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Asymmetric aldol reaction of 2-cyanopropionates catalyzed by a trans-chelating chiral diphosphine–rhodium(I) complex: highly enantioselective construction of quaternary chiral carbon centers at α-positions of nitriles

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Abstract

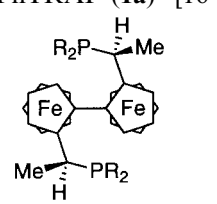
The aldol reaction of 2-cyanopropionates with aldehydes proceeded under neutral conditions in the presence of a catalytic amount of the rhodium complex generated in situ from $Rh(acac)(CO)_2$ and triphenylphosphine, to give the corresponding β-hydroxy-α-cyanocarboxylates bearing a quaternary chiral carbon center at the α-position of the cyano group. A high degree of asymmetric induction for the aldol reaction was achieved by use of trans-chelating chiral diphosphine ligands, (*R*,*R*)-2,2″-bis[(*S*)-1-(diarylphosphino)ethyl]-1,1″-biferrocenes (TRAPs). The asymmetric aldol reactions gave optically active β-hydroxy-α-cyanocarboxylates with up to 94% ee.

Keywords: Aldol reaction; Rhodium complex; Trans-chelating chiral ligand; Catalytic asymmetric synthesis

1. Introduction

Development of methodologies for enantioselective carbon–carbon bond formation is desired in organic synthesis [1]. In particular, catalytic asymmetric aldol reactions provide a powerful tool for stereoselective construction of a β-hydroxy α-substituted carbonyl unit with vicinal chiral centers [2], which constitutes various biologically active natural products [3]. Many efforts have recently been made toward the development of catalytic asymmetric aldol reactions[1] [4]. However, highly enantioselective synthesis of an aldol building block bearing a quaternary chiral carbon center has met with difficulty[2].

Recently, some low-valent transition metal complexes were found to catalyze the Michael and the aldol reactions of 2-cyanocarboxylates and related compounds under neutral conditions[3] [14]. Coordination of the cyano nitrogen to the transition metal atom enabled the 2-cyanocarboxylates to generate the enolate intermediate, which reacted with electrophiles [9b,15]. In the preceding papers, we described a highly enantioselective Michael reaction of 2-cyanopropionates with vinyl ketones and acrolein catalyzed by a rhodium(I) complex bearing a trans-chelating chiral diphosphine, (*S*,*S*)-(*R*,*R*)-PhTRAP (**1a**)[4] [16–19].



(*S*,*S*)-(*R*,*R*)-TRAP (**1**)

1a: R = Ph (PhTRAP)
1b: R = 4-MeO-C_6H_4
1c: R = 4-Cl-C_6H_4
1d: R = 2-Furyl (FurTRAP)
1e: R = ^{i}Pr (*i*-PrTRAP)
1f: R = Pr (PrTRAP)

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[1] For recent successful examples of catalytic asymmetric aldol reaction using isolated metal enolate, see Ref. [5].

[2] For a review of catalytic asymmetric construction of quaternary chiral carbon centers, see Ref. [6]. For catalytic asymmetric aldol reactions constructing quaternary chiral carbon centers on enolates, see Ref. [7]. For catalytic asymmetric aldol reactions constructing quaternary chiral carbon centers on electrophiles, see Ref. [8].

[3] For ruthenium catalyst, see Ref. [9]. For rhodium catalyst, see Ref. [10]. For iridium catalyst, see Ref. [11]. For rhenium catalyst, see Ref. [12]. For palladium catalyst, see [13].

[4] (*S*,*S*)-(*R*,*R*)-TRAP = (*R*,*R*)-2,2″-Bis[(*S*)-1-(dialkylphosphino)ethyl]-1,1″-biferrocene: Ref. [16].

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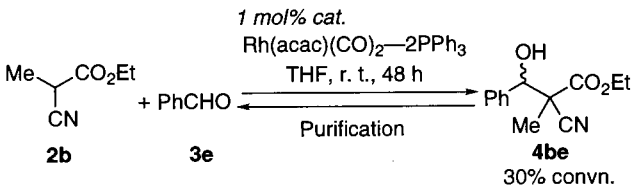
On the other hand, the catalytic aldol reaction has been limited to the Knoevenagel-type reaction giving achiral α,β-unsaturated nitriles [9,11,12] except for the aldol reaction of 2-alkoxymalononitrile catalyzed by a palladium complex [13]. Therefore, no asymmetric aldol reaction of 2-cyanocarboxylates has so far been reported.

Herein, we report a highly enantioselective aldol reaction of 2-cyanopropionates using a chiral rhodium catalyst, where TRAP (**1**) ligands are the most enantioselective[5]. The catalytic asymmetric aldol reaction produces the corresponding optically active β-hydroxy-α-cyanocarboxylates bearing a quaternary carbon center at the α-position of the cyano group with up to 94% ee [21].

2. Results and discussion

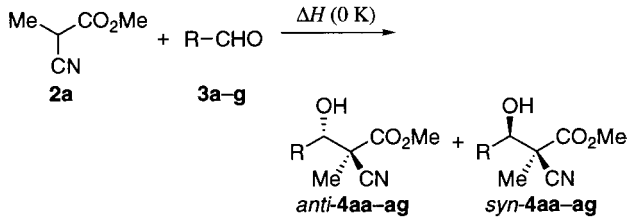
2.1. Aldol reaction of ethyl 2-cyanopropionate catalyzed by $Rh(acac)(CO)_2$–$2PPh_3$

Initially, we attempted the reaction of ethyl 2-cyanopropionate (**2b**) and benzaldehyde (**3e**) in the presence of the rhodium catalyst generated in situ from $Rh(acac)(CO)_2$ and 2 molar equivalents of triphenylphosphine (Eq. (1)).



(1)

The reaction proceeded in 30% conversion of **2b** to give the aldol product **4be** at room temperature (r.t.) for 48 h, which was detected by the ^{1}H-NMR analysis of the reaction mixture. Any techniques of purification, however, caused the retro-aldol reaction of **4be** to give the starting materials **2b** and **3e**. The result suggested to us that an aldol product made from **2b** and an aldehyde could be isolated without such decomposition if the aldol product was thermodynamically stable to the reactants. Then, we estimated theoretically the thermodynamical stabilities of the aldol products **4aa**–**ag** to the corresponding reactants, methyl 2-cyanopropionate (**2a**) and various aldehydes **3a**–**g**, by a DFT method (Eq. (2)).



(2)

Geometry optimization and computation of energy were performed at the B3LYP/6-31G(d) level[6]. The starting structures of **2a** and **3** for the geometry optimization were searched by the semiempirical AM1 method [25]. The conformations of **4** for the calculations were chosen carefully by the consideration to the σ–σ* interactions in the molecules [26], and several possible conformations were optimized and compared with each other in their potential energies. Vibrational analysis was carried out for determination of zero-point energy correction (ZPE), which was scaled with a factor of 0.9806 [27]. For discussion of energetics, enthalpy at 0 K was employed, which is the sum of the potential energy and scaled ZPE.

The calculated gaps of the enthalpies between **2** + **3** and **4** are given in Table 1. The enthalpy change of the aldol reaction of **2a** with **3e** is positive in agreement with the result of the above experiment (entry 5). As the size of substituent R of aldehyde decreases, the thermodynamics is favorable to the formation of **4** (entries 1–4). The results suggest that the aldol reaction of **2** and formaldehyde (**3a**) proceeds more favorably than those of other aldehydes, and that the aldol product can be isolated more easily than **4be**. Of note is that the formations of **4af** and **4ag** are thermodynamically preferable to the decomposition into the starting materials despite the bulkiness of **3f** and **3g**. The results may be caused by the instability of these aldehydes. Geometry optimization starting from the aldolate of **4aa** gives the two molecules, enolate of **2a** and **3a**, with no energy barrier, indicating that **4** will decompose into **2** and **3** under basic conditions.

On the above theoretical study, we examined the aldol reactions of **2b** with **3a** using a catalytic amount (1 mol%) of various rhodium complexes (Eq. (3), Table 2).

Table 1
Gaps of enthalpies (at 0 K) between **2a** + **3** and **4** (kcal mol^{-1})

Entry	R (**3**)	Product (**4**)	Δ*H* (*anti*)	Δ*H* (*syn*)
1	H (**3a**)	**4aa**	−8.68	
2	Me (**3b**)	**4ab**	−0.79	−1.73
3	Et (**3c**)	**4ac**	−1.22	−2.10
4	^{i}Pr (**3d**)	**4ad**	+1.87	+1.09
5	Ph (**3e**)	**4ae**	+4.85	+4.31
6	MeO_2C (**3f**)	**4af**	−7.13	−8.21
7	CF_3 (**3g**)	**4ag**	−9.21	−8.56

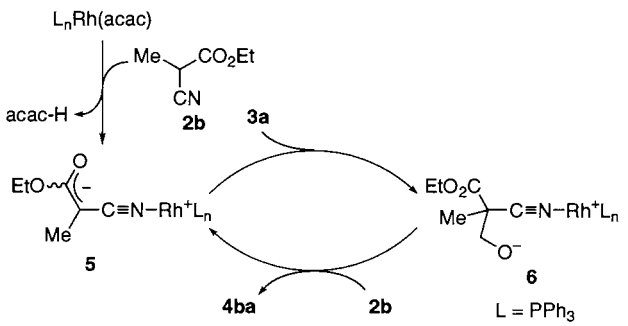
[5] Preliminary communication: Ref. [20].

[6] Hybrid functional B3LYP: Ref. [22]. 6-31G(d) basis set: Ref. [23]. These DFT calculations were performed with the GAUSSIAN 98 program by CRAY Origin 2000 in the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University: Ref. [24].

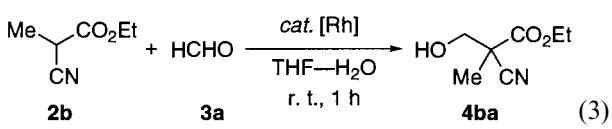
Table 2
Catalytic aldol reaction of **2b** with **3a** [a]

Entry	Catalyst	Yield (**4ba**) (%) [b]
1	$Rh(acac)(CO)_2$–$2PPh_3$	97
2	$RhH(PPh_3)_4$	97
3	$RhH(CO)(PPh_3)_3$	49
4	$Rh(acac)(CO)_2$–dppf [c]	79
5	$Rh(acac)(CO)_2$	18
6 [d]	$Rh(acac)(CO)_2$–$2PPh_3$	94
7 [e]	$Rh(acac)(CO)_2$–$2PPh_3$	41
8	$RhCl(CO)(PPh_3)_2$	9

[a] The reactions were carried out in THF (0.5 M) at r.t. 1 h unless otherwise noted. **2b**:**3a**:catalyst = 100:133:1. An aqueous solution of paraformaldehyde (10% wt) was used as a source of **3a**.
[b] Isolated yield by MPLC.
[c] dppf = 1,1′-bis(diphenylphosphino)ferrocene.
[d] Formalin (37% wt) was used instead of paraformaldehyde.
[e] Paraformaldehyde was used directly without dissolution in water.



Scheme 1.

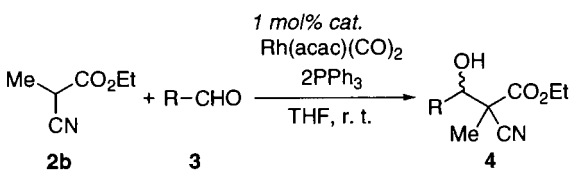


(3)

The reactions were carried out in THF at r.t. for 1 h. An aqueous solution of paraformaldehyde (10% wt) was used as a source of **3a**. The aldol reaction was completed within 1 h by the rhodium(I) complex generated in situ from $Rh(acac)(CO)_2$ and triphenylphosphine (entry 1). Any by-products and **2b** were not detected in the ^{1}H-NMR spectra of the evaporated reaction mixture and the crude product after extraction. The aldol **4ba** was isolated without decomposition in 97% yield by medium-pressure liquid chromatography on silica gel. $RhH(PPh_3)_4$ and $RhH(CO)(PPh_3)_3$ also promoted the aldol reaction, but the latter catalyst [10] presented lower catalytic activity (entries 2 and 3). Bidentate diphosphines were possible to use as a ligand on the rhodium catalyst (entry 4). Some phosphine ligand was indispensable to the catalytic reaction (entry 5). Commercially available formalin (37%) and paraformaldehyde itself, which are convenient sources of formaldehyde, were usable for the catalytic aldol reaction (entries 6 and 7). The latter reaction proceeded much slower because of the insolubility of paraformaldehyde to THF.

The anionic ligand on the rhodium atom plays a crucial role in the catalytic aldol reaction. $RhCl(CO)(PPh_3)_2$ gave **4ba** in only 9% yield (entry 8). The acetylacetonate and hydride ligands probably deprotonate from the α-carbon of **2b** to give a zwitter ionic rhodium–enolate complex **5**, where the cyano nitrogen of the enolate coordinates to the rhodium atom (Scheme 1) [15]. The enolate ligand reacts with **3a** to form a rhodium–aldolate complex **6**. The aldolate ligand deprotonates another **2b**, giving **4ba** and **5**.

The aldol reactions of ethyl 2-cyanopropionate (**2b**) with other aldehydes **3b**–**g** were examined in the presence of $Rh(acac)(CO)_2$–$2PPh_3$ catalyst (Eq. (4), Table 3).



(4)

The reactions of **2b** with **3b** and **3c** proceeded slowly to produce **4bb** and **4bc** in good yields, but the stereochemistries between 2- and 3-positions were not controlled at all (entries 1 and 2). A larger aldehyde **3d** did

Table 3
Aldol reaction of **2b** and **3** catalyzed by $Rh(acac)(CO)_2$–$2PPh_3$ catalyst [a]

Entry	R (**3**)	Time (h)	Products (**4**)	*anti*/*syn* [b]	Yield (%) [c]
1	Me (**3b**)	48	**4bb**	52/48	74
2	Et (**3c**)	72	**4bc**	53/47	51
3	^{i}Pr (**3d**)	No reaction			
4	EtO_2C (**3f**) [d]	1	**4bf**	46/53	99
5	CF_3 (**3g**) [e]	35	**4bg**	57/43	75

[a] All reactions were carried out in THF (0.5 M) at r.t. **2b**:**3**:$Rh(acac)(CO)_2$:PPh_3 = 100:150:1:2.
[b] Determined by ^{1}H-NMR analysis of the crude product.
[c] Total yield of *anti* and *syn* isomers.
[d] Commercially available polymeric **3f** (toluene solution) was used.
[e] Commercially available hydrate of **3g** was used.

Table 4
Asymmetric aldol reaction of **2** with **3a** [a]

Entry	X (**2**)	Ligand [b]	Solvent	Temperature (°C)	Time (h)	Product (**4**)	Yield (%) [c]	ee (%)
1	OEt (**2b**)	**1a**	THF	0	1.5	**4ba**	72	47 [d]
2	OEt (**2b**)	**1a**	Toluene	0	4	**4ba**	58	1 [d]
3	OEt (**2b**)	**1a**	CH_2Cl_2	0	19	**4ba**	90	11 [d]
4	OEt (**2b**)	**1a**	MeOH	0	3	**4ba**	76	1 [d]
5	OEt (**2b**)	**1a**	Et_2O	0	3	**4ba**	87	54 [d]
6	OEt (**2b**)	**1a**	Bu_2O	0	3	**4ba**	84	60 [d]
7	OEt (**2b**)	**1a**	$^iPr_2O$	0	3	**4ba**	87	1 [d]
8	OMe (**2a**)	**1a**	Bu_2O	−30	100	**4aa**	67	35 [e]
9	OEt (**2b**)	**1a**	Bu_2O	−30	42	**4ba**	85	74 [d]
10	O^{i}Pr (**2c**)	**1a**	Bu_2O	−30	90	**4ca**	86	78 [d]
11	O^{t}Bu (**2d**)	**1a**	Bu_2O	−30	70	**4da**	80	82 [d]
12	OCH^{i}Pr$_2$ (**2e**)	**1a**	Bu_2O	−10	24	**4ea**	82	91 [f]
13	OCH^{t}Bu$_2$ (**2f**)	**1a**	Bu_2O	−10	24	**4fa**	86	93 [g]
14	OCHPh$_2$ (**2g**)	**1a**	Bu_2O	−10	24	**4ga**	96	87 [h]
15 [i]	N(OMe)Me (**2h**)	**1a**	Bu_2O	0	5	**4ha**	80	61 [h]
16	OCH^{i}Pr$_2$ (**2e**)	**1b**	Bu_2O	−10	24	**4ea**	87	92 [f]
17	OCH^{i}Pr$_2$ (**2e**)	**1b**	Bu_2O	−30	24	**4ea**	47	94 [f]
18	OCH^{i}Pr$_2$ (**2e**)	**1c**	Bu_2O	−10	24	**4ea**	44	74 [f]
19	OCH^{i}Pr$_2$ (**2e**)	**1d**	Bu_2O	−10	24	**4ea**	54	70 [f]
20	OCH^{i}Pr$_2$ (**2e**)	**1e**	Bu_2O	−10	24	**4ea**	58	3 [f]
21	OCH^{i}Pr$_2$ (**2e**)	**1f**	Bu_2O	−10	24	**4ea**	86	22 [f]
22	OCH^{i}Pr$_2$ (**2e**)	BINAP [i]	Bu_2O	−10	45	**4ea**	48	12 [f]
23 [j]	OCH^{i}Pr$_2$ (**2e**)	**1a**	Bu_2O	−10	24	**4ea**	84	93 [f]

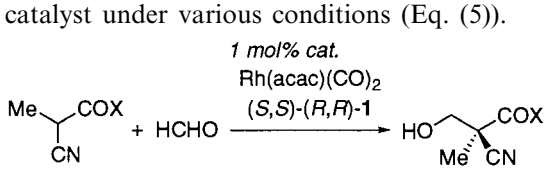
[a] **2** (0.25 M):**3a**:Rh(acac)$(CO)_2$:**1** = 100:133:1.0:1.1.
[b] (*S*,*S*)-(*R*,*R*)-**1** was used.
[c] Isolated yield.
[d] Determined by HPLC analysis with CHIRALCEL OD-H.
[e] Determined by HPLC analysis with CHIRALCEL OJ.
[f] Determined by HPLC analysis with CHIRALCEL AD.
[g] Determined by HPLC analysis with CHIRALCEL AS.
[h] Determined by HPLC analysis of its *N*-(3,5-dintrophenyl)carbamate derivative with SUMICHIRAL OA-4500.
[i] The reaction was carried out in 1.0 M. (*R*)-BINAP was used.
[j] Formalin (37% wt) was used.

not react with **2b** at all (entry 3). The aldol products **4bf** and **4bg** were obtained in good yields without their decomposition by retro-aldol reaction (entries 4 and 5).

2.2. Catalytic asymmetric aldol reaction of 2-cyanopropionates with formaldehyde

Next, we developed the asymmetric aldol reaction of 2-cyanopropionates (**2**) with aldehydes by use of optically active phosphine ligands instead of triphenylphosphine. Trans-chelating chiral ligands TRAP (**1**) were chosen in this study, because the chiral diphosphines were the most effective in related asymmetric reactions of **2** to the best of our knowledge [17,19].

Table 4 summarized the results of the asymmetric aldol reactions of **2** with formaldehyde (**3a**) using 1 mol% of Rh(acac)$(CO)_2$–(*S*,*S*)-(*R*,*R*)-PhTRAP (**1a**) catalyst under various conditions (Eq. (5)).



(5)

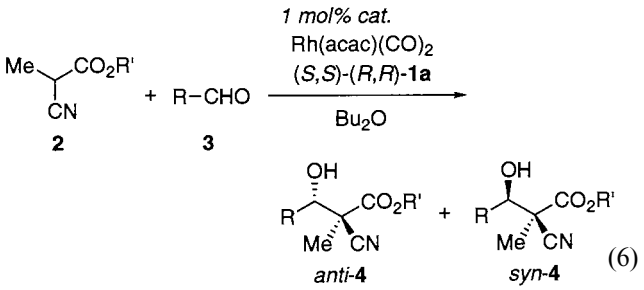
The enantiomeric excess of **4** was heavily dependent upon the reaction solvent (entries 1–7). Only ethereal solvents, such as THF and Et_2O, produced successful asymmetric induction for the asymmetric aldol reaction. In particular, Bu_2O was the most effective for the asymmetric aldol reaction of **2** using Rh(acac)$(CO)_2$–**1a** catalyst (entry 6). Coordination of an oxygen lone pair of the ethereal solvent to the rhodium atom is, perhaps, important for the enantioface-selection of the enolate of **2**. The reaction carried out in $^iPr_2O$ gave the nearly racemic product, because the large isopropyl groups of the solvent molecule might shield the oxygen lone pairs from the coordination to the rhodium atom (entry 7).

The size of the ester substituent of **2** was crucial for the enantioselectivity of the asymmetric aldol reaction (entries 8–14). Methyl ester **2a** gave **4aa** with only 35% ee. As the ester substituent of **2** was large, enantiomeric excess of **4** was increased. 2-Cyanopropionates **2e** and **2f** bearing a bulky secondary alkyl ester group gave aldol adducts **4ea** and **4fa** with high enantiomeric excesses, which have a quaternary chiral carbon center at the α-position of the cyano group. Such large secondary alkyl groups were more effective than the *tert*-butyl group. Diphenylmethyl ester **2g**, which is easily hydrolyzed with hydrogen or acid [28], also gave **4ga** with high enantiomeric excess (entry 14). *N*-Methoxy-*N*-methylamide **2h**, which is synthetically convertible to aldehyde or ketone [29], provided **4ha** with 61% ee (entry 15).

The enantioselectivity and the rate of the aldol reaction of **2e** were slightly improved by electron-donating ligand **1b** (entry 16), while the electron-withdrawing group on the *P*-aromatic substituents of **1c** caused lower enantioselectivity and catalytic activity (entry 18). The aldol reaction using **1b** proceeded at −30°C to yield **4ea** with 94% ee (entry 17). FurTRAP (**1d**), which has smaller 2-furyl groups on the phosphorus atoms, was less effective than **1a** (entry 19). Probably, the *P*-aromatic substituents of **1** play an important role in the enantioface selection of the enolate of **2** coordinating to the rhodium atom, because ligands **1e** and **1f** bearing *P*-aliphatic substituents presented low enantioselectivities (entries 20 and 21). On the other hand, cis-chelating chiral diphosphine ligands failed to give **4ea** with high enantiomeric excess, indicating that the trans-chelating property of **1** is a crucial factor of a high degree of the asymmetric induction (entry 22). To our surprise, commercially available formalin (37% wt in water) gave **4ea** without loss of the enantioselectivity (93% ee) in high yield, although the selectivity was heavily affected by the reaction solvent (entry 24).

2.3. Catalytic asymmetric aldol reaction of 2-cyanopropionates with other aldehydes

Other aldehydes **3b**–**f** were subjected to the asymmetric aldol reaction with (*S*,*S*)-(*R*,*R*)-TRAP–rhodium catalyst (Eq. (6), Table 5).



(6)

Table 5
Asymmetric aldol reaction of **2** with **3** [a]

Entry	2	3	Time (h)	Product (4)	Yield (%) [b]	*anti*/*syn* [c]	ee (*anti*) (%)	ee (*syn*) (%)
1	**2b**	**3b**	24	**4bb**	63	45/55	31 [d]	23 [d]
2	**2c**	**3b**	24	**4cb**	61	47/53	55 [e]	50 [e]
3	**2e**	**3b**	24	**4eb**	67	81/19	86 (2*S*,3*S*) [f]	33 [f]
4 [g]	**2e**	**3b**	24	**4eb**	80	77/23	78 (2*S*,3*S*) [f]	28 [f]
5 [h]	**2e**	**3b**	72	**4eb**	80	84/16	78 (2*S*,3*S*) [f]	43 [f]
6 [i]	**2e**	**3c**	48	**4ec**	76	75/25	57 (2*S*,3*S*) [j]	10 [j]
7	**2e**	**3e**	72	No reaction				
8 [k]	**2e**	**3f**	88	**4ef**	88	68/32	91 (2*S*,3*R*) [l]	63 (2*S*,3*S*) [l]

[a] All reactions were carried out in Bu_2O (0.25 M). **2**:**3**:Rh(acac)$(CO)_2$:(*S*,*S*)-(*R*,*R*)-**1a** = 100:750:1.0:1.1.
[b] Combined yield of *anti*- and *syn*-**4**.
[c] Determined by ^{1}H-NMR analysis of the crude product.
[d] Determined by HPLC analysis with CHIRALCEL AS.
[e] Determined by HPLC analysis of its *N*-(3,5-dintrophenyl)carbamate derivative with SUMICHIRAL OA-4100.
[f] Determined by HPLC analysis of its *N*-(3,5-dintrophenyl)carbamate derivative with SUMICHIRAL OA-4000.
[g] The reaction was carried out in Bu_2O–H_2O (10:1).
[h] (*S*,*S*)-(*R*,*R*)-**1b** was used.
[i] Ten equivalents of **3c** was used.
[j] Determined by HPLC analysis of its *N*-(3,5-dintrophenyl)carbamate derivative with SUMICHIRAL OA-4500.
[k] Two equivalents of **3f** was used.
[l] Determined by HPLC analysis of its *N*-(3,5-dintrophenyl)carbamate derivative with SUMICHIRAL OA-4400.

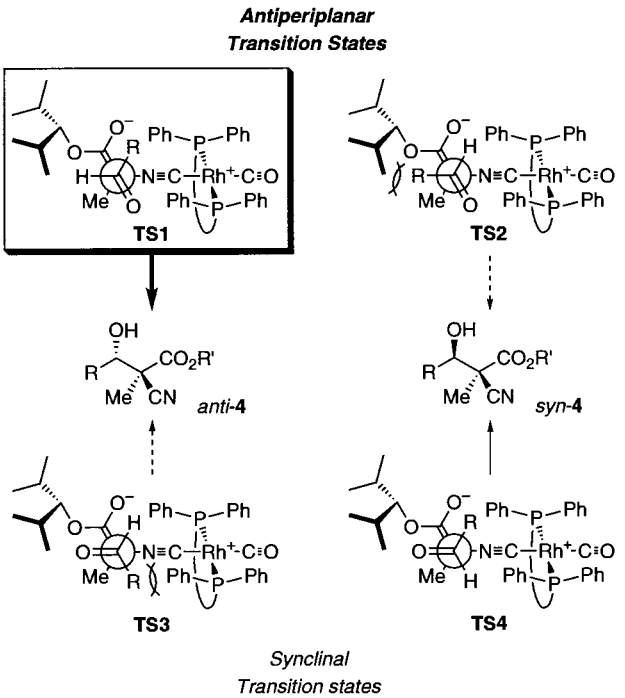


Fig. 1. Possible structures for the transition state of the aldol reaction of **2** with **3** using the **1a**–rhodium catalyst.

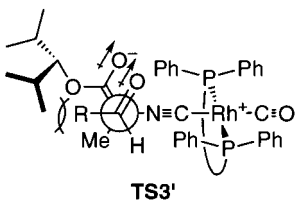


Fig. 2. Synclinal transition state **TS3′**.

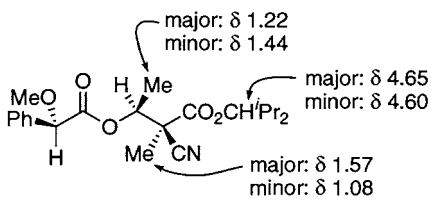


Fig. 3. The results of the ^{1}H-NMR analysis of **7**.

The ester substituent of **2** influenced heavily not only the enantioselectivity but also the ratio of *anti*- to *syn*-isomer. The aldol reactions of ethyl ester **2b** and isopropyl ester **2c** with **3b** resulted in low enantioselectivities and gave a mixture of both diastereomers in ca. 1:1 (entries 1 and 2). The use of large diisopropylmethyl ester **2e** improved remarkably the selectivities, giving *anti*-(2*S*,3*S*)-**4eb** with 86% ee in good *anti*-selectivity (*anti*:*syn* = 81:19) (entry 3). The enantioface selection of **3b** is controlled by the chiral ligand **1a** as well as the ester substituent, because a 1:1 mixture of *anti*- and *syn*-**4eb** was obtained from the aldol reaction of **2e** and **3b** using Rh(acac)$(CO)_2$–$2PPh_3$ catalyst. Addition of water reduced the diastereo- and enantioselectivities slightly (entry 4). Ligand **1b** improved the diastereoselectivity, but lowered the enantiomeric excess of *anti*-**4eb** (entry 5). The aldol reaction of **2e** with **3c** proceeded, but with lower stereoselectivity (entry 6). Benzaldehyde (**3e**) did not react at all because of the steric hindrance of TRAP ligand (entry 7). Ethyl glyoxylate (**3f**) reacted smoothly with **2e** giving a mixture of 91% ee of *anti*-(2*S*,3*R*)-**4ef** and 63% ee of *syn*-(2*S*,3*S*)-**4ef** in a ratio of 68:32 (entry 8).

2.4. Stereocontrol in the catalytic asymmetric aldol reaction

The observed stereochemistry at the 2-position of the aldol products **4** suggests that (*S*,*S*)-(*R*,*R*)-**1a** on the rhodium complex differentiates the steric bulkiness between the α-methyl and alkoxycarbonyl group of **2**, one of the *P*-phenyl substituents blocking the approach of an aldehyde to the *si*-face of the enolate coordinating to the rhodium atom [17b].

The preferential formation of *anti*-**4** in the aldol reactions of **2e** with **3** may suggest that this reaction proceeded through the antiperiplanar transition state **TS1** (Fig. 1). Compared with **TS2** giving *syn*-**4**, **TS1** avoids the steric repulsion between the aldehyde substituent (R) and the bulky CH^iPr_2 ester. The synclinal transition state **TS3** giving an *anti*-aldol may be less favorable than **TS4** due to the steric interaction between R and one of the *P*-phenyl groups of **1a**. Another type of synclinal transition states such as **TS3′**, in which the carbon–oxygen double bond of **3** lies in parallel with the carbon–anionic oxygen bond of **2**, are energetically disfavored on the basis of not only steric factor but also electrostatic considerations (Fig. 2).

The low diastereoselectivities in the reactions of **2b** and **2c** may be due to the lesser steric repulsion between the R and ester group, which results in the low diastereoselectivities. The aldol reaction with **3f** is anticipated to be affected by the electrostatic repulsion between the ethoxycarbonyl group of **3f** and the oxo anion in the zwitter ionic (enolato)rhodium, which may cause the deterioration of the diastereoselectivity.

2.5. Assignment of the absolute configurations of the aldol products

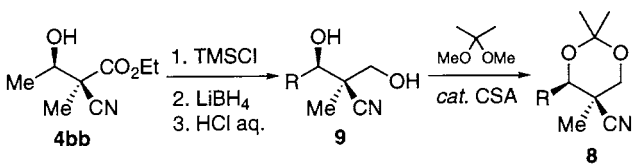
The absolute configuration of **4eb** was deduced by NMR techniques as follows. First, the absolute configuration on the 3-carbon atom of the major diastereomer of **4eb** obtained from the present asymmetric aldol reaction was assigned by the ^{1}H-NMR analysis of its (*R*)-*O*-methylmandelate **7**. Representative chemical shifts of the major and minor diastereomers of **7** are

shown in Fig. 3. Proton resonances belonging to the higher priority group of the major diastereomer of **4eb** appear in a lower magnetic field than those of the minor isomer, indicating the absolute configuration at the 3-position to be *S* according to the procedure proposed by Trost [30].

The relative configuration of **4eb** between the 2- and 3-positions was assigned by the $^1H\{^1H\}$-NOE experiment of acetonide **8**, which was prepared from a diastereomer of racemic **4bb** (Scheme 2). The diastereomer was separable from another isomer by medium-pressure liquid chromatography. After the protection of the hydroxyl group of **4bb** with trimethylsilyl group, the ethoxycarbonyl group was reduced successfully by lithium borohydride to give 1,3-diol **9** resulting from the treatment of the reaction mixture with acid. The trimethylsilyl protection was needed to prevent the retro-aldol reaction of **4bb**. The reaction of **9** with 2,2-dimethoxypropane in the presence of camphor sulfonic acid catalyst gave acetonide **8**. The result of the NOE experiments of **8** is shown in Fig. 4, indicating that the relative configuration of the starting **4bb** is *syn*. On the other hand, the diastereomeric mixture of **4eb** obtained from the asymmetric aldol reaction was converted into **9**. The ^1H-NMR analysis of the diastereomeric mixture indicates that the major diastereomer of **4eb** formed in the asymmetric aldol reaction using TRAP ligand has *anti*-(2*S*,3*S*) configuration. The absolute configurations of **4ec** and **4ef** were assigned in a similar manner.

3. Conclusions

The aldol reaction of 2-cyanopropionates (**2**) with aldehydes was promoted under neutral conditions by a catalytic amount of the rhodium complex generated from $Rh(acac)(CO)_2$ and triphenylphosphine. Successful isolation of the aldol products **4** depended on the thermodynamical stability of **4** to the reactants **2** + **3**.



Scheme 2.

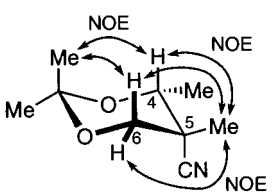


Fig. 4. The results of the $^1H\{^1H\}$-NOE experiments of **8**.

Moreover, we succeeded in a highly enantioselective catalytic aldol reaction of **2** with formaldehyde by use of a trans-chelating chiral diphosphine ligand, (*S*,*S*)-(*R*,*R*)-PhTRAP (**1a**) or **1b**. The catalytic asymmetric aldol reaction produced quaternary chiral carbon centers at the α-position of the cyano group with high enantiomeric excesses (up to 94% ee). The size of the ester substituent of **2** is essential for the high enantioselectivity. Aldehydes **3b** and **3f** gave preferentially *anti*-aldol products (2*S*,3*S*)-**4eb** and (2*S*,3*R*)-**4ef** with high enantiomeric excesses. Enantiofaces of aldehydes **3** reacting with the nucleophile is controlled by both the chiral ligand and ester substituent.

4. Experimental

4.1. General

Optical rotations were measured with a Perkin–Elmer 243 polarimeter. NMR spectra were obtained with a Varian Gemini-2000 spectrometer and a Varian VXR-200 spectrometer equipped with 7.0 T and 4.0 T magnets, respectively. Preparative medium-pressure liquid chromatographies were performed with a C.I.G. pre-packed column CPS-223L-1 (Kusano). Flash column chromatographies were performed with silica gel 60 (230–400 mesh, Merck).

4.2. Materials

Tetrahydrofuran (THF), dibutyl ether (Bu_2O), and toluene were distilled from sodium-benzophenone ketyl under nitrogen atmosphere. Dichloromethane was distilled from CaH_2. **2b** and **3b**–**e** were commercially available and purified with distillation before use. $Rh(acac)(CO)_2$ was commercially available and purified with sublimation before use. **2a**, **2c**–**g** [17b], and **3f** [31] used in the asymmetric aldol reaction were prepared according to literature procedures.

4.3. 2-Cyano-N-methoxy-N-methylpropionamide (2h)

A solution of trimethylaluminum (7.2 g, 100 mmol) in toluene (50 ml) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (9.77 g, 100 mmol) in toluene (50 ml) at 0°C for 30 min. The mixture was stirred at r.t. for 1 h. The resulting solution was added dropwise to a solution of **2b** (6.37 g, 50 mmol) in THF (50 ml) at 0°C for 20 min. After stirring at r.t. for 16 h, the mixture was diluted carefully with 5% HCl (aq.), and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with distillation, giving 4.25 g (60%) of **2h**: Colorless oil; bp 125°C/18 mmHg; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.54 (d,

$J = 7.3$ Hz, 3H), 3.25 (s, 3H), 3.83 (s, 3H), 3.86 (q, $J = 7.3$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 14.4, 28.5, 32.6, 61.5, 118.2, 166.4.

4.4. Catalytic aldol reaction of **2b** with **3a** [ethyl 2-cyano-3-hydroxy-2-methylpropionate (**4ba**)]

A suspension of paraformaldehyde (100 mg) in distilled water (1.0 ml) was stirred under reflux for 1 h, giving a clear solution of paraformaldehyde. A solution of $Rh(acac)(CO)_2$ (2.6 mg, 10 μmol) and PPh_3 (5.2 mg, 20 μmol) in THF (2.0 ml) was stirred at r.t. After 10 min, **2b** (127 mg, 1.0 mmol) and the solution of paraformaldehyde in water prepared freshly (0.4 ml, 1.3 mmol) were added to the solution. The mixture was stirred at r.t. for 1 h. The mixture was diluted with brine, and extracted with EtOAc. The organic phase was dried over Na_2SO_4, and evaporated. The residue was purified with medium-pressure liquid chromatography (EtOAc/hexane = 1/1), after passing through a short column of silica gel (EtOAc), giving 152 mg (97%) of **4ba**: Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.35 (t, $J = 7.1$ Hz, 3H), 1.59 (s, 3H), 2.56 (t, $J = 7.1$ Hz, 1H), 3.87 (dd, $J = 7.1$, 11.1 Hz, 1H), 3.95 (dd, $J = 7.1$, 11.1 Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.8, 19.4, 46.1, 63.1, 66.7, 118.9, 168.5.

4.5. General procedure of catalytic aldol reaction of **2b** with **3**

A solution of $Rh(acac)(CO)_2$ (2.6 mg, 10 μmol) and PPh_3 (5.2 mg, 20 μmol) in THF (2.0 ml) was stirred at r.t.. After 10 min, **2b** (127 mg, 1.0 mmol) and **3** (1.5 mmol) were added to the solution. After stirring at r.t. until completion of the reaction, the mixture was evaporated under reduced pressure. The residue was purified with medium-pressure liquid chromatography (EtOAc/hexane), after passing through a short column of silica gel (EtOAc), giving **4**.

4.6. Ethyl 2-cyano-3-hydroxy-2-methylbutanoate (**4bb**)

Each diastereomer of **4bb** was partially separated by medium-pressure liquid chromatography.

4.6.1. anti-**4bb**

Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.35 (t, $J = 7.2$ Hz, 3H), 1.38 (d, $J = 6.3$ Hz, 3H), 1.66 (s, 3H), 2.35 (br d, 1H), 4.16 (br quintet, 1H), 4.30 (q, $J = 7.2$ Hz, 2H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.9, 18.3, 20.1, 50.9, 63.0, 71.2, 118.3, 169.1.

4.6.2. syn-**4bb**

Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.35 (t, $J = 7.1$ Hz, 3H), 1.40 (d, $J = 6.3$ Hz, 3H), 1.56 (s, 3H), 2.49 (br d, 1H), 4.12 (br quintet, 1H), 4.32 (q, $J = 7.1$ Hz, 2H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.9, 18.5, 18.9, 49.9, 63.0, 70.4, 118.4, 168.9.

4.7. Ethyl 2-cyano-3-hydroxy-2-methylpentanoate (**4bc**)

Each diastereomer of **4bc** was not separated by medium-pressure liquid chromatography at all. Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.08 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.09 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.34 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.35 (t, $J = 7.1$ Hz, 3H of a diastereomer), 1.47–1.83 (m, 2H), 1.59 (s, 3H of a diastereomer), 1.65 (s, 3H of a diastereomer), 2.42 (d, $J = 6.9$ Hz, 1H of a diastereomer), 2.52 (d, $J = 7.8$ Hz, 1H of a diastereomer), 3.74–3.90 (m, 1H), 4.22–4.37 (m, 2H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 10.3, 10.5, 13.82, 13.85, 18.9, 20.0, 25.2, 26.1, 49.7, 50.3, 62.9, 63.0, 75.7, 76.5, 118.56, 118.64, 168.9, 169.2.

4.8. Diethyl 2-cyano-3-hydroxy-2-methylsuccinate (**4bf**)

Each diastereomer of **4bf** was not separated by medium-pressure liquid chromatography at all. Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.341 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.346 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.354 (t, $J = 7.2$ Hz, 3H of a diastereomer), 1.358 (t, $J = 7.1$ Hz, 3H of a diastereomer), 1.68 (s, 3H of a diastereomer), 1.71 (s, 3H of a diastereomer), 3.43 (d, $J = 5.9$ Hz, 1H of a diastereomer), 3.52 (d, $J = 7.2$ Hz, 1H of a diastereomer), 4.23–4.46 (m, 4H), 4.52 (d, $J = 7.2$ Hz, 1H of a diastereomer), 4.56 (d, $J = 5.9$ Hz, 1H of a diastereomer); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.8, 13.88, 13.93, 19.2, 19.9, 48.0, 48.3, 63.2, 63.3, 73.0, 73.4, 117.2, 117.5, 166.8, 167.2, 170.2, 170.6.

4.9. Ethyl 2-cyano-4,4,4-trifluoro-3-hydroxy-2-methylbutanoate (**4bg**)

Each diastereomer of **4bg** was completely separated by medium-pressure liquid chromatography.

4.9.1. anti-**4bg**

Yield, 43%; colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.35 (t, $J = 7.1$ Hz, 3H), 1.79 (s, 3H), 3.82 (br s, 1H), 4.32 (dq, $J = 10.9$, 7.1 Hz, 1H), 4.34 (dq, $J = 10.9$, 7.1 Hz, 1H), 4.44 (q, $J = 6.2$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.6, 20.5, 45.3, 63.9, 72.6 (q, $J = 32$ Hz), 116.1, 123.4 (q, $J = 282$ Hz), 166.7.

4.9.2. syn-**4bg**

Yield, 32%; colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.37 (t, $J = 7.2$ Hz, 3H), 1.74 (s, 3H),

4.08 (br s, 1H), 4.35 (q, $J = 7.2$ Hz, 2H), 4.44 (q, $J = 6.7$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.6, 19.6, 46.0, 64.1, 72.7 (q, $J = 32$ Hz), 116.5, 123.5 (q, $J = 282$ Hz), 167.5.

4.10. General procedure of catalytic asymmetric aldol reaction of **2** with **3a**

A suspension of paraformaldehyde (100 mg) in distilled water (1.0 ml) was stirred under reflux for 1 h, giving a clear solution of paraformaldehyde. A solution of $Rh(acac)(CO)_2$ (1.3 mg, 5.0 mmol) and (*S*,*S*)-(*R*,*R*)-**1a** (4.3 mg, 5.4 μmol) in Bu_2O (2.0 ml) was stirred at r.t. for 10 min. After cooling to the reaction temperature, **2** (0.5 mmol) and the solution of paraformaldehyde in water prepared freshly (0.2 ml, 0.67 mmol) were added to the solution. After stirring until completion of the reaction, the mixture was diluted with brine, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified with medium-pressure liquid chromatography, after passing through a short column of silica gel, giving **4**.

4.11. Methyl 2-cyano-3-hydroxy-2-methylpropionate (**4aa**)

Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.60 (s, 3H), 2.52 (br s, 1H), 3.87 (s, 3H), 3.88 (br d, $J = 9.3$ Hz, 1H), 3.95 (br d, $J = 9.3$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 19.4, 46.0, 53.7, 66.7, 118.8, 169.0. Anal. Found: C, 50.30; H, 6.35; N, 9.63. Calc. for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79%.

4.12. Ethyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4ba**)

Colorless oil; $[\alpha]_D^{20}$ −7.11 (*c* 1.02, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.35 (t, $J = 7.1$ Hz, 3H), 1.59 (s, 3H), 2.56 (t, $J = 7.1$ Hz, 1H), 3.87 (dd, $J = 7.1$, 11.1 Hz, 1H), 3.95 (dd, $J = 7.1$, 11.1 Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 13.8, 19.4, 46.1, 63.1, 66.7, 118.9, 168.5. Anal. Found: C, 53.52; H, 6.99; N, 8.73. Calc. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91%.

4.13. 2-Propyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4ca**)

Colorless oil; $[\alpha]_D^{20}$ −7.12 (*c* 0.98, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.32 (d, $J = 6.3$ Hz, 3H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.58 (s, 3H), 2.45–2.58 (br m, 1H), 3.86 (dd, $J = 6.6$, 11.3 Hz, 1H), 3.94 (dd, $J = 7.2$, 11.3 Hz, 1H), 5.12 (septet, $J = 6.3$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 19.3, 21.38, 21.41, 46.1, 66.7, 71.3, 118.9, 168.0.

4.14. 2-Methyl-2-propyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4da**)

Colorless oil; ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.53 (s, 9H), 1.55 (s, 3H), 2.42 (br, 1H), 3.84 (d, $J = 11.1$ Hz, 1H), 3.89 (d, $J = 11.1$ Hz); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 19.4, 27.7, 46.6, 66.7, 84.6, 119.2, 167.6.

4.15. 2,4-Dimethyl-3-pentyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4ea**)

Colorless oil; $[\alpha]_D^{20}$ −5.15 (*c* 0.97, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.91 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.927 (d, $J = 6.9$ Hz, 3H), 0.932 (d, $J = 6.9$ Hz, 3H), 1.62 (s, 3H), 1.91–2.09 (m, 2H), 2.46 (br s, 1H), 3.88 (d, $J = 11.1$ Hz, 1H), 3.96 (d, $J = 11.1$ Hz, 1H), 4.68 (t, $J = 6.2$ Hz, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 16.8, 17.1, 19.4, 19.6, 29.4, 46.3, 66.7, 86.4, 118.9, 168.7. Anal. Found: C, 63.30; H, 9.29; N, 5.95. Calc. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16%.

4.16. 2,2,4,4-Tetramethyl-3-pentyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4fa**)

Colorless oil; $[\alpha]_D^{20}$ −7.68 (*c* 1.03, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.05 (s, 9H), 1.07 (s, 9H), 1.63 (s, 3H), 2.45–2.60 (br m, 1H), 3.88 (dd, $J = 11.1$, 6.6 Hz, 1H), 3.98 (dd, $J = 6.9$, 11.1 Hz, 1H), 4.69 (s, 1H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 19.6, 28.4, 28.5, 37.3, 46.4, 66.6, 89.6, 119.0, 168.3. Anal. Found: C, 65.58; H, 9.74; N, 5.44. Calc. for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49%.

4.17. Diphenylmethyl (S)-2-cyano-3-hydroxy-2-methylpropionate (**4ga**)

White solid; m.p. 77–78°C; $[\alpha]_D^{20}$ −12.2 (*c* 0.98, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.57 (s, 3H), 2.54 (br s, 1H), 3.85 (dd, $J = 3.0$, 10.8 Hz, 1H), 3.94 (dd, $J = 3.6$, 10.8 Hz, 1H), 6.91 (s, 1H), 7.27–7.41 (m, 10H); $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$): δ 19.2, 46.3, 66.6, 79.5, 118.7, 126.8, 127.0, 128.4, 128.5, 128.76, 128.79, 139.0, 167.5.

4.18. (S)-2-Cyano-3-hydroxy-N-methoxy-2,N-dimethylpropionamide (**4ha**)

Colorless oil; ^1H-NMR (200 MHz, $CDCl_3$, TMS): δ 1.58 (s, 3H), 3.08 (t, $J = 7.5$ Hz, 1H), 3.26 (s, 3H), 3.85 (dd, $J = 7.5$, 11.3 Hz, 1H), 3.88 (s, 3H), 3.99 (dd, $J = 7.5$, 11.3 Hz, 1H); $^{13}C\{^1H\}$-NMR (50 MHz, $CDCl_3$): δ 18.4, 33.0, 43.0, 61.1, 67.0, 119.8, 168.3.

4.19. Isopropyl 2-cyano-3-hydroxy-2-methylbutanoate (**4cb**)

4.19.1. anti-**4cb**

Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.322 (d, $J = 6.3$ Hz, 3H), 1.324 (d, $J = 6.3$ Hz, 3H), 1.37 (d, $J = 6.3$ Hz, 3H), 1.64 (s, 3H), 2.35 (d, $J = 6.3$ Hz, 1H), 4.15 (quintet, $J = 6.3$ Hz, 1H), 5.11 (septet, $J = 6.3$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 18.4, 18.9, 21.4, 50.0, 70.3, 71.1, 118.5, 168.4.

4.19.2. syn-**4cb**

Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.326 (d, $J = 6.3$ Hz, 3H), 1.335 (d, $J = 6.3$ Hz, 3H), 1.40 (d, $J = 6.3$ Hz, 3H), 1.55 (s, 3H), 2.45 (d, $J = 6.9$ Hz, 1H), 4.11 (dq, $J = 6.9$, 6.3 Hz, 1H), 5.13 (septet, $J = 6.3$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 18.3, 20.0, 21.4, 21.5, 50.9, 71.2, 118.4, 168.6.

4.20. 2,4-Dimethyl-3-pentyl (2S,3S)-2-cyano-3-hydroxy-2-methylbutanoate (anti-**4eb**)

Isolated as a mixture of *anti*- and *syn*-**4eb**: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.89–0.96 (m, 12H), 1.40 (d, $J = 6.3$ Hz, 3H), 1.68 (s, 3H), 1.91–2.10 (m, 2H), 2.45 (d, $J = 6.3$ Hz, 1H), 4.23 (quintet, $J = 6.3$ Hz, 1H), 4.67 (t, $J = 6.0$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 16.9, 17.1, 18.6, 18.9, 19.40, 19.44, 20.5, 29.3, 29.4, 49.9, 70.0, 86.3, 118.5, 169.2. Anal. Found: C, 64.45; H, 9.45; N, 6.09. Calc. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80%.

4.21. 2,4-Dimethyl-3-pentyl 2-cyano-3-hydroxy-2-methylpentanoate (**4ec**)

4.21.1. anti-(2S,3S)-**4ec**

Colorless oil; $[\alpha]_D^{20}$ −5.39 (*c* 1.03, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.89–0.96 (m, 12H), 1.09 (t, $J = 7.5$ Hz, 3H), 1.51–1.83 (m, 2H), 1.67 (s,3H), 1.91–2.08 (m, 2H), 2.40 (d, $J = 6.3$ Hz, 1H), 3.90 (ddd, $J = 10.5$, 6.3, 2.4 Hz, 1H), 4.67 (t, $J = 6.0$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 10.6, 17.0, 17.1, 18.8, 19.4, 19.5, 25.9, 29.39, 29.43, 49.6, 75.3, 86.3, 118.7, 169.2. Anal. Found: C, 66.09; H, 9.77; N, 5.62. Calc. for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49%.

4.21.2. syn-**4ec**

Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.88–0.96 (m, 12H), 1.10 (t, $J = 7.4$ Hz, 3H), 1.50–1.68 (m, 1H), 1.62 (s, 3H), 1.71–1.86 (m, 1H), 1.92–2.09 (m, 2H), 2.53 (d, $J = 7.8$ Hz, 1H), 3.80 (ddd, $J = 10.8$, 7.8, 2.3 Hz, 1H), 4.68 (t, $J = 6.0$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 10.4, 16.8, 17.1, 19.38, 19.43, 20.6, 25.1, 29.3, 29.4, 50.6, 76.3, 86.3, 118.7, 169.5.

4.22. 2,4-Dimethyl-3-pentyl 2-cyano-3-ethoxycarbonyl-3-hydroxy-2-methylpropionate (**4ef**)

4.22.1. anti-(2S,3R)-**4ef**

Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.89–0.99 (m, 12H), 1.36 (t, $J = 7.1$ Hz, 3H), 1.68 (s, 3H), 1.88–2.14 (m, 2H), 3.42 (d, $J = 5.5$ Hz, 1H), 4.26–4.50 (m, 2H), 4.63–4.73 (m, 2H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 14.0, 16.9, 17.1, 19.1, 19.4, 19.5, 29.4, 29.5, 47.6, 63.4, 72.4, 86.9, 117.7, 166.9, 170.7. Anal. Found: C, 59.89; H, 8.58; N, 4.40. Calc. for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68%.

4.22.2. syn-(2S,3S)-**4ef**

Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.92 (d, $J = 6.9$ Hz, 6H), 0.936 (d, $J = 6.9$ Hz, 3H), 0.939 (d, $J = 6.6$ Hz, 3H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.74 (s, 3H), 1.93–2.06 (m, 2H), 3.54 (d, $J = 7.1$ Hz, 1H), 4.28–4.44 (m, 2H), 4.47 (d, $J = 7.1$ Hz, 1H), 4.68 (t, $J = 6.0$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 14.0, 17.0, 19.35, 19.41, 20.5, 29.4, 29.5, 48.6, 63.1, 73.4, 87.0, 117.5, 167.3, 170.4.

4.23. Preparation of (R)-O-methylmandelate of **4eb** (**7**)

Oxalyl chloride (8.7 μl, 100 μmol) and a catalytic amount of DMF (1 drop) were added to a suspension of (*R*)-*O*-methylmandelic acid (10 mg, 60 μmol) in CH_2Cl_2 (0.1 ml) at 0°C. After stirring at r.t. for 30 min, the solvent and excess oxalyl chloride were removed in vacuo. A solution of **4eb** (12 mg, 50 μmol) in CH_2Cl_2 (0.2 ml) and pyridine (20 μl, 250 μmol) were added to the residue at r.t.. After stirring for 8 h, the mixture was diluted with 8.5% H_3PO_4 (aq.) and extracted with Et_2O. The organic phase was washed with 8.5% H_3PO_4 (aq.), with brine, dried over $MgSO_4$, and evaporated. The residue was purified with preparative TLC, giving **7** as a diastereomeric mixture. The ratio of the diastereomers corresponded with the enantiomeric excess of starting *anti*-**4eb**.

4.24. (2S*,3S*)-2-Cyano-2-methyl-1,3-butanediol (*syn*-**9**)

Trimethylsilylchloride (282 mg, 2.6 mmol) and pyridine (256 mg, 3.2 mmol) were added to a solution of *syn*-**4bb** (214 mg, 1.25 mmol) in THF (2.5 ml). The mixture was stirred at r.t. for 2.5 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. Lithium borohydride (39 mg, 1.79 mmol) was added to a solution of the residue (270 mg) in Et_2O (1.0 ml) and toluene (2.0 ml). The mixture was stirred at r.t. for 12 h, diluted with 10% HCl (aq.), and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and

evaporated. The residue was purified with flash column chromatography, giving 56 mg (35%) of *syn*-**9**: ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 1.24 (s, 3H), 1.37 (d, $J = 6.3$ Hz, 3H), 3.00–3.70 (br, 2H), 3.73–3.96 (m, 3H).

4.24.1. (4S*, 5S*)-5-Cyano-2,2,4,5-tetramethyl-1,3-dioxane (**8**)

2,2-Dimethoxypropane (85 mg, 0.81 mmol) was added to a solution of *syn*-**9** (40 mg, 0.31 mmol) and D-10-camphorsulfonic acid (3.9 mg, 17 μmol) in CH_2Cl_2 (0.6 ml). The mixture was stirred at r.t. for 16 h, diluted with saturated Na_2CO_3 (aq.), and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified with flash column chromatography, giving 23 mg (43%) of **8**: ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 1.19 (s, 3H), 1.35 (d, $J = 6.0$ Hz, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 3.67 (d, $J = 11.7$ Hz, 1H), 3.74 (q, $J = 6.0$ Hz, 1H), 3.92 (d, $J = 11.7$ Hz, 1H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 17.0, 17.7, 18.5, 29.2, 38.5, 67.1, 71.0, 99.4, 120.9.

4.25. Preparation of **9** from **4eb**

Trimethylsilylchloride (51 mg, 0.473 mmol) and pyridine (68 mg, 0.87 mmol) were added to a solution of a diastereomeric mixture of **4eb** (32.9 mg, 0.14 mmol) in THF (0.25 ml). The mixture was stirred at r.t. for 18 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. Lithium borohydride (10 mg, 0.46 mmol) was added to a solution of the residue (26.1 mg) in Et_2O (0.5 ml). The mixture was stirred at r.t. for 48 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. A solution (1.0 M) of TBAF in THF (0.10 ml, 0.10 mmol) was added to a solution of the residue (8.8 mg) prepared above in THF (0.1 ml). The mixture was stirred at r.t. for 1.5 h, diluted with 1 N HCl (aq.), and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified with flash column chromatography, giving 5.6 mg (31%) of a diastereomeric mixture of **9**.

4.25.1. anti-**9**

^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 1.29 (s, 3H), 1.36 (d, $J = 6.4$ Hz, 3H), 2.74 (br s, 2H), 3.73 (d, $J = 11.2$ Hz, 1H), 3.82 (d, $J = 11.2$ Hz, 1H), 4.13 (q, $J = 6.4$ Hz, 1H).

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