$O) worked well but provided low enantioselectivities (Table 4, entries 5 and 7), which might be attributed to the coordination with the titanium of the complex. Toluene gave the moderate enantioselectivity (Table 4, entry 6). The inferior data employing ClCH$_2$CH$_2$Cl might be a result of its greater polarity than that of CH$_2$Cl$_2$ (Table 4, entry 8). The best result was obtained in CH$_2$Cl$_2$ (Table 4, entry 1).

Lowering the concentration of benzaldehyde led to a dramatic drop in reactivity (Table 5, entries 1 and 2). When the concentration of benzaldehyde was increased to 0.5 M from 0.25 M, better enantioselectivity could be obtained (Table 5, entry 4 vs 3). Further increase of the concentration of benzaldehyde led to less satisfying enantioselectivity (Table 5, entry 5). It suggested that there might involve dimeric or polymeric

TABLE 3. Asymmetric Cyanation of Benzaldehyde Catalyzed by the Combination of Three-Ligand and Ti(IV)

entry[a]	third ligand	time (h)	yield (%)[b]	ee (%)[c,d]
1		48	99	69
2	**2a**	40	99	68
3	**2b**	40	99	65
4	**3a**	10	99	58
5	**3b**	10	99	74
6	**3b**	30	99	65[e]
7	**3c**	10	99	47

[a] Conditions: 10 mol % of catalyst (**1e**/**2a**/indicated ligand/Ti(IV) = 1/1/1/1, concentration of benzaldehyde: 0.25 M in CH$_2$Cl$_2$, −20 °C, EtOCOCN: 1.2 equiv. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column. [d] The absolute configuration of the major product (*R*) was determined by comparison with the reported value of optical rotation (ref 5a). [e] Add **3b** to the complex of **1e**, **2a**, and Ti(IV).

TABLE 4. Lewis Acid and Solvent Effect

entry[a]	metals	solvent	time (h)	yield (%)[b]	ee (%)[c,d]
1	Ti(O*i*-Pr)$_4$	CH$_2$Cl$_2$	10	99	74
2	Al(O*i*-Pr)$_3$	CH$_2$Cl$_2$	10	99	11
3	Zn(OTf)$_2$	CH$_2$Cl$_2$	72	0	
4	Zr(O*i*-Pr)$_4$	CH$_2$Cl$_2$	10	99	19
5	Ti(O*i*-Pr)$_4$	Et$_2$O	24	95	2
6	Ti(O*i*-Pr)$_4$	toluene	10	99	69
7	Ti(O*i*-Pr)$_4$	THF	15	99	19
8	Ti(O*i*-Pr)$_4$	Cl(CH$_2$)$_2$Cl	10	99	20

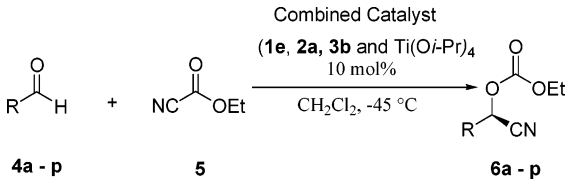
[a] Conditions: 10 mol % of catalyst (**1e**/**2a**/**3b**/Ti(IV) = 1/1/1/1), concentration of benzaldehyde: 0.25 M, −20 °C, EtOCOCN: 1.2 equiv. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column. [d] The absolute configuration of the major product (*R*) was determined by comparison with the reported value of optical rotation (ref 5a).

TABLE 5. Benzaldehyde Concentration and Temperature Effect

entry[a]	benzaldehyde concn (mol/L)	*T* (°C)	time (h)	yield (%) [b]	ee (%)[c,d]
1	0.125	−20	60	90	57
2	0.15	−20	20	99	65
3	0.25	−20	10	99	74
4	0.5	−20	10	99	79
5	1.0	−20	9	99	71
6	0.5	0	5	99	56
7	0.5	−45	48	95	90
8	0.5	−45	96	57	51[e]
9	0.5	−78	96	83	88
10	0.5	−78	100	trace	34[e]

[a] EtOCOCN: 1.3 equiv. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD column. [d] The absolute configuration of the major product (*R*) was determined by comparison with the reported value of optical rotation (ref 5a). [e] No **3b**.

TABLE 6. Substrate Scope



entry[a]	aldehydes	time (h)	yield (%)[b]	ee (%)[c]
1	benzaldehyde (**4a**)	48	95	90(*R*)
2	2-methylbenzaldehyde (**4b**)	50	78	83
3	3-methylbenzaldehyde (**4c**)	72	82	90
4	4-methylbenzaldehyde (**4d**)	55	81	93(*R*)
5	2-methoxybenzaldehyde (**4e**)	72	75	74(*R*)
6	3-methoxybenzaldehyde (**4f**)	72	81	82(*R*)
7	4-methoxybenzaldehyde (**4g**)	90	88	93(*R*)
8	3-phenoxybenzaldehyde (**4h**)	72	85	87
9	1-naphthaldehyde (**4i**)	50	83	84(*R*)
10	2-naphthaldehyde (**4j**)	55	82	94
11	4-fluorobenzaldehyde (**4k**)	100	78	82
12	4-chlorobenzaldehyde (**4l**)	96	81	58(*R*)
13	heliotropin (**4m**)	48	87	76
14	(*E*)-cinnamaldehyde (**4n**)	80	83	82(*R*)
15	hexanal (**4o**)	72	88	45(*R*)[d]
16	cyclohexanecarbaldehyde (**4p**)	72	75	70(*R*)[d]

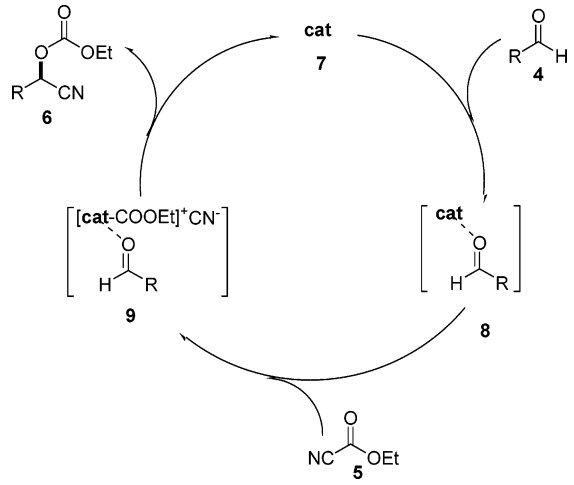
[a] Conditions: concentration of aldehydes = 0.5 M, EtOCOCN: 1.3 equiv. [b] Isolated yield. [c] Determined by HPLC on Chiralcel OD or OD-H column; the absolute configuration of the major product was compared with the reported value of optical rotation (refs 5a and 7a). [d] Determined by GC on Chirasil DEX CB; the absolute configuration of the major product was compared with the reported value of optical rotation (refs 5a and 7a).

Ti(IV) species which was attributed to the effect of concentration of catalyst. To our delight, the enantioselectivity was increased to 90% ee when the three-ligand system was used at −45 °C (Table 5, entry 7). However, lowering the reaction temperature to −78 °C led to a decrease in reactivity and slightly affected enantioselectivity (Table 5, entry 9). In contrast, when the double-ligand system was used under the same conditions, the enantioselectivity was only 51 and 34% ee, respectively (Table 5, entries 8 and 10). Additionally, when the reaction temperature was increased to 0 °C from −20 °C, the enantioselectivity decreased from 79 to 56% ee (Table 5, entry 6).

Moreover, the percent molar ratio of the component, catalyst loading, and the amount of EtOCOCN were investigated, but the enantioselectivity could not be improved (see Supporting Information for details). Hence, the optimal conditions were 10 mol % multicomponent catalyst (**1e**/**2a**/**3b**/Ti(IV) = 1/1/1/1), 0.5 M, CH_2Cl_2, −45 °C.

Substrate Generality: Encouraged by the results obtained from benzaldehyde under the optimized conditions, a series of aldehydes were evaluated (Table 6). Most of the aromatic, α,*β*-unsaturated, aliphatic aldehydes could be converted into the corresponding cyanohydrin carbonates in moderate to high yields with up to 94% ee. *para*-Substituted benzaldehydes led to higher enantioselectivities than benzaldehyde (Table 6, entries 4 and 7 vs entry 1), *ortho*- and/or *meta*-substituted benzaldehydes generally gave low enantioselectivity values than did the *para*-isomers (Table 6, entries 2, 3, 5, 6, 8, and 13). 2-Naphthaldehyde provided the highest enantioselectivity (up to 94% ee) with good yield (Table 6, entry 10), but the 1-naphthaldehyde afforded unsatisfactory results (Table 6, entry 9). Halogen-substituted benzaldehydes gave lower enantioselectivity values and required longer reaction time (Table 6, entries 11 and 12). When (*E*)-cinnamaldehyde was subjected to the reaction, only the 1,2-addition product was afforded in 83% yield with 82% ee (Table 6, entry 14). Cyclohexanecarbaldehyde gave the corresponding product with moderate enantioselectivity and yield (Table 6, entry 16). However, the hexanal gave a poor result (Table 6, entry 15), in contrast to Shibasaki and co-workers' result.[5a] These results showed that the multicomponent catalyst was effective for the asymmetric cyanation of a wide range of aldehydes.

SCHEME 1. Proposed Catalytic Cycle



Mechanism: On the basis of Shibasaki and other work groups' reports on the cyanation of carbonyl compounds with a bifunctional catalyst,[3f,6,9d,f,g,j] we considered that the complex of (*S*)-6,6′-Br_2−BINOL (**1e**) with Ti(IV) might act as the Lewis acid to activate electrophiles (carbonyl group),[3e,8,9] while the tertiary amine of ligands **2a** and **3b** might play Lewis base to activate the nucleophiles (EtOCOCN).[4,6,8,9] Herein, a possible catalytic cycle consisting of three steps was proposed (Scheme 1). **Step I**: The aldehyde coordinated with the titanium complex **7** to form a catalytically active species **8**.[5,6,8] **Step II**: The EtOCOCN was activated by the Lewis base to generate complex **9**.[4,6,8] **Step III**: The cyanide would react with the aldehydes to provide the product **6** and accomplish one catalytic cycle.

In conclusion, we have developed a novel multicomponent bifunctional titanium complex to catalyze the enantioselective cyanation of aldehydes. Under the optimized conditions, excellent reactivity and enantioselectivity could be generated (up to 95% yield and up to 94% ee). The strategy described in the present work demonstrated the ability of a multicomponent catalyst to promote an enantioselective cyanation of aldehydes, which might provide a new direction to the design of chiral catalysts for asymmetric catalysis. Investigations of the scope of these applications are currently underway.

Experimental Section

2-Ethoxycarbonyl-(*R*)-2-hydroxy-2-phenyl acetonitrile (6a): Ti(O*i*-Pr)$_4$ (1.0 M in toluene, 25 μL, 0.025 mmol) was added to a solution of **1e** (11.1 mg, 0.025 mmol), **2a** (7.35 mg, 0.025 mmol), and **3b** (4.48 mg, 0.025 mmol) in CH_2Cl_2, and the mixture was stirred at 35 °C for 1 h under N_2. This was followed by the addition of benzaldehyde (0.25 mmol) and EtOCOCN (0.325 mmol) at −45 °C. The contents were stirred for 48 h, and then the solution was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether, 10:1) to afford the product. Colorless oil; yield 95%; $[\alpha]_D^{23.4}$ +16.0 (*c* 2.0, $CHCl_3$) (90% ee). HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm) t_R 13.4 and 17.5 min, lit.[5a,c] $[\alpha]_D^{21.7}$ +16.2 (*c* 2.8, $CHCl_3$) for the *R* enantiomer in 94%

ee. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 7.2 Hz, 3H), 4.26−4.32 (m, 2H), 6.27 (s, 1H), 7.45−7.49 (m, 3H), 7.53−7.56 (m, 2H).

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Supporting Information Available: Investigation of the percent molar ratio of the component, catalyst loading, and the amount of EtOCOCN, characterization of products, including ^{1}H and ^{13}C NMR, HRMS data, HPLC, and GC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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