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Asymmetric Cyanoethoxycarbonylation of Aldehydes Catalyzed by Heterobimetallic Aluminum Lithium Bis(binaphthoxide) and Cinchonine

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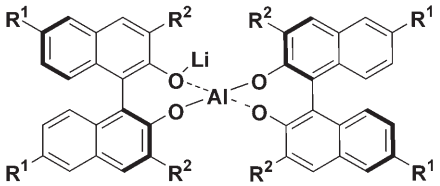
Abstract: Highly efficient catalytic asymmetric cyanoethoxycarbonylation of aldehydes was achieved by 10 mol% cinchonine with 10 mol% heterometallic (*S*)-aluminum lithium bis(binaphthoxide), which gave the cyanohydrins ethyl carbonates in excellent isolated yields (up to 99%) with moderate to high enantioselectivities (up to 95% *ee*) under mild conditions (at −20 °C). Especially, the solid aluminum lithium bis(binaphthoxide) free of tetrahydrofuran was obtained by a new procedure using (*S*)-bi(2-naphthol), aluminum isopropoxide and *n*-butyllithium in dichloromethane, which was insensitive to air and moisture and was very convenient to store and use. A catalytic cycle based on experimental phenomena was proposed to explain the nature of the asymmetric induction.

Keywords: aldehyde; asymmetric catalysis; C–C bond formation; cyanoethoxycarbonylation; cyanohydrins; ethyl carbonates

Introduction

The catalytic asymmetric cyanation of carbonyl compounds is a powerful strategy to prepare cyanohydrins which are highly versatile synthetic building blocks and chiral auxiliaries in organic synthesis.[1] Much effort has, therefore, been devoted to develop various catalytic systems for the enantioselective cyanation of aldehydes and ketones using trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN) as cyanide source to obtain the optically active cyanohydrins over the last two decades.[2,3] Asymmetric cyanation employing cyanoformate ester (ROCOCN), acetyl cyanide, diethyl cyanophosphonate, or benzoyl cyanide as the cyanide source to afford the corresponding functionalized cyanohydrins has been realized by BINOL,[4] salen[5] and dimeric *Chincona* alkaloid derivatives etc.[6] Recently, our group has reported the titanium complex-promoted enantioselective cyanation of aldehydes using ethyl cyanoformate as cyanide source.[7] During the course of this study, we were very interested in the conception of the heterobimetallic multifunctional catalyst developed by Shibasaki et al.[8,9] Amongst of their works, the AlLibis(binaphthoxide) complex (ALB),[9h,i] which consisted of aluminum, lithium, and two molecules of BINOLs, enabled excellently enantioselective Michael reactions of malonates with enones in up to 99% *ee* (Figure 1,

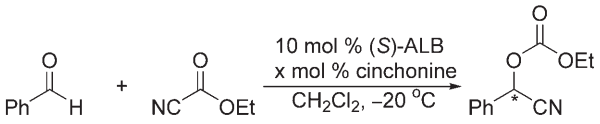


Al(*S*)-(1a-j)$_2$Li

1a: $R^1 = R^2 = H$ **1f**: $R^1 = H$, $R^2 = I$
1b: $R^1 = Br$, $R^2 = H$ **1g**: $R^1 = H$, $R^2 = Br$
1c: $R^1 = I$, $R^2 = H$ **1h**: $R^1 = H$, $R^2 = P(O)Ph_2$
1d: $R^1 = CH_3$, $R^2 = H$ **1i**: $R^1 = H$, $R^2 = SiPh_3$
1e: $R^1 = H$, $R^2 = CH_3$ **1j**: $R^1 = H$, $R^2 = Si(t\text{-}Bu)Ph_2$

Figure 1. The designed AlLi complexes of BINOL derivatives.

Table 1. Asymmetric cyanation of benzaldehyde catalyzed by (*S*)-ALB and cinchonine.



2a **3** **4a**

Entry[a]	Metal reagents		Solvent (catalyst preparation)	Cinchonine (x mol%)	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	$AlLiH_4$		THF	0	96	0	-
2	$AlLiH_4$		THF	10	96	10	0
3	$AlLiH_4$		CH_2Cl_2	10	48	0	
4	$AlEt_3$	*n*-BuLi	CH_2Cl_2	10	48	90	0
5	$AlEt_2Cl$	*n*-BuLi	CH_2Cl_2	10	48	0	-
6	$Al(O\text{-}i\text{-}Pr)_3$	*n*-BuLi	CH_2Cl_2	10	15	99	75(*S*)
7	$Al(O\text{-}i\text{-}Pr)_3$	LiBr	CH_2Cl_2	10	48	0	-
8	$Al(O\text{-}i\text{-}Pr)_3$	$LiBr.H_2O$	CH_2Cl_2	10	48	0	-
9	$Al(O\text{-}i\text{-}Pr)_3$	*n*-BuLi	CH_2Cl_2	0	48	trace	-

[a] *Conditions:* the catalyst prepared *in situ* (see Supporting Information), concentration of benzaldehyde: 0.25 M in CH_2Cl_2, EtOCOCN: 1.3 equivs.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configuration of the major product was *S* compared with the reported value of optical rotation (ref[4a]).

1a). Herein, we have successfully developed a new approach to prepare the heterobimetallic multifunctional AlLibis(binaphthoxide) (ALB) and applied it in the high enantioselective cyanoethoxycarbonylation of aldehydes.

Results and Discussion

Initial studies indicated that the (*S*)-ALB complex prepared from $LiAlH_4$ in THF could not catalyze the addition of benzaldehyde with ethyl cyanoformate (EtOCOCN) at −20 °C (Table 1, entry 1).[9h,i] When cinchonine was combined with (*S*)-ALB in this reaction, the cyanohydrin ethyl carbonate could be obtained with 10% yield, but without enantioselectivity (Table 1, entry 2), which might be attributed to the coordination of the ether solvent (THF) with the central metal and resulted in the poor results.[9h,i,k] So, we aimed to develop a new procedure for the preparation of the (*S*)-ALB complex free of THF and applied it in the cyanoethoxycarbonylation of aldehydes.

To our delight, (*S*)-2-mandelonitrile ethyl carbonate **4a** could be obtained with moderate enantioselectivity (75% *ee*) and high yield (up to 99%) catalyzed by 10 mol% of the (*S*)-ALB complex that was prepared from $Al(O\text{-}i\text{-}Pr)_3$, *n*-BuLi and (*S*)-BINOL in CH_2Cl_2 combined with 10 mol% cinchonine (Table 1, entry 6). However, no reaction (Table 1, entries 3 and 5, 7–8) or no enantioselctivity (Table 1, entry 4) was observed when using other AlLi complexes under the same conditions. It was worthy of note that the result was unsatisfactory if no cinchonine was added in this reaction system (Table 1, entry 9).

When the solvent used for preparing catalyst was evaporated in vacuum, the solid (*S*)-ALB could be obtained. Moreover, the enantioselectivity and reactivity were impoved remarkably when the solid (*S*)-ALB was employed in this reaction (Table 2, entry 2 *vs.* 1). Herein, the *i*-PrOH produced in the catalyst preparation step might play some unknown role in this catalytic system. So, the external addition of different amount of *i*-PrOH to the (*S*)-ALB prepared from $AlEt_3$ and *n*-BuLi was investigated (Table 2, entries 3–6). Almost the same result could be obtained when 20 mol% *i*-PrOH was added in this system (Table 2, entry 4). Lowing or increasing the amount of *i*-PrOH led to diminished enantioselectivities and slightly affected the reactivity (Table 2, entries 3 and 6). Different from the previous catalyst preparation, comparable outcomes could be obtained when the solvent used for the preparation of ALB with $AlEt_3$ was evaporated (Table 2, entry 5 *vs.* 4). However, when *i*-PrOH was replaced by other hydroxy compounds, the enantioselectivity and reactivity were decreased to different extents (Table 2, entries 7–12).

It was found that the solid (*S*)-LAB complex was insensitive to air or water (Table 3, entries 2–6 *vs.* entry 1). The enantioselectivity were affected little even when the solid (*S*)-LAB was stored at room temperature for 7 days before use (Table 3, entry 3).

Then, some other AlLi complexes of BINOL derivatives were investigated (Table 4, entries 1–11). The data showed that **1a** [(*S*)-ALB] gave the best result

Table 2. Effect of different hydroxy compounds.

Entry[a]	Al source	R-OH [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	$Al(O\text{-}i\text{-}Pr)_3$	0	15	99	75
2	$Al(O\text{-}i\text{-}Pr)_3$	0	3	99	85[e]
3	$AlEt_3$	*i*-PrOH (10)	16	95	78
4	$AlEt_3$	*i*-PrOH (20)	3	99	86
5	$AlEt_3$	*i*-PrOH (20)	3	99	85[e]
6	$AlEt_3$	*i*-PrOH (30)	4.5	96	82
7	$AlEt_3$	CH_3OH (20)	4	98	74
8	$AlEt_3$	C_2H_5OH (20)	3.5	99	74
9	$AlEt_3$	PhOH (20)	10	90	52
10	$AlEt_3$	1-adamantanol (20)	10	91	75
11	$AlEt_3$	$(CH_3)_3COH$ (20)	5.5	99	81
12	$AlEt_3$	cyclopentanol (20)	5.5	98	78

[a] *Conditions:* 10 mol% (*S*)-ALB, the experimental procedure of preparing the (*S*)-ALB: see Supporting Information, 10 mol% cinchonine, concentration of benzaldehyde: 0.25 M, −20 °C, EtOCOCN: 1.3 equivs.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configuration of the major product was *S* compared with the reported value of optical rotation (ref[4a]).
[e] The solvent used for the prearation of catlyst was evaporated.

Table 3. Investigations for stabilization of the (*S*)-ALB complex.

Entry[a]	H_2O [mol%]	*t* [h]	*ee* [%][b,c]
1	0	1.5	86
2	0	2	85[d]
3	0	2.5	82[e]
4	10	2.5	85
5	20	4	83
6	30	6	80

[a] *Conditions:* 10 mol% solid (*S*)-ALB, 10 mol% cinchonine, concentration of benzaldehyde: 0.25 M, −20 °C, EtOCOCN: 1.3 equivs., isolated yield: >90%.
[b] Determined by HPLC on a Chiralcel OD-H column.
[c] The absolute configuration of the major product was *S* compared with the reported value of optical rotation (ref.[4a]).
[d] Without N_2 protection.
[e] The catalyst stored at room temperature for 7 days.

Table 4. Asymmetric cyanation of benzaldehyde catalyzed by the Al(*S*)-(**1a–j**)$_2$Li and cinchonine.

Entry[a]	**1a–j**	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**1a**	1.5	99	86
2	**1b**	3	97	84
3	**1c**	2	95	64
4	**1d**	4	99	63
5	**1e**	4	96	14
6	**1f**	4	93	12
7	**1g**	4.5	91	11
8	**1h**	3.5	99	65
9	**1i**	4	99	0
10	**1j**	4.5	98	0
11	**1a**	23	94	17[e]

[a] *Conditions*: 10 mol% (*S*)-AlLi complex which prepared using $AlEt_3$, *n*-BuLi and 20 mol% *i*-PrOH, 10 mol% cinchonine, concentration of benzaldehyde: 0.25 M in CH_2Cl_2, −20 °C, EtOCOCN: 1.3 equivs.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configuration of the major product was S compared with the reported value of optical rotation (ref.[4a]).
[e] (*R*)-**1a** was used.

(Table 4, entry 1). Other AlLi complexes could also catalyze the reaction in excellent yields under the same conditions, but with lower enantioselectivities (Table 4, entries 2–10). Notablely, when (*S*)-ALB was replaced by (*R*)-ALB in this catalytic system, the enantioselectivity and reactivity were dramatically decreased (Table 4, entry 11).

When cinchonine was replaced by MS or H_2O in this system, very poor results were observed (Table 5, entries 9 and 10 *vs.* entry 1). Other basic reagents were employed in this reaction, such as quinidine, Et_3N and $P(O)Ph_3$ etc., excellent yields could be obtained (up to 99%), but the enantioselectivities were unsatisfactory (Table 5, entries 2–8, 11 and 12 *vs.* entry 1).

Lowing the concentration of benzaldehyde led to a slightly drop in reactivity (Table 6, entry 1). When the concentration of benzaldehyde was increased to 0.5 M, better enantioselectivity could be seen than other conditions (Table 6, entry 3 *vs.* entries 2, 4 and 5). The enantioselectivity decreased when the reaction temperature was lowed from −20 to −45 °C or −78 °C (Table 6, entries 7 and 8). When the reaction temperature was increased from −20 to 0 °C, the

Table 5. Effect of other substitutes of cinchonine.

Entry[a]	Substitute	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	cinchonine	3	99	86
2	cinchonidine	3.5	99	32
3	quinine	3	99	8
4	quinidine	3	99	36
5	DMAP	4	94	16
6	Et_3N	4	99	15
7	(*1R,2S*)-methylephedrine	5	99	0
8	$P(O)Ph_3$	3.5	99	57
9	H_2O	48	trace	-
10	MS	48	trace	-
11	*n*-BuLi	3	99	0
12	*n*-BuLi	1	99	63[e]

[a] *Conditions:* 10 mol% (*S*)-ALB, 10 mol% corresponding substitute, concentration of benzaldehyde: 0.25 M in CH_2Cl_2, −20 °C, EtOCOCN: 1.3 equivs.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configuration of the major product was *S* compared with the reported value of optical rotation (ref.[4a]).
[e] 10 mol% cinchonine was used.

enantioselectivity decreased from 90% to 67% *ee* (Table 6, entry 6). Larger or smaller catalyst loadings afforded inferior results (Table 6, entries 9–14 *vs.* entry 3). Above all, the optimal conditions were 10 mol% solid (*S*)-ALB and 10 mol% cinchonine, concentration of aldehydes: 0.5 M in CH_2Cl_2, −20 °C (effect of reaction solvent: see Supporting Information for details).

Substrate Generality

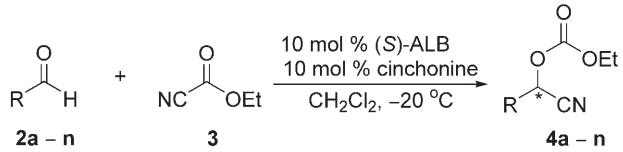
A representative selection of aldehydes **2** were evaluated under the optimized conditions and the results obtained were summarized in Table 7. Most of the aromatic, α,β-unsaturated, aliphatic aldehydes could be converted into the corresponding cyanohydrins carbonates in 88–99% yields with 74–95% *ee*s. *ortho*-Methoxy-substituted benzaldehyde led to higher enantioselectivity than benzaldehyde (Table 7, entry 3); methoxy- or methyl-substituents at *para*- or *meta*-positions generally gave lower enantioselectivity than benzaldehyde (Table 7, entries 2, 4 and 5 *vs.* 1). Moreover, *para*-methoxybenzaldehyde was converted into the desired product albeit requiring longer reaction times (Table 7, entry 5). *meta*-Phenoxybenzaldehyde gave 91% *ee* with 98% yield (Table 7, entry 6), and the cyanohydrins ethyl carbonate **4f** might be applicable in the synthesis of the insecticide fenvalerate A_α.[1a] 2-Naphthaldehyde achieved excellent enantioselectivity when the temperature was decreased from −20 to −45 °C (Table 7, entry 8 *vs.* 7). Halogen-substituted benzaldehydes gave moderate *ee* values and excellent yields (Table 7, entries 9 and 10). When (*E*)-cinnamaldehyde was subjected to the reaction, only the 1,2-addition product was obtained in 90% isolated yield with 80% *ee* (Table 7, entry 11). Aliphatic aldehydes gave the corresponding products with moderate *ee* values and excellent yields (Table 7, entries 12–15), which were better than our previous results.[7a] All these results illustrated that solid (*S*)-ALB complex combined with cichonine was an efficient catalyst system for the asymmetric cyanation of a wide range of aldehydes.

Table 6. Effect of the benzaldehyde concentration, temperature and catalyst loading.

Entry[a]	Benzaldehyde conc. [M]	(*S*)-ALB [mol%]	Cinchonine [mol%]	*T* [°C]	*t* [h]	*ee* [%][b,c]
1	0.125	10	10	−20	5	75
2	0.25	10	10	−20	3	86
3	0.5	10	10	−20	1.5	90
4	1.0	10	10	−20	1	85
5	1.5	10	10	−20	1	82
6	0.5	10	10	0	1	67
7	0.5	10	10	−45	24	81
8	0.5	10	10	−78	96	80
9	0.5	2.5	2.5	−20	10	72
10	0.5	5	5	−20	6	82
11	0.5	15	15	−20	1	84
12	0.5	0	10	−20	10	13[d]
13	0.5	10	5	−20	96	79
14	0.5	10	15	−20	96	83

[a] *Conditions:* EtOCOCN: 1.3 equivs., isolated yield > 90%.
[b] Determined by HPLC on a Chiralcel OD-H column.
[c] The absolute configuration of the major product was S, determined by the comparison with the reported value of optical rotation (ref.[4a]).
[d] The yield is very low.

Table 7. Asymmetric cyanation of aldehydes catalyzed by solid (*S*)-ALB and cinchonine.

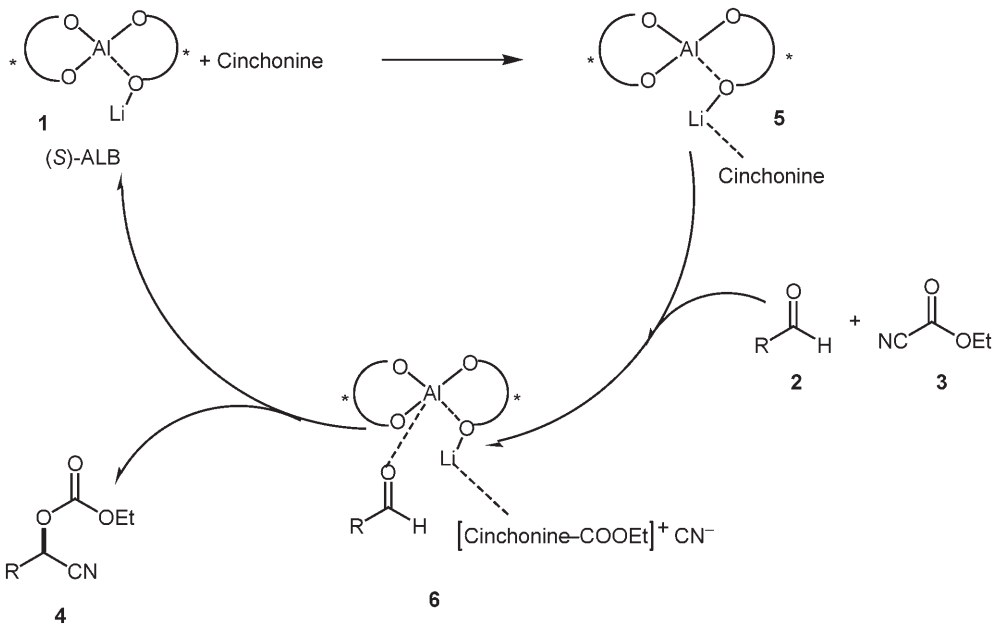


Entry[a]	Aldehydes	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	benzaldehyde (**2a**)	1.5	99	90 (*S*)
2	2-methylbenzaldehyde (**2b**)	1.5	98	83
3	2-methoxybenzaldehyde (**2c**)	2.0	96	95 (*S*)
4	3-methoxybenzaldehyde (**2d**)	2.0	97	82 (*S*)
5	4-methoxybenzaldehyde (**2e**)	10	89	85 (*S*)
6	3-phenoxybenzaldehyde (**2f**)	1.5	96	91
7	2-naphthaldehyde (**2g**)	1.5	97	86
8	2-naphthaldehyde (**2g**)	24	88	90[d]
9	4-fluorobenzaldehyde (**2h**)	1.5	97	84
10	4-chlorobenzaldehyde (**2i**)	2.0	96	81 (*S*)
11	(*E*)-cinnamaldehyde (**2j**)	2.5	90	80 (*S*)
12	propionaldehyde (**2k**)	1.5	94	80 (*S*)[e]
13	isobutyraldehyde (**2l**)	1.5	95	78 (*S*)[e]
14	hexanal (**2m**)	1.5	95	81 (*S*)[e]
16	cyclohexanecarbaldehyde (**2n**)	2.0	96	74 (*S*)[e]

[a] Conditions: concentration of aldehyde: 0.5 M, EtOCOCN: 1.5 equivs.
[b] Isolated yield.
[c] Determined by HPLC on Chiralcel OD-H column, the absolute configuration of the major product was compared with the reported value of optical rotation (ref.[4a,5b]).
[d] At −45 °C.
[e] Determined by GC on Chirasil DEX CB.

Mechanism

A possible catalytic cycle for the cyanation of aldehydes with EtOCOCN was shown in Scheme 1. Herein, the lithium naphthoxide moiety functioned as a Lowry–Brønsted base and the alumium center functioned as a Lewis acid on the basis of Shibasaki's heterobimetallic multifunctional catalytic system.[9h,i] Cin-



Scheme 1. Proposed catalytic cycle.

chonine coordinated with the lithium to form **5** and the aldehyde **2** coordinated with the alumium of the (*S*)-ALB complex **1** respectivily, EtOCOCN **3** was activated by the tertiary amine (cinchonine) and formed the transition state **6**.[6] The activated cyanide reacted with the activated aldehyde to generate the product **4** and accomplished a catalytic cycle.

Conclusions

In conclusion, we have successfully developed a new approach to prepare the heterobimetallic AlLibis(binaphthoxide) (ALB) and applied it in the enantioselective cyanation of aldehydes. Moreover, the solid ALB is insensitive to air and moisture, so it is very convenient to store and use. Under mild reaction conditions, excellent reactivity and enantioselectivity could be generated (up to 99% yield and 95% *ee*) for a variety of aldehydes. The strategy described in the present work shows a different application of the heterobimetallic AlLibis(binaphthoxide) in the catalytic asymmetric reaction, which might lead to further progress in this area. Investigations of the scope of these applications are currently underway.

Experimental Section

General Remarks

^{1}H NMR spectra were recorded with a commercial (300 MHz) spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.26$). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, *m* = multiplet), coupling constants (Hz), integration. 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). All aldehydes were used after purification, EtOCOCN was commercially available and used directly without further purification. Solvents were purified by the usual methods.

Preparation of Solid (*S*)-ALB Complex using Al(O-*i*-Pr)$_3$ and *n*-BuLi

A solution of (*S*)-BINOL (143 mg, 0.5 mmol) and Al(O-*i*-Pr)$_3$ (51.1 mg, 0.25 mmol) was stirred in CH_2Cl_2 (10 mL) at 25 °C under a N_2 atmosphere for 1.0 h, *n*-BuLi (156.5 μL, 0.25 mmol, 1.6 M in hexane) was added to the solution at 25 °C. After stirring for 1.0 h, the solvent was removed under vacuum to afford a gray solid; m.p. 230 °C (dec). The solid (*S*)-ALB was stored at 25 °C without N_2 protection.

Procedure for the Catalytic Asymmetric Cyanoethoxycarbonylation of Benzaldehyde

Benzaldehyde (25 μL, 0.25 mmol) was added to a solution of solid (*S*)-ALB (0.025 mmol, 15.5 mg) and cinchonine (0.025 mmol, 7.35 mg) in CH_2Cl_2 at 25 °C. After stirring for 0.5 h, EtOCOCN (1.5 equivs.) was added at −20 °C and the contents were stirred at −20 °C for the time indicated in the Tables. The mixture was purified by silica gel column chromatography (petroleum ether/diethyl ether, 10:1, *v*/*v*) to afford the 2-ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile (**4a**); yield 99%; colorless oil; $[\alpha]_D^{25}$: −17.9 (*c* 2.0 in $CHCl_3$) (90% *ee*); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane = 1/99, flow 1.0 mL min^{-1}, detection at 254 nm): t_R 9.42 min and 10.71 min; Lit.[4a] $[\alpha]_D^{21.7}$: +16.2 (*c* 2.8, $CHCl_3$) for *R* enantiomer in 94% *ee*; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (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).

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