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Asymmetric Michael Reaction of α-Cyano Carboxylates Catalyzed by a Rhodium Complex with Trans-Chelating Chiral Diphosphine PhTRAP

Masaya Sawamura, Hitoshi Hamashima, and Yoshihiko Ito*

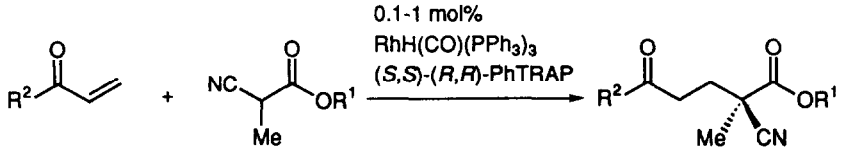
Department of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering,
Kyoto University, Kyoto 606-01, Japan

Abstract: Asymmetric Michael reaction of 2-cyanopropionates with vinyl ketones or acrolein in the presence of 0.1-1 mol% of a rhodium catalyst prepared in situ from $RhH(CO)(PPh_3)_3$ and a trans-chelating chiral diphosphine ligand (*S,S*)-(*R,R*)-PhTRAP in benzene at 3-5 °C gave optically active Michael adducts with high enantiomeric excesses (83-93% ee) in high yields. The reaction of 2-cyanopropionate with methacrolein and crotonaldehyde proceeded somewhat slowly, giving diastereomer mixtures in moderate enantioselectivities but in low diastereoselectivities. The reaction of 2-cyanobutyrate and 2-cyano-3-methylbutyrate with acrolein gave corresponding Michael adducts with much lower enantiomeric excesses than that of 2-cyanopropionates. The Michael addition product from acrolein was converted into an optically active α-methyl-α-amino acid.

The nucleophilic addition of enolates or their analogues to the carbon-carbon double bond of α,β-unsaturated ketones, aldehydes, nitriles, or carboxylic acid derivatives, so called the Michael reaction, is a fundamental but useful carbon-carbon bond forming reaction. For the last decade, there have been great advances for the asymmetric Michael reactions employing stoichiometric amounts of chiral auxiliary, which include the reaction of enamines or imines with chiral amine components,[1,2] and chiral carboxylic acid derivatives as Michael donors[3] as well as chiral Michael acceptors.[4] However, catalytic asymmetric Michael reactions have been remaining to be challenged,[5] even though there have been reported several examples which are successful to some extent. Thus, moderate to high enantioselectivities have been achieved for the asymmetric Michael reaction catalyzed by Co(II),[6] Ni(II),[6c,7] Cu(II),[8] and Sn(II)[9] complexes with chiral amine ligands, alkaloid catalysts such as quinine,[10] and an amino acid salt catalyst.[11] Chiral crown ether-KO^{t}Bu complexes also catalyze Michael reaction in high enantioselectivity[12] but with moderate catalyst-turnover number.

It has recently been reported that the Michael reaction of nitriles activated by an additional electron withdrawing group is effectively catalyzed by low valent transition metal complexes such as $RuH_2(PPh_3)_4$ and $RhH(CO)(PPh_3)_3$ (Scheme 1).[13] The presence of cyano group is indispensable for the reaction, indicating that the Michael donor could be activated through the coordination of cyano group to the metal. The discovery of the novel synthetic reactions prompted us to study the asymmetric Michael reaction with a new chiral diphosphine ligand, 2,2"-bis[1-(diphenylphosphino)ethyl]-1,1"-biferrocene (abbreviated to PhTRAP),[14] which was designed and synthesized to form transition metal complexes in a trans-chelating manner. And it was found that Rh(I)-PhTRAP complex catalyzes the asymmetric Michael reaction of 2-cyanopropionates with vinyl ketones or acrolein

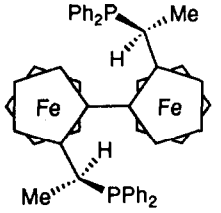
Scheme 1



2a: R^2 = Me
2b: R^2 = Et
2c: R^2 = Ph
2d: R^2 = 4-MeOPh
2e: R^2 = 2-MeOPh
2f: R^2 = 4-ClPh
2g: R^2 = H

1a: R^1 = Me
1b: R^1 = Et
1c: R^1 = *i*-Pr
1d: R^1 = *t*-Bu
1e: R^1 = $CH(i\text{-}Pr)_2$

3a-e: R^2 = Me
R^1 = Me, Et, *i*-Pr, *t*-Bu,$CH(i\text{-}Pr)_2$
4c,e: R^2 = Et, R^1 = *i*-Pr, $CH(i\text{-}Pr)_2$
5c: R^2 = Ph, R^1 = *i*-Pr
6c: R^2 = 4-MeOPh, R^1 = *i*-Pr
7c: R^2 = 2-MeOPh, R^1 = *i*-Pr
8c: R^2 = 4-ClPh, R^1 = *i*-Pr
9c,e: R^2 = H, R^1 = *i*-Pr, $CH(i\text{-}Pr)_2$



(*S,S*)-(*R,R*)-PhTRAP

in high enantioselectivities which have never been achieved with the conventional cis-chelating chiral diphosphine ligands.[15] In this article we wish to describe full accounts of the asymmetric Michael reaction of 2-cyanocarboxylates catalyzed by the Rh(I)-PhTRAP complex and its application to the synthesis of an optically active α-methyl-α-amino acid.

RESULTS AND DISCUSSION

Asymmetric Michael Reaction of 2-Cyanopropionates. Several commercially available chiral phosphine ligands and the trans-chelating ligand PhTRAP were examined in benzene at 30 °C for enantioselectivity in the rhodium-catalyzed asymmetric Michael reaction of methyl 2-cyanopropionate (**1a**) with methyl vinyl ketone (**2a**). The rhodium catalysts prepared in situ from 1 mol% of $RhH(CO)(PPh_3)_3$ and 1.1 mol% of these ligands showed almost the same catalytic activity, producing Michael adduct **3a**, which contains a quaternary asymmetric carbon center, in quantitative yields. The ligand that showed a significant level of enantioselectivity, however, was only trans-chelating ligand PhTRAP; chiral ligands employed and enantioselectivities for the reaction were as follows: (*R,R*)-CHIRAPHOS,[16] 3% ee (*S*); (*R,R*)-DIOP,[17] 10% ee (*R*); (*R*)-BINAP,[18] 9% ee (*R*); (*S,S*)-(*R,R*)-PhTRAP, 60% ee (*R*) (Table 1, entry 1). Higher selectivity for the reaction with PhTRAP was obtained at lower reaction temperature; 71% ee at 10 °C, 73% ee at 5 °C (entries 2, 3). Benzene is the solvent of choice (entries 3-9). The reaction temperature lower than 0 °C failed to improve the selectivity (entry 6). Remarkable improvement was made by employing 2-cyanopropionates (**1b-e**) with bulkier ester groups (entries 10-13). The highest enantioselectivity of 93% ee in the reaction of **1** with **2a** was attained with diisopropylmethyl ester **1e**.

Table 1. Asymmetric Michael Reaction of 2-Cyanopropionates **1** with **2** Catalyzed by the Rhodium Complex with (*S*,*S*)-(*R*,*R*)-PhTRAP (Scheme 1)[a]

	2	**1**			temp	time	product (3-9)		
entry	R^2	R^1	solvent	S/C[b]	°C	h[c]	yield, %[d]	ee, %[e]	$[\alpha]^{20}_D$[f]
1	Me (**2a**)	Me (**1a**)	C_6H_6	100	30	8[g]	92 (**3a**)	60 (*R*)	
2	Me (**2a**)	Me (**1a**)	C_6H_6	100	10	23[g]	96 (**3a**)	71 (*R*)	
3	Me (**2a**)	Me (**1a**)	C_6H_6	100	5	21[g]	99 (**3a**)	73 (*R*)	+2.6
4	Me (**2a**)	Me (**1a**)	toluene	100	5	21[g]	95 (**3a**)	73 (*R*)	
5	Me (**2a**)	Me (**1a**)	toluene	100	0	19[g]	98 (**3a**)	68 (*R*)	
6	Me (**2a**)	Me (**1a**)	toluene	100	-5	17[g]	97 (**3a**)	58 (*R*)	
7	Me (**2a**)	Me (**1a**)	mesitylene	100	5	22[g]	98 (**3a**)	68 (*R*)	
8	Me (**2a**)	Me (**1a**)	THF	100	5	27[g]	95 (**3a**)	58 (*R*)	
9	Me (**2a**)	Me (**1a**)	CH_2Cl_2	100	5	6[g]	97 (**3a**)	31 (*R*)	
10	Me (**2a**)	Et (**1b**)	C_6H_6	100	5	10[g]	95 (**3b**)	81 (*R*)	+4.0
11	Me (**2a**)	*i*-Pr (**1c**)	C_6H_6	100	3	10[g]	97 (**3c**)	86 (*R*)	+4.5
12	Me (**2a**)	*t*-Bu (**1d**)	C_6H_6	100	5	10[g]	95 (**3d**)	81 (*R*)	+2.7
13	Me (**2a**)	CH(*i*-Pr)$_2$ (**1e**)	C_6H_6	100	3	23[g]	99 (**3e**)	93 (*R*)	+0.70
14	Et (**2b**)	*i*-Pr (**1c**)	C_6H_6	100	3	10[g]	98 (**4c**)	85 (*R*)	+4.5
15	Et (**2b**)	CH(*i*-Pr)$_2$ (**1e**)	C_6H_6	100	3	52[g]	99 (**4e**)	91[i](*R*)	+1.5
16	Ph (**2c**)	*i*-Pr (**1c**)	C_6H_6	100	5	2 (1.5)	95 (**5c**)[h]	83[j] (*R*)	+6.4
17	4-MeOPh (**2d**)	*i*-Pr (**1c**)	C_6H_6	100	3	2 (1.5)	99 (**6c**)[h]	89[j] (*R*)	+5.4
18	2-MeOPh (**2e**)	*i*-Pr (**1c**)	C_6H_6	100	3	2.5 (1.5)	98 (**7c**)[h]	86[j] (*R*)	+0.79[k]
19	4-ClPh (**2f**)	*i*-Pr (**1c**)	C_6H_6	100	3	4.5 (4)	98 (**8c**)[h]	85[j] (*R*)	+6.7
20	H (**2g**)	*i*-Pr (**1c**)	C_6H_6	100	3	3.5 (2.5)	88 (**9c**)[h]	87 (*R*)	+3.1
21	H (**2g**)	CH(*i*-Pr)$_2$ (**1e**)	C_6H_6	100	3	3.5 (2.5)	88 (**9e**)[h]	92 (*R*)	0
22	H (**2g**)	*i*-Pr (**1c**)	C_6H_6	500	5	6.5 (6)	91 (**9c**)[h]	89 (*R*)	
23	H (**2g**)	*i*-Pr (**1c**)	C_6H_6	1000	3	5.5 (5)	93 (**9c**)[h]	84 (*R*)	

[a] **1**/**2** = 1/1.5. $RhH(CO)(PPh_3)_3$/PhTRAP = 1/1.1. [b] Substrate/Catalyst. [c] Reaction time including the addition time. Number in parentheses is the addition time; solution of **2** in benzene was added to a mixture of **1** and the catalyst over a given period. [d] Isolated yield by bulb-to-bulb distillation unless otherwise noted. [e] Determined by GLC analysis unless otherwise noted. [f] *c* 5.0-5.1 in $CHCl_3$ unless otherwise noted. [g] Neat **2** was added within 1 min. [h] Isolated yield by MPLC. [i] Determined by GLC analysis after transformation to the corresponding methyl ester. [j] Determined by HPLC analysis of *N*-(3,5-dinitrophenyl)amide derivatives. [k] *c* 5.08 in EtOH.

The rhodium-PhTRAP catalyst is also effective for the Michael reaction of various vinyl ketones including ethyl (**2b**), phenyl (**2c**), and other aryl ketones (**2d-f**) with electron donating or withdrawing substituents on the aromatic rings (83-91% ee, entries 14-19). Reaction rates of the aryl ketones (**2c-f**) were much faster than those of alkyl vinyl ketones. However, high selectivities were obtainable when a solution of **2c-f** was slowly added to a mixture of **1** and the catalyst in benzene.

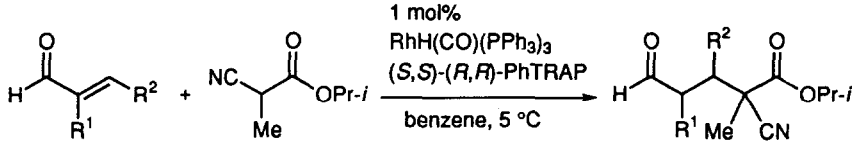
Acrolein (**2g**) is an attractive Michael acceptor for the present asymmetric Michael reaction, because some synthetic applications of the adduct **9** are feasible through the synthetic elaboration of the terminal aldehyde group by stereoselective addition of carbon nucleophiles, Wittig-type reactions, and so on. Highly enantioselective Michael reactions of acrolein with **1c,e** were achieved in the slow addition conditions using 1 mol% of the catalyst, producing the desired Michael adducts **9c,e** with high enantiomeric excesses (87% ee for **9c**, 92% ee for **9e**, entries 20, 21). Increase in the substrate/catalyst ratio up to 1000 caused only a slight decrease in enantioselectivity without a substantial decrease in the reaction rate (entries 22, 23).

Similar Michael reaction of methyl acrylate with **1c** was sluggish even at 25 °C and required about 2 weeks to complete, resulting in the formation of corresponding Michael adduct with only 11% ee (*R*). Although the reaction of acrylonitrile with **1c** completed in a reasonable reaction time (26 h), the enantioselectivity was also low (15% ee).

Some Michael acceptors bearing a substituent at the olefinic carbons as well as α-substituted α-cyanocarboxylates as Michael donors were examined for diastereoselectivity and enantioselectivity. α,β-Unsaturated ketones bearing β-substituents such as *trans*-3-penten-2-one and *trans*-4-methoxy-3-buten-2-one failed to react with **1c** even at 25 °C, whereas crotonaldehyde (**11**) reacted at 5 °C for 72 h, producing **13** as a mixture of diastereomers in a ratio of 51:49, whose enantiomeric excesses were 75% ee and 74% ee, respectively (Scheme 2). The reaction of methacrolein (**10**) with **1c** proceeded smoothly (5 °C, 8 h), affording a 1:1 mixture of diastereomers whose enantioselectivity were, however, moderate (81% ee and 78% ee, respectively).

Michael reactions of a few α-alkyl-α-cyanocarboxylates are shown in Scheme 3. The reactions of 2-cyanocarboxylates bearing α-ethyl (**14**) and α-isopropyl substituents (**15**) with **2g** proceeded as smoothly as that of **1c**, affording adducts **16** and **17** in good yields. However, the enantioselectivities were only 21% and 1%, respectively.

Scheme 2

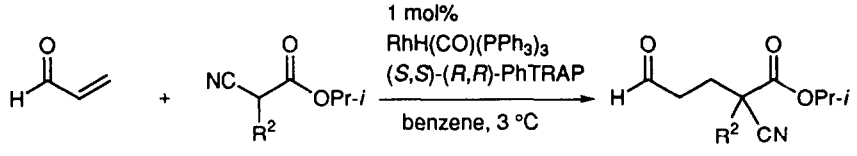


10: R^1 = Me, R^2 = H
11: R^1 = H, R^2 = Me

1c

12: R^1 = Me, R^2 = H
13: R^1 = H, R^2 = Me

Scheme 3



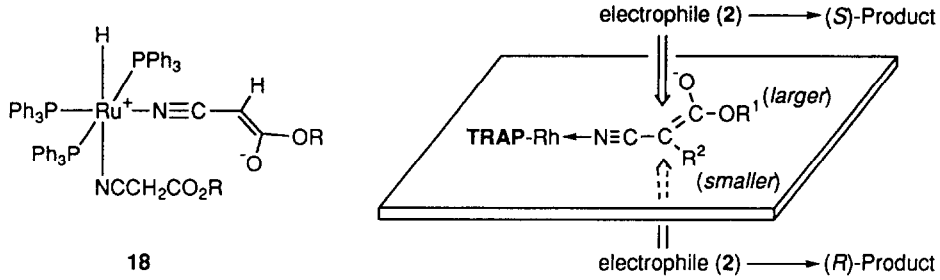
2g

14: R^2 = Et
15: R^2 = *i*-Pr

16: R^2 = Et (82%, 21 % ee)
17: R^2 = *i*-Pr (80%, 1 % ee)

Although the mechanism of the ruthenium/rhodium-catalyzed Michael reaction is not clear, Murahashi et al. proposed a mechanism involving an oxidative addition of active methylene/methine C-H bond onto a low-valent ruthenium species.[13a] This mechanism has been supported by Komiya's finding that the reaction of $Ru(C_2H_4)$

Scheme 4

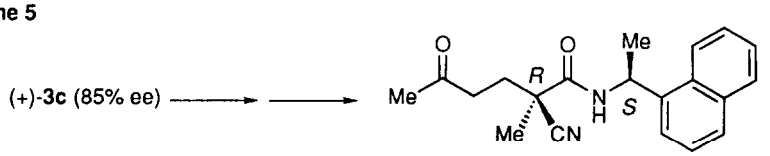


18

$(PPh_3)_3$ with cyanoacetate formed oxidative addition product *mer*-$RuH(NCCHCO_2R)(NCCH_2CO_2R)(PPh_3)_3$ (**18**).[19] The ruthenium complex **18** gave not only (*E*)-$PhCH{=}C(CN)CO_2R$ and $(NCCH_2CH_2)_2C(CN)CO_2R$ in stoichiometric reactions with benzaldehyde and acrylonitrile respectively, but also catalyzed the aldol and Michael reactions with cyanoacetate. Interestingly, X-ray crystal structure of **18** (R = Me) reveals that the activated cyanoacetate ($NCCHCO_2Me$ group) are coordinating with the ruthenium not through the methine carbon but through the cyano nitrogen.[19] It may be conceived that the present rhodium-catalyzed asymmetric Michael reaction involves an enolate intermediate in which the enantioselective carbon-carbon bond formation would be accomplished at the carbon atom very distant from the metal center as shown in Scheme 4. The distance of about 4.6 Å is estimated from the X-ray data of **18**. In this model a chiral ligand on the rhodium must differentiate steric bulkiness between α-alkyl group (R^2) and $=C(O^-)OR^1$ group of the enolate intermediate and simultaneously control the direction of the approach of Michael acceptor (**2**). Such a remote enantiofacial differentiation may be achieved efficiently by the concave chiral surroundings of PhTRAP rather than the convex chiral surroundings of cis-chelating diphosphine ligands. This model is in accord with the observation that 2-cyanopropionates **1** with larger ester groups gave the products with higher enantiomeric excesses and cyano esters **14** and **15**, both of which have larger α-alkyl groups than **1**, gave the products with low enantiomeric excesses. Moreover, the findings that the two diastereomeric Michael adducts, both of which are of the almost same degree of the enantiomeric excesses, were produced in low diastereoselectivity in the reaction of β-substituted acceptor **11**, can be explained by assuming an extended transition state where the acceptor is directly approaching at the enolate carbon.

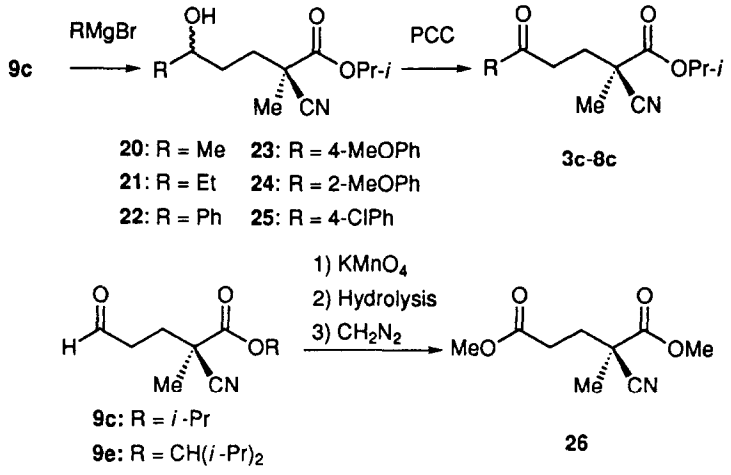
Determination of Absolute Configurations of Michael Adducts. The absolute configuration of Michael adduct (+)-**3c** was determined to be *R* based on the X-ray crystal structure[20] of its *N*-(*S*)-1-naphthylethylamide derivative **19** obtained from (+)-**3c** with the enantiomeric excess of 85% (Scheme 5). The configurations of **3a**,**b**,**d**,and **3e** were also confirmed to be *R* by being related to (*R*)-**3c**. The configuration of **4e** was found to be *R* by transformation to the corresponding methyl ester and comparison of its retention times on GLC with those of the authentic sample derived from (*R*)-**4c** (described below). Acrolein

Scheme 5



19

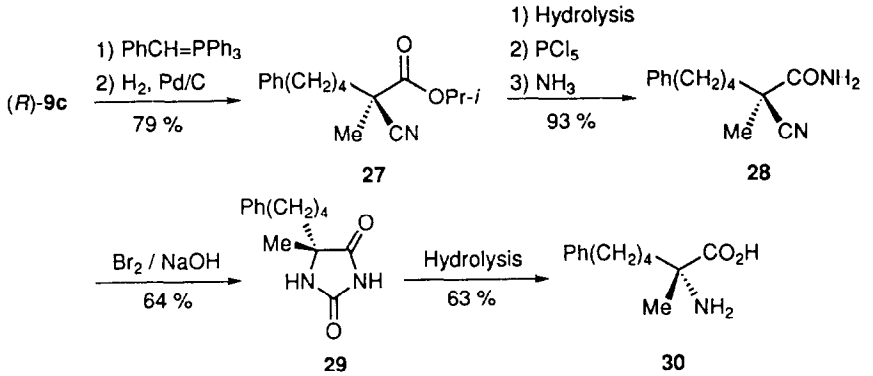
Scheme 6



adduct (+)-**9c** (82% ee) was treated with MeMgBr at 0 °C, and resulting methyl carbinol **20** was oxidized to ketone **3c** (Scheme 6). Its configuration was confirmed to be *R* by comparing the optical rotation with that of authentic (*R*)-**3c**. Similarly, the configurations of **4c-8c** were also found to be *R* by comparing the optical rotations with those of authentic samples derived from (*R*)-**9c** via the corresponding carbinols **21-25**. The configuration of **9e** was confirmed to be *R* by converting to dimethyl ester **26** and comparing the optical rotation with that of the authentic sample derived from (*R*)-**9c**. The configurations of **12**, **13**, **16**,and **17** have not been determined yet.

Synthesis of an α-Methyl-α-amino Acid. Since all products of the present asymmetric Michael reaction contain a quaternary asymmetric carbon center with three different functional groups, some synthetic elaborations are useful in organic synthesis.[21,22] As an example of simple application, the Michael adduct (*R*)-**9c** was used as a starting material for an asymmetric synthesis of new optically active α-methyl-α-amino acid **30** bearing a long-extended C_α-side chain (Scheme 7). α-Alkylated-α-amino acids and peptides containing these amino acids are of increasing interest, because of their unique biological activities and conformational characteristics.[23,24] The Michael adduct (*R*)-**9c** (89% ee) was treated with benzyltriphenylphosphonium ylide, and the

Scheme 7



newly formed carbon-carbon double bond was hydrogenated to give cyano ester **27**, of which the isopropyl ester was converted to primary amide **28**. Hofmann rearrangement of the amide group (Br_2/NaOH) accompanied by hydrolysis of the cyano group afforded hydantoin **29**, whose optical purity was not found to be lost by HPLC analysis, indicating the rearrangement proceeded with almost 100% retention of configuration. Finally, the hydrolysis of **29** furnished optically active α-alkyl-α-amino acid **30** as colorless crystals.

EXPERIMENTAL SECTION

General. Optical rotations were measured with a Perkin-Elmer 243 polarimeter. NMR spectra were obtained with a Varian VXR-200 spectrometer. Unless otherwise noted, ^{1}H NMR (200 MHz) spectra were recorded in δ ppm relative to Me_4Si (δ 0), and ^{13}C NMR (50.3 MHz) spectra were recorded in δ ppm relative to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0). IR spectra were recorded with a Hitachi 270-30 spectrophotometer. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 spectrometer. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel prepacked C.I.G. (Kusano) column. Determination of % ee by GLC analysis was performed with a chiral capillary column Chiraldex G-TA (0.25 mm × 30 m). Unless otherwise noted, determination of % ee by HPLC analysis was performed with a chiral stationary phase column Sumichiral OA-4400 (4 mm × 250 mm).

Materials. $RhH(CO)(PPh_3)_3$ was prepared as described.[26] (*R*,*R*)-CHIRAPHOS, (*R*,*R*)-DIOP, and (*R*)-BINAP were commercially available and used without further purification. **1b** was commercially available and purified by MPLC before use. **2a**, **2b**, **2g** were commercially available and purified by distillation before use.

Methyl 2-cyanopropionate (1a): Prepared from propionitrile and dimethyl carbonate according to a literature procedure[27] and purified by MPLC (62% yield): Oil; bp ca. 110 °C / 24 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.61 (d, *J* = 7.4 Hz, 3 H), 3.57 (q, *J* = 7.4 Hz, 1 H), 3.84 (s, 3 H).

Isopropyl 2-cyanopropionate (1c): Prepared from propionitrile and isopropyl chloroformate by the same procedure as above (86% yield): Oil; bp 88-92 °C / 22 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, *J* = 6.3 Hz, 3 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.59 (d, *J* = 7.5 Hz, 3 H), 3.51 (q, *J* = 7.5 Hz, 1 H), 5.09 (sept, *J* = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.21, 21.46, 21.49, 31.76, 70.85, 117.39, 166.01; IR (neat) 2256, 1744 cm^{-1}; Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.34; H, 8.11; N, 9.76.

***tert*-Butyl 2-cyanopropionate (1d):** Prepared from propionitrile and di-*tert*-butyl dicarbonate by the same procedure as above (91% yield): Oil; bp ca. 110 °C / 25 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H), 1.55 (d, *J* = 7.4 Hz, 3 H), 3.44 (q, *J* = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.23, 27.75, 32.51, 83.91, 117.71, 165.47; IR (neat) 2256, 1740 cm^{-1}; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.63; H, 8.63; N, 8.91.

3-(2,4-Dimethyl)pentyl 2-cyanopropionate (1e). **1b** (9.04 g, 71.1 mmol) was hydrolyzed in the mixture of 10% aqueous KOH (35 mL) and ethanol (35 mL) at 50 °C for 1 h. The reaction mixture was cooled and concentrated, then acidified with 6N HCl. The aqueous solution was saturated with adding solid NaCl, then extracted three times with ether. The organic layer was dried over $MgSO_4$ and evaporated to give 2-cyanopropionic acid in a quantitative yield.

To a solution of the carboxylic acid (7.05 g, 71.1 mmol), 2,4-dimethyl-3-pentanol (16.5 g, 142 mmol), and 4-dimethylaminopyridine (6.92 g, 56.6 mmol) in CH_2Cl_2 (71 mL) was added 1,3-dicyclohexylcarbodiimide (16.0 g, 77.5 mmol) in portions at 0 °C. The reaction mixture was stirred at room temperature for 23 h. After

addition of ethyl acetate (70 mL), the mixture was filtered, washed with ethyl acetate, and evaporated. Some additional precipitates were filtered off, MPLC purification (hexane/ethyl acetate = 10/1) followed by distillation gave 9.48 g (68%) of pure **1e**: Oil; bp ca. 105 °C / 0.4 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3 H), 0.910 (d, J = 6.8 Hz, 3 H), 0.914 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.62 (d, J = 7.4 Hz, 3 H), 1.85-2.1 (m, 2 H), 3.58 (q, J = 7.4 Hz, 1 H), 4.66 (t, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.51, 16.97, 17.12, 19.44, 29.35, 29.41, 31.67, 85.99, 117.46, 166.55; IR (neat) 2256, 1752 cm^{-1}; Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.11; H, 9.53; N, 7.07.

Isopropyl 2-cyanobutyrate (14): Prepared from isopropyl cyanoacetate and acetaldehyde according to a literature procedure[28] and purified by MPLC (83% yield): Oil; bp ca. 100 °C / 19 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.4 Hz, 3 H), 1.30 (d, J = 6.3 Hz, 6 H), 1.9-2.1 (m, 2 H), 3.43 (dd, J = 7.2 and 6.3 Hz, 1 H), 5.09 (sept, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.16, 21.55 (2 C), 23.64, 39.24, 70.74, 116.51, 165.59; IR (neat) 2256, 1748 cm^{-1}; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.16; H, 8.53; N, 8.95.

Isopropyl 2-cyano-3-methylbutyrate (15) : Prepared from isopropyl cyanoacetate and acetone by the same procedure as above (76% yield): Oil; bp ca. 120 °C / 24 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.30 (d, J = 6.3 Hz, 6 H), 2.41 (d-sept, J = 5.4 and 6.8 Hz, 1 H), 3.37 (d, J = 5.4 Hz, 1 H), 5.10 (sept, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.76, 20.63, 21.53, 21.59, 29.97, 45.54, 70.61, 115.50, 165.40; IR (neat) 2256, 1740 cm^{-1}; Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.76; H, 8.86; N, 8.17.

Preparation of Aryl Vinyl Ketones. 2c was prepared in 3 steps: 1) Mannich reaction[29a] of acetophenone, paraformaldehyde, and dimethylamine hydrochloride. 2) Treatment with aqueous Na_2CO_3 to give free amino ketone. 3) Reaction of the tertiary amino group with iodomethane in ether, followed by treatment with aqueous K_2CO_3 in two-phase condition at room temperature (54% overall yield). **2d**[29b] and **2f** were prepared according to the above procedure. **2e** was prepared by the reaction of 2-methoxybenzaldehyde with vinylmagnesium bromide[30] (79% yield), followed by oxidation with MnO_2 in CH_2Cl_2 (29% yield, 64% recovery).

Rhodium-Catalyzed Asymmetric Michael Reaction. General procedure. In a nitrogen atmosphere, $RhH(CO)(PPh_3)_3$ (9.2 mg, 0.010 mmol) and PhTRAP (8.8 mg, 0.011 mmol) were dissolved in a dry solvent (5 mL). Cyano ester **1** (1.0 mmol) was added and the mixture was cooled to a given reaction temperature. Neat **2** (1.5 mmol) was added within 1 min and the mixture was kept stirring at the temperature. For the reaction of aryl vinyl ketones and acrolein (**2c-g**), the catalyst was dissolved in 3 mL of a dry solvent and the solution of **2** (1.5 mmol) in the same solvent (2 mL) was added dropwise at the given temperature and for the given addition time. After **1** was consumed, the product was isolated by the procedure described below. An analytical sample for HPLC was prepared as follows: an aliquot of the adduct was hydrolyzed with aqueous KOH-ethanol at 50 °C, and the resulting carboxylic acid was treated with $SOCl_2$ in CH_2Cl_2 at 0 °C, followed by addition of triethylamine and 3,5-dinitroaniline.

3a: Isolated by bulb-to-bulb distillation: Oil; bp ca. 100 °C / 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3 H), 1.9-2.3 (m, 2 H), 2.19 (s, 3 H), 2.5-2.8 (m, 2 H), 3.83 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 23.57, 29.96, 31.62, 39.20, 42.99, 53.62, 119.44, 169.36, 205.69; IR (neat) 2248, 1748, 1724 cm^{-1}; Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.77; H, 7.16; N, 7.36.

3b: Isolated by bulb-to-bulb distillation: Oil; bp ca. 100 °C / 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3 H), 1.61 (s, 3 H), 2.0-2.3 (m, 2 H), 2.19 (s, 3 H), 2.5-2.8 (m, 2 H), 4.27 (q, J = 7.1 Hz, 2 H); ^{13}C

NMR ($CDCl_3$) δ 13.98, 23.54, 29.98, 31.54, 39.21, 43.09, 62.96, 119.53, 168.86, 205.76; IR (neat) 2248, 1740, 1722 cm^{-1}; Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.03; H, 7.73; N, 6.81.

3c: Isolated by bulb-to-bulb distillation: Oil; bp ca. 110 °C / 1 mmHg; ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 6.3 Hz, 3 H), 1.32 (d, J = 6.3 Hz, 3 H), 1.60 (s, 3 H), 1.9-2.3 (m, 2 H), 2.19 (s, 3 H), 2.5-2.8 (m, 2 H), 5.07 (sept, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.44, 21.51, 23.44, 29.96, 31.43, 39.16, 43.20, 70.98, 119.54, 168.31, 205.78; IR (neat) 2248, 1740, 1724 cm^{-1}; Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.62; H, 8.26; N, 6.63.

3d: Isolated by bulb-to-bulb distillation: Oil; bp ca. 110 °C / 1 mmHg; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9 H), 1.59 (s, 3 H), 1.9-2.3 (m, 2 H), 2.19 (s, 3 H), 2.5-2.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.44, 27.70, 29.96, 31.42, 39.19, 43.78, 84.08, 119.79, 167.76, 205.88; IR (neat) 2248, 1740, 1732 cm^{-1}; Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.90; H, 8.66; N, 6.29.

3e: Isolated by bulb-to-bulb distillation: Oil; bp ca. 140 °C / 0.3 mmHg; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 6 H), 1.64 (s, 3 H), 1.8-2.2 (m, 3 H), 2.19 (s, 3 H), 2.2-2.3 (m, 1 H), 2.5-2.8 (m, 2 H), 4.65 (t, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.00, 17.12, 19.47, 19.56, 23.94, 29.32, 29.43, 29.98, 31.20, 39.32, 43.39, 86.11, 119.55, 168.87, 205.78; IR (neat) 2248, 1740, 1726 cm^{-1}; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.46; H, 9.61; N, 5.10.

4c: Isolated by bulb-to-bulb distillation: Oil; bp ca. 120 °C / 0.5 mmHg; ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 7.3 Hz, 3 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.60 (s, 3 H), 2.0-2.3 (m, 2 H), 2.47 (q, J = 7.3 Hz, 2 H), 2.4-2.8 (m, 2 H), 5.07 (sept, J = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.67, 21.40, 21.47, 23.39, 31.51, 35.98, 37.77, 43.26, 70.89, 119.54, 168.31, 208.54; IR (neat) 2248, 1740, 1724 cm^{-1}; Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.00; H, 8.50; N, 6.22. Found: C, 64.07; H, 8.71; N, 6.19.

4e: Isolated by bulb-to-bulb distillation: Oil; bp ca. 140 °C / 0.25 mmHg; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 6 H), 1.07 (t, J = 7.3 Hz, 3 H), 1.64 (s, 3 H), 1.9-2.3 (m, 4 H), 2.46 (q, J = 7.3 Hz, 2 H), 2.5-2.8 (m, 2 H), 4.65 (t, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.74, 17.01, 17.12, 19.48, 19.56, 23.93, 29.31, 29.43, 31.30, 36.06, 37.98, 43.49, 86.08, 119.60, 168.92, 208.65; IR (neat) 2248, 1738, 1724 cm^{-1}; Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 67.99; H, 9.90; N, 4.91.

5c: Isolated by MPLC (hexane/ethyl acetate = 3/1) after passing through a short column of silica gel to remove the catalyst: Oil; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.2 Hz, 6 H), 1.66 (s, 3 H), 2.1-2.5 (m, 2 H), 3.0-3.3 (m, 2 H), 5.10 (sept, J = 6.2 Hz, 1 H), 7.4-7.6 (m, 3 H), 7.9-8.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.45, 21.52, 23.55, 32.05, 34.37, 43.42, 70.98, 119.66, 127.96, 128.67, 133.40, 136.27, 168.36, 197.41; IR (neat) 2248, 1740, 1694, 1600, 1584 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.39; H, 7.01; N, 5.12. Found: C, 70.49; H, 7.14; N, 5.08.

6c: Isolated by MPLC (hexane/ethyl acetate = 3/1) after passing through a short column of silica gel to remove the catalyst: Oil; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 6 H), 1.66 (s, 3 H), 2.1-2.5 (m, 2 H), 3.0-3.3 (m, 2 H), 3.88 (s, 3 H), 5.10 (sept, J = 6.3 Hz, 1 H), 6.95 (deformed d, 2 H), 7.95 (deformed d, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.49, 21.57, 23.57, 32.27, 34.03, 43.53, 55.49, 70.98, 113.84, 119.76, 129.39, 130.30, 163.72, 168.45, 195.97; IR (neat) 2248, 1740, 1682, 1604, 1580 cm^{-1}; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.04; H, 7.04; N, 4.44.

7c: Isolated by MPLC (hexane/ethyl acetate = 3/1) after passing through a short column of silica gel to remove the catalyst: Oil; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 6 H), 1.64 (s, 3 H), 2.1-2.4 (m, 2 H), 3.0-3.4 (m, 2 H), 3.93 (s, 3 H), 5.09 (sept, J = 6.3 Hz, 1 H), 6.98 (dd, J = 7.3 and 1.0 Hz, 1 H), 7.01 (ddd, J = 7.6, 7.4 and 1.0 Hz, 1 H), 7.48 (ddd, J = 7.4, 7.3 and 1.9 Hz, 1 H), 7.72 (dd, J = 7.6 and 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.48, 21.55, 23.42, 32.58, 39.58, 43.58, 55.51, 70.80, 111.56, 119.84, 120.72, 127.42, 130.47, 133.93, 158.73, 168.59, 199.64; IR (neat) 2248, 1740, 1678, 1600 cm^{-1}; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.24; H, 7.05; N, 4.55.

8c: Isolated by MPLC (hexane/ethyl acetate = 4/1) after passing through a short column of silica gel to remove the catalyst: Oil; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 6 H), 1.66 (s, 3 H), 2.1-2.5 (m, 2 H), 3.0-3.3 (m, 2 H), 5.10 (sept, J = 6.3 Hz, 1 H), 7.46 (deformed d, 2 H), 7.91 (deformed d, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.49, 21.57, 23.66, 31.96, 34.43, 43.40, 71.10, 119.64, 129.06, 129.42, 134.59, 139.97, 168.34, 196.24; IR (neat) 2248, 1740, 1692, 1592 cm^{-1}; Anal. Calcd for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.40; H, 5.96; N, 4.37.

9c: Isolated by MPLC (hexane/ethyl acetate = 3/2) after passing through a short column of silica gel to remove the catalyst: Oil; bp ca. 75 °C / 0.25 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 6 H), 1.62 (s, 3 H), 2.0-2.4 (m, 2 H), 2.5-2.8 (m, 2 H), 5.08 (sept, J = 6.3 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.45, 21.53, 23.47, 29.94, 39.77, 43.15, 71.17, 119.37, 168.16, 199.05; IR (neat) 2744, 2248, 1738 cm^{-1}; Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.60; H, 7.78; N, 7.06.

9e: Isolated by MPLC (hexane/ethyl acetate = 4/1) after passing through a short column of silica gel to remove the catalyst: Oil; bp ca. 125 °C / 0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.905 (d, J = 6.8 Hz, 3 H), 0.912 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 6 H), 1.66 (s, 3 H), 1.9-2.1 (m, 2 H), 2.1-2.2 (m, 1 H), 2.2-2.4 (m, 1 H), 2.6-2.9 (m, 2 H), 4.66 (t, J = 6.2 Hz, 1 H), 9.81 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.99, 17.14, 19.47, 19.56, 23.96, 29.30, 29.42, 29.64, 39.90, 43.32, 86.28, 119.37, 168.72, 199.10; IR (neat) 2740, 2248, 1738 cm^{-1}; Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.19; H, 9.41; N, 5.47.

12: Isolated as a diastereomeric mixture by MPLC (hexane/ethyl acetate = 2/1) after passing through a short column of silica gel to remove the catalyst: Oil; 93% yield; bp ca. 115 °C / 0.3 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.19, 1.27 (d, d, diastereomers, J = 7.4 Hz, J = 7.4 Hz, 3 H), 1.30, 1.32, 1.33 (d, d, d, diastereomers, J = 6.3 Hz, J = 6.3 Hz, J = 6.3 Hz, 6 H, 3 H, 3 H), 1.8-2.0, 2.3-2.8 (m, diastereomers, totally 3 H), 5.05 (sept, J = 6.3 Hz, 1 H), 9.58, 9.67 (d, d, diastereomers, J = 1.4 Hz, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.29 and 14.97 (diastereomers), 21.43, 24.27 and 24.60 (diastereomers), 37.00 and 37.96 (diastereomers), 42.97 and 43.02 (diastereomers), 43.64, 71.21 and 71.25 (diastereomers), 119.45 and 119.80 (diastereomers), 168.29 and 168.67 (diastereomers), 201.82; IR (neat) 2732, 2248, 1740 cm^{-1}; Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.42; H, 8.26; N, 6.67.

13: Isolated by MPLC (hexane/ethyl acetate = 3/1) after passing through a short column of silica gel to remove the catalyst: Oil; bp ca. 125 °C / 0.2 mmHg; Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.33; H, 8.24; N, 6.66. The spectroscopic data of diastereomers separated were as follows: **13α:** 49% yield; $[\alpha]^{20}_D$ +4.4° (c 4.98, $CHCl_3$); 75% ee by GLC; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.32 (d, J = 6.3 Hz, 3 H), 1.57 (s, 3 H), 2.4-2.6 (m, 2 H, attached to C-4), 2.6-2.8 (m, 1 H, attached to C-3), 5.08 (sept, J = 6.3 Hz, 1 H), 9.75 (t, J = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.22, 20.79, 21.43, 21.55, 33.83, 47.26, 48.51, 71.12, 118.66, 168.29, 199.08; IR (neat) 2744, 2248, 1740 cm^{-1}: **13β:** 47% yield; $[\alpha]^{20}_D$ +13.0° (c 5.14, $CHCl_3$); 74% ee by GLC; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7.2 Hz, 3 H),

1.317 (d, J = 6.3 Hz, 3 H), 1.324 (d, J = 6.3 Hz, 3 H), 1.55 (s, 3 H), 2.48 (ddd, J = 18.2, 10.4, and 1.6 Hz, 1 H, attached to C-4), 2.6 - 2.8 (m, 2 H, each attached to C-3 and C-4), 5.10 (sept, J = 6.3 Hz, 1 H), 9.80 (d, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.64, 21.07, 21.46, 21.56, 34.09, 46.14, 48.65, 71.06, 118.77, 168.06, 199.28; IR (neat) 2744, 2248, 1740 cm^{-1}.

16: Isolated by MPLC (hexane/ethyl acetate = 2/1) after passing through a short column of silica gel to remove the catalyst: Oil; 82% yield; $[\alpha]^{20}_D$ +0.66° (*c* 5.17, $CHCl_3$); 21% ee by GLC; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.4 Hz, 3 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.33 (d, J = 6.3 Hz, 3 H), 1.8-2.1 (m, 2 H), 2.0-2.3 (m, 2 H), 2.5-2.9 (m, 2 H), 5.10 (sept, J = 6.3 Hz, 1 H), 9.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.64, 21.59, 28.79, 30.91, 39.80, 49.77, 71.07, 118.61, 167.87, 199.13; IR (neat) 2744, 2248, 1740 cm^{-1}; Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.32; H, 7.98; N, 6.63. Found: C, 62.54; H, 8.11; N, 6.57.

17: Isolated by MPLC (hexane/ethyl acetate = 3/1) after passing through a short column of silica gel to remove the catalyst: Oil; 79% yield; bp ca. 125 °C / 0.3 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J = 6.8 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 3 H),1.31 (d, J = 6.3 Hz, 3 H), 1.33 (d, J = 6.3 Hz, 3 H), 2.0-2.3 (m, 3 H), 2.4-2.6 (m, 1 H), 2.7-2.9 (m, 1 H), 5.11 (sept, J = 6.3 Hz, 1 H), 9.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.63, 18.89, 21.62, 27.07, 35.08, 40.01, 54.71, 70.96, 117.69, 168.00, 199.21; IR (neat) 2744, 2248, 1740 cm^{-1}; Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.18; H, 8.77; N, 6.20.

Determination of Absolute Configuration of 3. *N*-[(*S*)-1-(1-Naphthyl)ethyl]-(*R*)-2-cyano-2-methyl-5-oxohexanamide (19)(Scheme 5). A mixture of 202 mg (0.955 mmol) of (+)-**3c** (85% ee), 2 mL of 10% aqueous KOH and 2 mL of ethanol was stirred at 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature, acidified with 5% HCl, and extracted three times with ether. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure, leaving crude (*R*)-2-cyano-2-methyl-5-oxohexanoic acid. For the amidation of the carboxylic acid, the residue was mixed with 202 mg (1.18 mmol) of (*S*)-1-(1-naphthyl)-ethylamine, 0.57 mL (2.4 mmol) of tri-*n*-butylamine, and 316 mg (1.24 mmol) of 2-chloro-1-methylpyridinium iodide in 4 mL of CH_2Cl_2, and refluxed for 30 min. The mixture was cooled to room temperature, added 10 mL of ether and 4 mL of 5% HCl, and stirred at room temperature for 30 min. The organic layer was separated, washed twice with 10% HCl and twice with water, dried over $MgSO_4$, and evaporated. MPLC purification (hexane/ethyl acetate = 1/1) gave 261 mg (85%) of *N*-[(*S*)-1-(1-Naphthyl)ethyl]-2-cyano-2-methyl-5-oxohexanamide as a diastereomeric mixture, which was recrystallized twice from ethanol to give 168 mg of diastereomerically pure **19** (analyzed by HPLC, silica gel, hexane/1,2-dichloroethane/ethanol = 100/20/1). Crystals for the X-ray diffraction study were obtained by further recrystallization from ethanol: mp 137-138 °C; $[\alpha]^{20}_D$ +12.0° (*c* 5.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3 H), 1.72 (d, J = 6.8 Hz, 3 H), 1.9-2.4 (m, 2 H), 2.18 (s, 3 H), 2.5-2.7 (m, 2 H), 5.92 (dq, J = 7.8 and 6.8 Hz, 1 H), 6.53 (broad d, J = 7.8 Hz, 1 H), 7.4-7.6 (m, 4 H), 7.8-8.0 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.64, 24.13, 29.93, 31.39, 39.27, 43.36, 45.68, 121.15, 122.58, 122.72, 125.23, 125.96, 126.63, 128.78, 128.99, 130.85, 133.93, 136.91, 166.31, 205.90; IR (KBr) 3332, 2248, 1716, 1668, 1602, 1540 cm^{-1}; Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.79; H, 6.89; N, 8.71.

Determination of absolute configurations of 3a, 3b, 3d. (*R*)-(+)-**3c** (0.1 mmol) obtained by the asymmetric Michael reaction was dissolved in the mixture of 10% aqueous KOH (0.5 mL) and ethanol (0.5 mL), and hydrolyzed at 50 °C for 1 h. The mixture was allowed to cool to room temperature, acidified with 6N HCl, and extracted three times with ether. The combined extracts were dried over $MgSO_4$. After filtration, to the

carboxylic acid solution was added diazomethane solution in ether at 0 °C until the yellow color did not disappear. Evaporation of the solvent afforded (*R*)-**3a**, which was used as an authentic sample for GLC analysis.

Absolute configurations of (+)-**3a** obtained by the asymmetric Michael reaction was determined to be *R* by comparison of retention times on GLC with those of the authentic sample. (+)-**3b** and (+)-**3d** obtained by the asymmetric Michael reaction were transformed into **3a** as described above, whose configurations were determined to be *R* by comparison of retention times on GLC with those of the authentic sample.

Determination of absolute configuration of 3e. A mixture of (+)-**3e** (124 mg, 0.464 mmol) obtained by the asymmetric Michael reaction, ethylene glycol (0.5 mL), and *p* -toluenesulfonic acid monohydrate (10 mg) in benzene (5 mL) was refluxed for 1 h. The reaction mixture was allowed to cool to room temperature, washed three times with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Evaporation of the solvent afforded an acetal derivative of **3e** in a quantitative yield. It was dissolved in the mixture of 10% aqueous KOH (0.5 mL) and ethanol (0.5 mL), and refluxed for 5 h. The reaction mixture was allowed to cool to room temperature, acidified with 6N HCl, and 5 mL of ether was added. The mixture was stirred at room temperature for 20 min to cleave the acetal. The organic layer was extracted three times with ether, dried over $MgSO_4$. After filtration, the carboxylic acid was converted to **3a** with diazomethane as described above (overall 88%), whose configuration was determined to be *R* by comparison of retention times on GLC with those of the authentic sample.

Determination of absolute configuration of 4e. (*R*)-(+)-**4c** (whose absolute configuration was determined below) was transformed to the corresponding methyl ester according to the procedure for **3c** to **3a**, which was used as an authentic sample of GLC analysis. (+)-**4e** obtained by the asymmetric Michael reaction was converted to the corresponding methyl ester according to the procedure for **3e** to **3a**. The configuration of the methyl ester was determined to be *R* by comparison of retention times on GLC with those of the authentic sample.

Determination of absolute configuration of 9c (Scheme 6). To a solution of 390 mg (1.98 mmol) of (+)-**9c** (82% ee) in 10 mL of ether was added 0.82 mL of 2.74 M MeMgBr in ether at 0 °C. The mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl (5 mL) was added and the organic phase was extracted twice with ether, washed with brine, dried over $MgSO_4$, and evaporated. MPLC purification (hexane/ethyl acetate = 1/1) gave 237 mg (56%) of **20** as 1:1 epimeric mixture: ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.2 Hz, 3 H), 1.31 (d, J = 6.2 Hz, 6 H), 1.5-2.2 (m, 4 H), 1.60 (s, 3 H), 3.83 (m, 1 H), 5.09 (sept, J = 6.2 Hz, 1 H).

To a solution of 66.5 mg (0.312 mmol) of **20** in 1 mL of CH_2Cl_2 was added 97 mg (0.45 mmol) of pyridinium chlorochromate (PCC) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether, filtered, and evaporated. Bulb-to-bulb distillation gave 62.7 mg (95%) of (+)-**3c**, whose configuration was confirmed to be *R* by comparison of the optical rotation with that of authentic (*R*)-**3c**: $[\alpha]^{20}_D$ = +4.0° (*c* 4.37, $CHCl_3$); 81% ee by GLC.

Determination of absolute configurations of 4c-8c (Scheme 6). (*R*)-(+)-**9c** (82% ee) obtained by the asymmetric Michael reaction was treated with corresponding Grignard reagent RMgBr in ether as described above. (**2*R*)-21**: R = Et; 1:1 epimeric mixture (49%); ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3 H), 1.31 (d, J = 6.2 Hz, 6 H), 1.4-2.2 (m, 6 H), 1.60 (s, 3 H), 3.51 (m, 1 H), 5.09 (sept, J = 6.2 Hz, 1 H). (**2*R*)-22**: R = Et; 1:1 epimeric mixture (59%); ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.2 Hz, 6 H), 1.55 (s, 3 H), 1.6-2.4 (m, 4 H), 4.67 (m, 1 H), 5.05 (sept, J = 6.2 Hz, 1 H), 7.2-7.4 (m, 5 H). (**2*R*)-23**: R = 4-$MeOC_6H_4$; 1:1 epimeric mixture (27%); ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.2 Hz, 6 H), 1.56 (s, 3 H), 1.6-2.2 (m, 4 H), 3.81

(s, 3 H), 4.66 (m, 1 H), 5.06 (sept, J = 6.2 Hz, 1 H), 6.89 (deformed d, 2 H), 7.26 (deformed d, 2 H). **(2*R*)-24**: R = 2-$MeOC_6H_4$; 1:1 epimeric mixture (68%); ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.2 Hz, 6 H), 1.57 (s, 3 H), 1.7-2.3 (m, 4 H), 3.85 (s, 3 H), 4.85 (m, 1 H), 5.06 (sept, J = 6.2 Hz, 1 H), 6.8-7.0 (m, 2 H), 7.2-7.3 (m, 2 H). **(2*R*)-25**: R = 4-ClC_6H_4; 1:1 epimeric mixture (44%); ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.2 Hz, 6 H), 1.56 (s, 3 H), 1.6-2.2 (m, 4 H), 4.70 (m, 1 H), 5.06 (sept, J = 6.2 Hz, 1 H), 7.2-7.4 (m, 2 H).

These alcohols were oxidized to the corresponding ketones with PCC according to the above procedure. **(*R*)-4c**: 91% yield; $[\alpha]^{20}_D$ = +4.3° (*c* 4.99, $CHCl_3$). **(*R*)-5c**: 27% yield; $[\alpha]^{20}_D$ = +5.8° (*c* 2.86, $CHCl_3$). **(*R*)-6c**: 76% yield; $[\alpha]^{20}_D$ = +4.9° (*c* 6.47, $CHCl_3$); 82% ee by HPLC analysis of its *N*-(3,5-dinitrophenyl)amide derivative. **(*R*)-7c**: 65% yield; $[\alpha]^{20}_D$ = +2.5° (*c* 4.27, EtOH); 83% ee by HPLC analysis of its *N*-(3,5-dinitrophenyl)-amide derivative. **(*R*)-8c**: 59% yield; $[\alpha]^{20}_D$ = +5.4° (*c* 5.56, $CHCl_3$); 81% ee by HPLC analysis of its *N*-(3,5-dinitrophenyl)amide derivative. These were used as authentic samples.

Absolute configurations of (+)-**4c-8c** obtained by the asymmetric Michael reaction were determined to be *R* by comparison of optical rotations with those of the authentic samples.

Determination of absolute configuration of 9e (Scheme 6). (*R*)-(+)-**9c** (181 mg, 0.916 mmol, 83% ee) was dissolved in 5 mL of acetone and cooled to 0 °C. To the solution was added $KMnO_4$ (214 mg, 1.35 mmol) in 4 mL of water. The reaction mixture was stirred at 0 °C for 2.5 h. Methanol (5 mL) was added, and the mixture was stirred at room temperature for 30 min to decompose the excess permanganate. Dark brown precipitate formed was filtered off, and the filtrate was evaporated to remove acetone. To the aqueous solution was added 1.5 mL of 10% aqueous KOH and 4 mL of ethanol, and hydrolyzed at 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature, acidified with 6N HCl. After saturated by adding solid NaCl, the aqueous solution was extracted three times with ether, and dried over Na_2SO_4. The solution was filtered and evaporated to leave crude (*R*)-2-cyano-2-methylglutaric acid. To the solution of the acid in 5 mL of ether was added diazomethane solution in ether at 0 °C until the yellow color did not disappear. Evaporation of the solvent followed by bulb-to-bulb distillation afforded 121 mg (66%) of (*R*)-dimethyl 2-cyano-2-methylglutarate (**26**) which was used as an authentic sample for GLC analysis: Oil; $[\alpha]^{20}_D$ +1.7° (*c* 5.09, $CHCl_3$); 82% ee by GLC; bp ca. 110 °C / 0.25 mmHg; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 2.0-2.7 (m, 4 H), 2.4-2.6 (m, 1 H), 3.70 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 23.45, 30.01, 32.87, 43.01, 51.96, 53.66, 119.15, 169.19, 171.93; IR (neat) 2248, 1746 cm^{-1}; Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.19; H, 6.75; N, 6.97.

Optically active **9e** obtained by the asymmetric Michael reaction was also converted to **26** as the same procedure except the ester hydrolysis was performed at reflux temperature for 4 h. The configuration was determined to be *R* by comparison of optical rotation and retention times on GLC with those of the authentic sample.

Isopropyl (*R*)-2-cyano-2-methyl-6-phenylhexanoate (27): To a suspension of benzyltriphenylphosphonium chloride (3.83 g, 9.85 mmol) in 40 mL of THF was added 6.7 mL of 1.6 M n-BuLi/Hexane (10.4 mmol) at 0 °C. The deep orange suspension was stirred at room temperature for 3 h. After the mixture was cooled to -70 °C, (*R*)-**9c** (1.83 g, 9.28 mmol, 89% ee) in 10 mL of THF was added dropwise over 20 min. The reaction mixture was stirred at -70 °C for 1 h, and allowed to warm to room temperature. The mixture was diluted with ether, filtered, and the product was isolated by MPLC (hexane/ethyl acetate = 10/1) to give 2.04 g of an oil. The oil was dissolved in 8 mL of ethanol, and hydrogenated (50 atm) over 5% Pd/C (200 mg) in an autoclave at room temperature for 1 h. The catalyst was filtered off and the filtrate was evaporated to give 2.01 g (79%) of (*R*)-**28**: Oil; $[\alpha]^{20}_D$ +8.5 ° (*c* 5.16, $CHCl_3$); 89% ee by HPLC analysis of *N*-(3,5-dinitrophenyl)amide

derivative; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.3 Hz, 3 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.3-2.1 (m, 6 H), 1.56 (s, 3 H), 2.63 (m, 2 H), 5.05 (sept, J = 6.3 Hz, 1 H), 7.1-7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.45, 21.51, 23.37, 24.95, 31.01, 35.50, 38.07, 44.06, 70.65, 120.10, 125.84, 128.30, 128.34, 141.85, 168.88; IR (neat) 2248, 1740 cm^{-1}; Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.47; H, 8.67; N, 5.01.

(*R*)-2-cyano-2-methyl-6-phenylhexamide (28): (*R*)-**27** (2.01 g, 7.34 mmol) was dissolved in the mixture of 6 mL of 10% aqueous KOH and 6 mL of ethanol, and hydrolyzed at 50 °C for 1 h. The reaction mixture was cooled and concentrated, then acidified with 6N HCl. The aqueous solution was extracted three times with ether, dried over Na_2SO_4 and evaporated to give crude (*R*)-2-cyano-2-methyl-6-phenylhexanoic acid. To a mixture of the carboxylic acid and hexane (35 mL) was added PCl_5 (1.53 g, 7.35 mmol), and the mixture was stirred at room temperature. The reaction mixture became homogeneous. After 1 h, the solution was transferred to a dropping funnel, and added dropwise to 25% aqueous NH_3 (35 mL) cooled at -10 °C under stirring. The mixture was stirred at the temperature for 1 h and warmed to room temperature. Water was added, and the organic phase was extracted three times with ether, washed with brine, and dried over $MgSO_4$. The solution was evaporated to give 1.57 g (93%) of (*R*)-**28** as white powder. It was used for the following reaction without further purification. An analytical sample was obtained by recrystallization from isopropyl ether/hexane: Colorless needles; mp 87-88 °C; ^{1}H NMR ($CDCl_3$) δ 1.3-1.8 (m, 5 H), 1.57 (s, 3 H), 1.9-2.1 (m, 1 H), 2.63 (m, 2 H), 5.98 (broad s, 1 H), 6.30 (broad s, 1 H), 7.1-7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.81, 25.18, 30.98, 35.50, 37.80, 43.77, 121.75, 125.83, 128.29, 128.33, 141.88, 170.41; IR (KBr) 3436, 3324, 2244, 1698 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.23; H, 7.94; N, 12.16.

(*R*)-5-Methyl-5-(4-phenyl)butylhydantoin (29): Bromine (733 mg, 4.59 mmol) was added to ice-cooled NaOH (1.57 g, 39.3 mmol) solution in water (15 mL). Solid (*R*)-**28** (883 mg, 3.83 mmol) was added to the solution, and the mixture was stirred at 0 °C until the solid was completely dissolved (usually for 1 h). The mixture was then heated at 80 °C for 30 min. After the solution was cooled to room temperature, 10% HCl was added to made acidic. Precipitated crystals were extracted three times with $CHCl_3$, and the combined organic phases were dried over Na_2SO_4. Evaporation of the solvent and MPLC purification (hexane/ethyl acetate = 1/1) gave 607 mg (64%) of **29** as white powder: $[\alpha]^{20}_D$ +20.4° (*c* 2.50, $CHCl_3$); 89% ee by HPLC [Daicel Chiralcel OD-H (4.6 mm × 250 mm), hexane/2-propanol/acetic acid = 90/10/0.5]; mp 148-151 °C; ^{1}H NMR ($CDCl_3$) δ 1.2-1.9 (m, 6 H), 1.44 (s, 3 H), 2.60 (m, 2 H), 5.81 (broad s, 1 H), 7.1-7.4 (m, 5 H), 8.24 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.18, 23.88, 31.20, 35.59, 37.55, 63.69, 125.84, 128.29, 128.35, 141.94, 156.20, 177.20; IR (KBr) 3204, 1778, 1740 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.12; H, 7.36; N, 11.23.

(*R*)-2-Amino-2-methyl-6-phenylhexanoic acid (30): A mixture of the hydantoin **29** (607 mg, 2.46 mmol) and calcium hydroxide (654 mg, 8.83 mmol) in 4 mL of water was heated in an autoclave at 150 °C for 10 h. The reaction mixture was filtered and washed with hot water. Ammonium carbonate (500 mg) was added to the filtrate, and the mixture was stirred at room temperature for 10 min, then heated at 80 °C for 10 min. The precipitate was filtered off, and the filtrate was washed with $CHCl_3$ to remove the unreacted starting material. The aqueous layer was heated to boiling, carefully added some activated charcoal, and filtered while hot. Evaporation of the water gave 340 mg (63%) of **30** as colorless needles: $[\alpha]^{20}_D$ -5.0° (*c* 2.03, MeOH); mp 272-273 °C (dec.); ^{1}H NMR (CD_3OD) δ 1.2-2.0 (m, 6 H), 1.43 (s, 3 H), 2.62 (m, 2 H), 7.1-7.3 (m, 5 H); ^{13}C NMR (CD_3OD) δ 23.69, 24.60, 32.91, 36.68, 39.04, 62.42, 126.74, 129.31, 129.39, 143.55, 176.54; IR (KBr) 3700-2100, 1630 cm^{-1}; HRMS: Calcd for $C_{13}H_{19}NO_2$, 221.1416. Found (m/z) 221.1422.

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