Highly Enantioselective Cyanation of Aldehydes Catalyzed by Multicomponent Titanium Complex

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General Remarks: ^1H NMR spectra were recorded with a commercial (300 MHz) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 , $\delta = 7.26$). Data are reported as follows: Chemical shift, multiplicity (s-singlet, d-doublet, t-triplet, m-multiplet), coupling constants (Hz), integration. ^{13}C NMR spectroscopic data were collected with a commercial (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm relative to tetramethylsilane with the solvent resonance as internal standard (CDCl_3 , $\delta = 77.0$ ppm). Enantiomeric excesses (ee) were determined by HPLC (around 3 to 4%) or GC

(around 1 to 2%). Optical rotations were reported as follows: $[\alpha]_D^T$ (c g/100 mL, in solvent). HRMS was recorded on a commercial apparatus (ESI Source). All aldehydes, EtOCOCN were commercially available, and used directly without further purification. Solvents were purified by the usual methods. CH_2Cl_2 and $\text{ClCH}_2\text{CH}_2\text{Cl}$ were distilled over CaH_2 . CHCl_3 was passed through a column of basic alumina. THF, toluene and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl.

BINOL derivatives (**1b-e**, **1h**)¹, (**1f-g**)² were synthesized according to the literature. **1a**, **1h**, **2a-d**, **3a-b** were commercially available. **3c** was synthesized according to the literature³.

Table 1. Effect of the Multicomponent's Ratio

Entry ^a	Ligands (mol%)			Ti(Oi-Pr) ₄ (mol%)	Time (h)	Yield (%) ^b	Ee (%) ^{c,d}
	1e	2a	3b				
1	10	10	10	10	10	99	74
2	5	10	10	10	10	99	60
3	10	5	5	10	72	65	67
4	10	5	10	10	18	99	30
5	5	5	10	10	10	99	64
6	10	10	10	20	10	99	57
7	10	10	5	5	10	99	72
8	10	10	10	5	10	99	33
9	10	10	20	10	9	99	66
10	10	20	10	10	8	99	65

^a Conditions: concentration of benzaldehyde: 0.25 M in CH_2Cl_2 , -20 °C, EtOCOCN: 1.2 eq. ^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. 4)

Table 2. Optimization of the Catalyst Loading and the Amount of EtOCOCN

Entry ^a	Catalyst (mol%)	EtOCOCN (eq.)	Time (h)	Yield (%) ^b	Ee (%) ^{c,d}
1	10	1.2	10	99	74 ^e
2	10	1.2	18	99	64 ^f
3	5	1.2	10	99	60
4	15	1.2	8	99	72
5	20	1.2	7	99	71
6	10	1.0	10	72	66
7	10	1.1	10	87	71
8	10	1.3	10	99	76
9	10	1.4	9.5	99	76
10	10	1.5	8	99	76

^a Conditions: concentration of benzaldehyde: 0.25 M in CH₂Cl₂, -20 °C. ^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. 4). ^e The solvent was evaporated in vacuo after the preparation of catalyst. ^f Add **3b** to the complex of **1e**, **2a** and Ti(IV).

Preparation of Optically Active cyanohydrin ethyl carbonates

General Procedure: Ti(Oi-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 CH₂Cl₂, and the mixture was stirred at 35 °C for 1h under N₂. Followed by the addition of aldehyde (0.25 mmol) and EtOCOCN (0.325 mmol) at -45 °C. The contents were stirred for the indicated time in Table, and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether, 10:1) to afford the corresponding cyanohydrins carbonates.

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-phenyl-acetonitrile (**6a**):

colorless oil; Yield 95%. $[\alpha]_D^{23.4} +16.0$ (*c* 2.0 in 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 min and 17.5 min. Lit.⁴ $[\alpha]_D^{21.7} +16.2$ (*c* 2.8, CHCl_3) for *R* enantiomer in 94% ee. ^1H NMR (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).

2-Ethoxycarbonyl 2-hydroxy-2-(2-methylphenyl)-acetonitrile (6b):

colorless oil; Yield 78%. $[\alpha]_D^{23} +20.42$ (*c* 2.0 in CHCl_3) (83% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 8.4 min and 10.2 min. ^1H NMR (CDCl_3), δ 1.32 (t J = 7.2 Hz, 3H), 2.40 (s, 3H), 4.23-4.34 (m, 2H), 6.23 (s, 1H), 7.26-7.35 (m, 4H). ^{13}C NMR (CDCl_3), δ 14.1, 21.2, 65.5, 66.3, 115.8, 124.9, 128.4, 129.1, 131.1, 131.3, 139.2, 153.4. HRMS (ESI methanol) m/z 242.0784 [$\text{M} + \text{Na}^+$]; calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{Na}^+ = 242.0788$.

2-Ethoxycarbonyl 2-hydroxy-2-(3-methylphenyl)-acetonitrile (6c):

colorless oil; Yield 82%. $[\alpha]_D^{23.3} +11.0$ (c 2.0 in CHCl_3) (90% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 10.3 min and 12.6 min. ^1H NMR (CDCl_3), δ 1.33 (t $J =$

7.1 Hz, 3H), 2.5 (s, 3H), 4.25-4.33 (m, 2H), 6.39 (s, 1H), 7.24-7.39 (m, 3H), 7.58 (d $J = 6.4$ Hz, 1H).

^{13}C NMR (CDCl_3), δ 14.1, 18.9, 64.5, 65.6, 115.6, 126.7, 128.6, 129.3, 130.6, 131.3, 136.7, 153.4.

HRMS (ESI methanol) m/z 242.0778 $[\text{M} + \text{Na}^+]$; calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{Na}^+ = 242.0788$.

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(4-methylphenyl)-acetonitrile (6d):

colorless oil; Yield 81%. $[\alpha]_D^{23.3} +3.5$ (c 2.0 in CHCl_3) (93% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 8.6 min and 9.9 min. Lit.⁵ $[\alpha]_D^{16} -5.1$ (c 2.0, CHCl_3) for *S* enantiomer in

94% ee. ^1H 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).

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(2-methoxyphenyl)-acetonitrile (6e):

colorless oil; Yield 75%. $[\alpha]_{\text{D}}^{23.4} -10.0$ (c 2.0 in CHCl_3) (74% ee). HPLC (DAICEL

CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254

nm. t_{R} 6.9 min and 10.2 min. Lit.⁵ $[\alpha]_{\text{D}}^{20} +57.0$ (c 1.4 in CHCl_3) for *S* enantiomer

in 98% ee. ^1H 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 (d t $J = 8.2, 1.6$ Hz, 1H), 7.42 (d t $J = 8.2,$

1.6, Hz, 1H), 7.58 (dd $J = 8.2, 1.6$ Hz, 1H).

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(3-methoxyphenyl)-acetonitrile (6f):

colorless oil; Yield 81%. $[\alpha]_D^{23.4} +8.1$ (c 2.0 in CHCl_3) (82% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 15.6 min and 21.1 min. Lit.⁵ $[\alpha]_D^{20} -11.3$ (c 1.2 in CHCl_3) for *S* enantiomer in 99% ee. ^1H 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).

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(4-methoxyphenyl)-acetonitrile (6g):

colorless oil; Yield 88%. $[\alpha]_D^{20}$ -6.0 (*c* 2.0 in CHCl_3) (93% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 14.5 min and 18.7 min. Lit.⁵ $[\alpha]_D^{20}$ +1.8 (*c* 1.8 in CHCl_3) for *S* enantiomer in 95% ee. ^1H 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).

2-Ethoxycarbonyl 2-hydroxy-2-(3-phenoxyphenyl)-acetonitrile (6h):

colorless oil; Yield 85%. $[\alpha]_D^{23.1}$ +8.0 (*c* 2.0 in CHCl_3) (87% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R 11.25 min and 14.13 min. ^1H 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). ^{13}C NMR (CDCl_3), δ 14.1, 65.7, 65.9, 115.5, 117.7, 119.3, 120.3, 122.1, 124.1, 129.9, 130.6, 132.9, 153.3, 156.13, 158.16. HRMS (ESI methanol) m/z 320.0889 $[\text{M} + \text{Na}^+]$; calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_4\text{Na}^+$ = 320.0893.

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(1-naphthyl)-acetonitrile (6i):

colorless oil; Yield 83%. $[\alpha]_D^{23.1} +30.5$ (c 2.0 in CHCl_3) (84% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm.

t_R 6.2 min and 7.0 min. Lit.⁴ $[\alpha]_D^{23.0} +36.2$ (c 2.00 in CHCl_3) for *R* enantiomer in 90%

ee. ^1H NMR (CDCl_3) δ 1.32 (t J = 7.5 Hz 3H), 4.25-4.37(m, 2H), 6.45 (s, 1H), 7.50-

7.65 (m, 3H), 7.82 (d J = 7.1 Hz 1H), 7.91-7.98 ((m, 2H), 8.08 (d J = 8.4 Hz 1H).

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-(2-naphthyl)-acetonitrile (6j):

white solid; Yield 82%. $[\alpha]_D^{23.1}$ -8.5 (*c* 2.0 in CHCl_3) (94% ee). HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm. t_R 11.07 min and 11.94 min ^1H 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). ^{13}C NMR (CDCl_3), δ 14.1, 65.6, 66.6, 115.8, 124.2, 127.1, 127.7, 127.8, 128.1, 128.4, 129.5, 132.8, 133.9, 153.5. HRMS (ESI methanol) m/z 278.0785 $[\text{M} + \text{Na}^+]$; calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{Na}^+$ = 278.0788.

2-Ethoxycarbonyl 2-hydroxy-2-(4-fluorophenyl)-acetonitrile (6k):

colorless oil; Yield 78%. $[\alpha]_D^{23.1}$ +6.5 (*c* 2.0 in CHCl_3) (82% ee). HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at 254 nm. t_R 9.8 min and 11.7 min. ^1H 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), 7.52-7.57 (m, 2H). ^{13}C NMR (CDCl_3), δ 14.1, 65.6, 65.7, 115.6, 116.3, 116.6, 130.1, 130.2, 153.3, 162.2, 165.5. HRMS (ESI methanol)

m/z 246.0532 [M + Na⁺]; calcd for C₁₁H₁₀NO₃Na⁺ = 246.0537.

2-Ethoxycarbonyl *R*-2-hydroxy-2-(4-chlorophenyl)-acetonitrile (6l):

colorless oil; Yield 81%. [α]_D^{22.9} +0.71 (*c* 2.0 in CHCl₃) (58% ee). Lit.⁵ [α]_D²⁰ -2.9 (*c* 1.3 in CHCl₃) for *S* enantiomer in 94% ee. HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow 1.0 mL/min, detection at

254 nm. *t*_R 11.7 min and 15.4 min ¹H NMR (CDCl₃) δ 1.33 (t *J* = 7.2 Hz, 3H), 4.23-4.34 (m, 2H), 6.23 (s, 1H), 7.41-7.51 (m, 4H).

2-Ethoxycarbonyl 2-hydroxy-2-(benzo[d][1,3]dioxole-5-yl) -acetonitrile (6m):

colorless oil; Yield 87%. $[\alpha]_D^{23.3}$ -3.0 (*c* 2.0 in CHCl_3) (76% ee). HPLC

(DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min,

detection at 254 nm. t_R 9.6 min and 13.5 min. ^1H NMR (CDCl_3), δ 1.33 (t J

= 7.2 Hz, 3H), 4.22-4.33 (m, 2H), 6.02 (s, 2H), 6.16 (s, 1H), 6.82–6.85 (d J = 7.8 Hz, 1H), 6.99-7.04

(m, 2H). ^{13}C NMR (CDCl_3)

δ 14.1, 65.6, 66.2, 101.79, 108.2, 108.6, 115.7, 122.5, 124.8, 148.4, 149.6,

153.4. HRMS (ESI methanol) m/z 272.0527 $[\text{M} + \text{Na}^+]$; calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_5\text{Na}^+$ = 272.0529.

2-Ethoxycarbonyl (*R*)-2-hydroxy-4-phenyl-but-3-enonitrile (6n):

colorless oil; Yield 83%. $[\alpha]_D^{23.3}$ -19.0 (*c* 2.0 in CHCl_3) (82% ee). HPLC

(DAICEL CHIRALCEL OD, 2-propanol/hexane 10/90, flow 1.0 mL/min,

detection at 254 nm. t_R 12.4 min and 13.9 min Lit.⁴ $[\alpha]_D^{20}$ -17.2 (*c* 0.9, CHCl_3)

for *R* enantiomer in 88% ee. ^1H 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).

(*R*)-2-Ethoxycarboxyheptanenitrile (60):

colorless oil; Yield 88%. GC[Varian Chirasil DEXCB (0.25 mm x 25 m),

injection temp. 110 °C; initial column temp. 230 °C; detection temp. 250 °C; t_R

30.0 min and 31.1 min. $[\alpha]_D^{22.9} +24.7$ (c 2.0 in CHCl_3) (45% ee). Lit.⁴ $[\alpha]_D^{27.4}$ -

7.12 (c 2.21, CHCl_3) for *R* enantiomer in 94% ee. ^1H 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).

2-Ethoxycarbonyl (*R*)-2-hydroxy-2-cyclohexylethanitrile (6p):

colorless oil; Yield 75%. $[\alpha]_D^{22.9} +2.8$ (*c* 2.0 in CHCl_3) (70% ee). GC[Varian Chirasil

DEXCB (0.25 mm x 25 m), injection temp. 130 °C; initial column temp. 250 °C;

detection temp 250 °C; t_R 27.0 min and 28.1 min. Lit.⁴ $[\alpha]_D^{27.4} +53.4$ (*c* 2.21, CHCl_3)

for *R* enantiomer in 96% ee. ^1H 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).

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Figure 1. ^1H NMR of 6b

Figure 2. ^{13}C NMR of 6b

Figure 3. ^1H NMR of 6c

Figure 4. ^{13}C NMR of 6c

Figure 5. ^1H NMR of 6h

CCOC(=O)C(C#N)(c1ccc(Oc2ccccc2)cc1)c3ccccc3

Figure 7. ^1H NMR of 6j

Figure 8. ^{13}C NMR of 6j

Figure 9. ^1H NMR of 6k

Figure 10. ^{13}C NMR of 6k

Figure 11. ^1H NMR of 6m

Figure 12. ^{13}C NMR of 6m