Rhodium-Catalyzed Enantioselective Michael Addition of (1-Cyanoethyl)phosphonate: Synthesis of Optically Active Phosphonic Acid Derivatives with Phosphorus-Substituted Quaternary Asymmetric Carbon Center

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Asymmetric Michael addition of diethyl (1-cyanoethyl)phosphonate with vinyl ketones or acrylaldehyde in the presence of 0.01 molar amount of a rhodium catalyst prepared in situ from Rh(acac)$(CO)_2$ and a *trans*-chelating chiral diphosphine ligand (*R,R*)-(*S,S*)-2,2″-bis[1-(diphenylphosphino)ethyl]-1,1″-biferrocene (PhTRAP) in benzene at 3 °C gave optically active phosphonates having a phosphorus-substituted quaternary asymmetric carbon center with high enantiomeric excesses (92—93% ee) in high yields. The Michael addition product from acrylaldehyde was converted into an optically active (1-aminoalkyl)phosphonic acid derivative.

Asymmetric synthesis of α-amino alkylphosphonic acids, which are phosphonic acid analogs of α-amino acids, has been an active area of research in recent years.[1] While a number of methods have so far been developed,[2,3] asymmetric synthesis of α-alkylated α-amino alkylphosphonic acids is very rare, in spite of the potential importance of the α-alkylated derivatives as biologically active compounds.[4,5] We report here a route to α-alkylated α-amino alkylphosphonic acids through an enantioselective Michael addition of (1-cyanoethyl)phosphonate to activated olefins catalyzed by a rhodium(I) complex coordinated with *trans*-chelating chiral phosphine ligand, (*R,R*)-(*S,S*)-2,2″-bis[1-(diphenylphosphino)ethyl]-1,1″-biferrocene (PhTRAP).[6,7] This is also a rare case for the enantioselective synthesis of an optically active phosphonic acid derivative with a phosphorus-substituted quaternary asymmetric carbon center.[8] The Michael addition produced optically active (1-cyano-1-methyl-4-oxoalkyl)phosphonates with high enantiomeric excesses in high chemical yields. One of the α-cyano alkylphosphonates was converted into an optically active (α-amino-α-methyl)alkylphosphonic acid ester as an *N*-protected form.

Results and Discussion

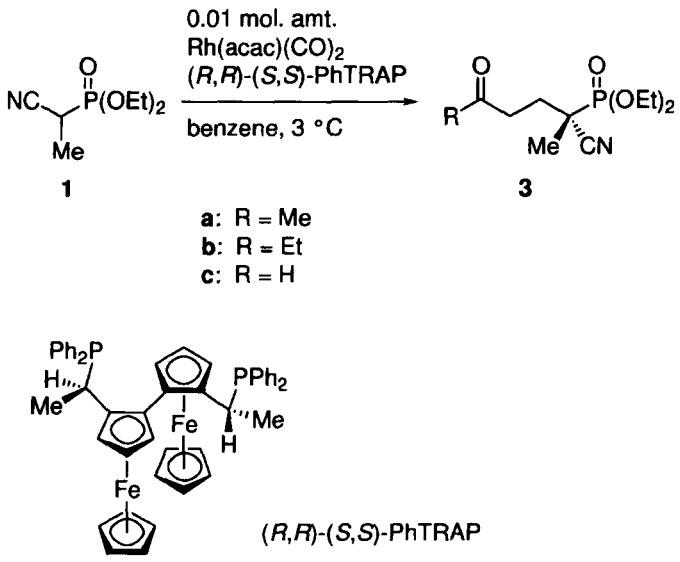
Enantioselective Michael Addition. Diethyl (1-cyanoethyl)phosphonate (**1**) was subjected to the Michael addition with vinyl ketones or acrylaldehyde in the presence of 0.01 mol of the rhodium(I) catalyst prepared in situ from (acetylacetonato)dicarbonylrhodium(I) and (*R,R*)-(*S,S*)-PhTRAP. The reaction was slower than those of 2-cyanopropionate and *N*-methoxy-*N*-methyl-2-cyanopropionamide,[7] but proceeded smoothly at 3 °C to give the Michael adduct in high yield and high enantioselectivity (up to 93% ee) (Scheme 1, Table 1). The reaction with methyl vinyl ketone (**2a**) is typical (Table 1, Entry 1). To a solution of Rh(acac)$(CO)_2$ (2.6 mg, 0.010 mmol), (*R,R*)-(*S,S*)-PhTRAP (8.3 mg, 0.0105 mmol), and **1** (191 mg, 1.0 mmol) in dry benzene (1 mL) was added **2a** (105 mg, 1.5 mmol) at 3 °C. The mixture was stirred at this temperature for 37 h. The solution was passed through a column of silica gel (17 mm×20 mm, ethyl acetate) to remove the catalyst. Then bulb-to-bulb distillation gave 251 mg (96%) of Michael adduct **3a**. The enantiomeric excess was determined to be 93% by GLC analysis with a chiral capillary column (Chiraldex G-TA).

The reaction of ethyl vinyl ketone (**2b**) and acrylaldehyde (**2c**) produced conjugate addition products **3b** and **3c**, respectively, with high enantioselectivities (> 90% ee) (Table 1, Entries 2 and 3). Even in the case with acrylaldehyde, no 1,2-carbonyl addition product was formed. Although unambiguous assignments of product absolute configurations

Table 1. Enantioselective Michael Addition of Diethyl (1-Cyanoethyl)phosphonate **1** with **2** Catalyzed by the Rhodium Complex of (*R,R*)-(*S,S*)-PhTRAP (Scheme 1)[a]

Entry	**2** R	Amount of benzene[b]/mL	Time/h	Product (**3**) Yield[c]/%	ee/%	$[\alpha]_D^{20}$[d]
1	Me (**2a**)	1	37	96 (**3a**)	93	−1.6
2	Et (**2b**)	1	43	98 (**3b**)	93	−2.1
3	H (**2c**)	2	7	80 (**3c**)	92	−4.9

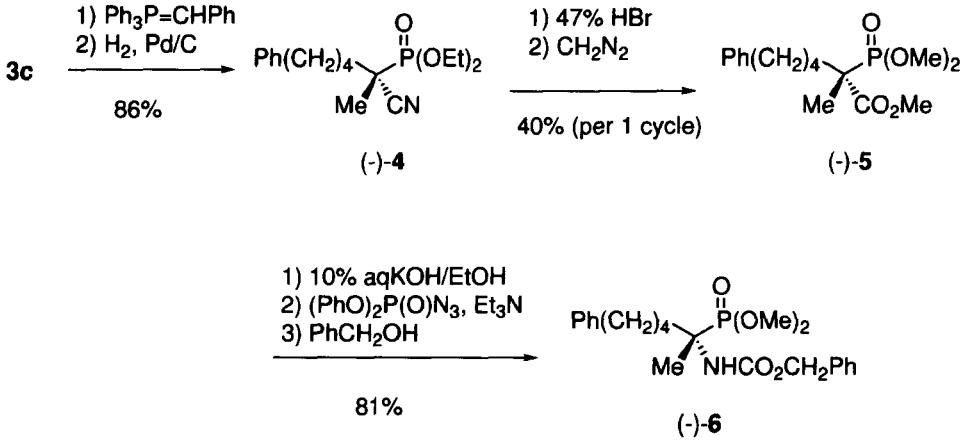
a) **1**/**2**/Rh(acac)$(CO)_2$/PhTRAP = 1/1.5/0.01/0.0105. b) Amount of benzene in mL per mmol of **1**. c) Isolated yield by bulb-to-bulb distillation. d) *c* 5.2—5.3 in $CHCl_3$.



Scheme 1.

are yet to be performed, we assume tentatively that all the Michael adducts have (*S*) configurations on the basis of the separation patterns in the GLC analysis and the mechanism of the enantioselection in the Michael addition of corresponding carboxylic esters and amides.[7,8] We have not examined the reaction of a Michael acceptor with a substituent at the olefinic carbon atoms (α and/or β) because of expected low 1,2- and/or 1,3-diastereoselectivities.[7b] Another limitation of this methodology is found in the phosphonate substrate. Namely, (1-cyanoethyl)phosphonate **1** is the only phosphonate substrate examined in this research. It is expected that the reaction of a (cyanomethyl)phosphsphonate would suffer from racemization due to high acidity of the α-proton. In addition, our knowledge on the steric effect of the α-alkyl substituent of 2-cyano carboxylate on the stereoselectivity and reactivity[7b] prevented us from examining the reaction of a phosphonate substrate bearing α-substituent with steric demand larger than that of methyl group.

Synthesis of an Optically Active (1-Aminoalkyl)phosphonic Acid Derivative. As an application of the Michael addition, the adduct (−)-**3c** was used as a starting material for an asymmetric synthesis of a new optically active (1-aminoalkyl)phosphonic acid derivative **6**, which has a phosphorus-substituted quaternary asymmetric carbon atom (Scheme 2). (4-Oxoalkyl)phosphonate (−)-**3c** (91% ee) was treated with benzyltriphenylphosphonium ylide, and the newly formed carbon-carbon double bond was hydrogenated to give (−)-**4**. Chemoselective hydrolysis of the cyano group in **4** was found to be difficult because of hydrolysis of the phosphonate in both acidic and basic conditions. Hydrolysis in alkaline media formed at first a half ester of the phosphonic acid, and subsequently afforded a mixture of primary amide and carboxylic acid with the phosphonic acid half-ester moiety intact. Hydrolysis under acidic conditions in turn resulted in complete hydrolysis of the phosphonate and gave a mixture of carboxylic acid and unchanged cyanide. The unchanged cyanide could be reused for the hydrolysis. Consequently, the acidic hydrolysis was employed and the product was isolated as dimethyl ester (−)-**5** after esterification with diazomethane. The methoxycarbonyl group of (−)-**5** was selectively hydrolyzed, and the remaining carboxylic acid was treated with diphenyl phosphoroazidate. The Curtius rearrangement followed by reaction with benzyl alcohol afforded a [1-(*N*-benzyloxycarbonylamino)alkyl]phosphonic acid di-



Scheme 2.

methyl ester (−)-**6** as a colorless oil, whose enantiomeric excess was determined to be 88% by HPLC analysis with a chiral stationary phase column (Chiralpak AD).

Experimental

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 relative to Me_4Si (δ = 0), and $^{13}C\{^1H\}$ NMR (50.3 MHz) spectra were recorded in δ relative to $CDCl_3$ (δ = 77.0) or $CDCl_3$ (δ = 49.0). Letters in parentheses are the multiplicities determined by DEPT experiments: s, quaternary carbon; d, CH; t, CH_2; q, CH_3. $^{31}P\{^1H\}$ NMR (81.0 MHz) spectra were recorded in δ relative to external H_3PO_4 (δ = 0). IR spectra were recorded with a Hitachi 270-30 spectrophotometer. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-DX300 spectrometer. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel prepacked C.I.G. (Kusano CPS-223L-1) column.

Materials. $Rh(acac)(CO)_2$ was commercially available and purified by sublimation (90 °C/0.2 mmHg) before use. Alkyl vinyl ketone (**2a-b**) and acrylaldehyde (**2c**) are commercially available and were purified by distillation before use.

Diethyl (1-Cyanonethyl)phosphonate (1). Prepared from propiononitrile and diethyl phosphorochloridate according to the literature procedure[9] and purified by MPLC (hexane/1,2-dichloroethane/ethanol = 15/15/2) and distillation: Oil; 80% yield; bp 73—75 °C/0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ = 1.39 (t, J_{H-H} = 7.1 Hz, 6H), 1.57 (dd, J_{P-H} = 16.7, J_{H-H} = 7.3 Hz, 3H), 2.98 (dq, J_{P-H} = 23.4, J_{H-H} = 7.3 Hz, 1H), 4.25 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H), 4.27 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H).

Rhodium-Catalyzed Asymmetric Michael Addition. General Procedure. In a nitrogen atmosphere, $Rh(acac)(CO)_2$ (2.6 mg, 0.010 mmol) and (*R,R*)-(*S,S*)-PhTRAP (8.3 mg, 0.0105 mmol) were dissolved in dry benzene (1—2 mL). Diethyl (1-cyanoethyl)-phosphonate (**1**) (191 mg, 1.0 mmol) was added and the mixture was cooled to 3 °C. Neat **2** (1.5 mmol) was added within 1 min and the mixture was stirred at this temperature for 7—43 h. After **1** was consumed, the solution was passed through a column of silica gel (17 mm×20 mm, EtOAc) to remove the catalyst, and the product was isolated by bulb-to-bulb distillation. The reaction conditions and results are summarized in Table 1.

Diethyl (1-Cyano-1-methyl-4-oxopentyl)phosphonate (3a): Oil; $[\alpha]_D^{20}$ −1.6 (*c* 5.34, $CHCl_3$); 93% ee; bp ca. 140 °C/0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ = 1.39 (t, J_{H-H} = 7.0 Hz, 3H), 1.40 (t, J_{H-H} = 7.0 Hz, 3H), 1.55 (d, J_{P-H} = 15.4 Hz, 3H), 1.9—2.3 (m, 2H), 2.20 (s, 3H), 2.6—3.0 (m, 2H), 4.25 (dq, J_{P-H} = 8.4, J_{H-H} = 7.0 Hz, 2H), 4.27 (dq, J_{P-H} = 8.4, J_{H-H} = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 16.39 (d, J_{P-C} = 5.6 Hz, 2C) (q), 20.13 (d, J_{P-C} = 5.3 Hz) (q), 28.19 (d, J_{P-C} = 3.6 Hz) (t), 30.02 (q), 35.13 (d, J_{P-C} = 146.5 Hz) (s), 39.05 (d, J_{P-C} = 6.8 Hz) (t), 64.13 (d, J_{P-C} = 7.4 Hz) (t), 64.23 (d, J_{P-C} = 7.4 Hz) (t), 119.32 (d, J_{P-C} = 7.5 Hz) (s), 206.14 (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 21.74; IR (neat) 2240, 1724, 1258 cm^{-1}; Anal. Found: C, 50.73; H, 2.85; N, 5.09%. Calcd for $C_{11}H_{20}NO_4P$: C, 50.57; H, 7.72; N, 5.36%.

Diethyl (1-Cyano-1-methyl-4-oxohexyl)phosphonate (3b): Oil; $[\alpha]_D^{20}$ −2.1 (*c* 5.28, $CHCl_3$); 93% ee; bp ca. 140 °C/0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ = 1.08 (t, J_{H-H} = 7.3 Hz, 3H), 1.39 (t, J_{H-H} = 7.1 Hz, 3H), 1.40 (t, J_{H-H} = 7.1 Hz, 3H), 1.55 (d, J_{P-H} = 15.2 Hz, 3H), 1.9—2.4 (m, 2H), 2.50 (q, J_{H-H} = 7.3 Hz, 2H), 2.6—2.9 (m, 2H), 4.26 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H), 4.27 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 7.63 (q), 16.30 (2C, d, J_{P-C} = 5.6 Hz) (q), 19.95 (d, J_{P-C} = 5.2 Hz) (q), 28.08 (d, J_{P-C} = 3.6 Hz) (t), 35.05 (d, J_{P-C} = 146.4 Hz) (s), 35.96 (t), 37.58 (d, J_{P-C} = 6.9 Hz) (t), 64.02 (d, J_{P-C} = 7.3 Hz) (t), 64.10 (d, J_{P-C} = 7.3 Hz) (t), 119.25 (d, J_{P-C} = 7.0 Hz) (s), 208.92 (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 21.89; IR (neat) 2240, 1720, 1258 cm^{-1}; Anal. Found: C, 52.09; H, 7.86; N, 4.92%. Calcd for $C_{12}H_{22}NO_4P$: C, 52.36; H, 8.06; N, 5.09%.

Diethyl (1-Cyano-3-formyl-1-methylpropyl)phosphonate (3c): Oil; $[\alpha]_D^{20}$ −4.9 (*c* 5.28, $CHCl_3$); 92% ee; bp ca. 135 °C/0.25 mmHg; ^{1}H NMR ($CDCl_3$) δ = 1.39 (t, J_{H-H} = 7.1 Hz, 3H), 1.40 (t, J_{H-H} = 7.1 Hz, 3H), 1.57 (d, J_{P-H} = 15.4 Hz, 3H), 1.9—2.4 (m, 2H), 2.7—3.0 (m, 2H), 4.26 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H), 4.28 (dq, J_{P-H} = 8.4, J_{H-H} = 7.1 Hz, 2H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ = 16.38 (d, J_{P-C} = 5.7 Hz, 2C) (q), 19.98 (d, J_{P-C} = 5.3 Hz) (q), 26.75 (d, J_{P-C} = 3.7 Hz) (t), 35.06 (d, J_{P-C} = 146.6 Hz) (s), 39.60 (d, J_{P-C} = 7.0 Hz) (t), 64.26 (d, J_{P-C} = 7.6 Hz, 2C) (t), 119.13 (d, J_{P-C} = 7.4 Hz) (s), 199.43 (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 21.60; IR (neat) 2744, 2240, 1728, 1258 cm^{-1}; Anal. Found: C, 48.33; H, 7.51; N, 5.63%. Calcd for $C_{10}H_{18}NO_4P$: C, 48.58; H, 7.34; N, 5.67%.

Diethyl (1-Cyano-1-methyl-5-phenylpentyl)phosphonate (4). To a suspension of benzyltriphenylphosphonium chloride (692 mg, 1.78 mmol) in 6.4 mL of THF was added 1.1 mL of 1.55 M BuLi/hexane (1.7 mmol) at 0 °C (1 M = 1 mol dm^{-3}). The deep orange solution was stirred at room temperature for 3 h. After the mixture was cooled to −78 °C, (−)-**3c** (399 mg, 1.61 mmol, 91% ee) in 1.6 mL of THF was added dropwise over 1 min. The reaction mixture was stirred at −70 °C for 2 h, and allowed to warm to room temperature. The mixture was diluted with hexane, filtered, and the product was isolated by MPLC (hexane/EtOAc = 1/1.5) to give 449 mg of an oil. The oil was dissolved in 2.5 mL of EtOH, and hydrogenated (50 atm) over 5% Pd/C (45 mg) in an autoclave at room temperature for 1 h. The catalyst was filtered off and the filtrate was evaporated to give 447 mg (86%) of **4**: Oil; $[\alpha]_D^{20}$ −1.12 (*c* 5.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.37 (t, J_{H-H} = 7.0 Hz, 6H), 1.53 (d, J_{P-H} = 15.8 Hz, 3H), 1.5—1.8 (m, 5H), 1.8—2.1 (m, 1H), 2.65 (m, 2H), 4.237 (dq, J_{P-H} = 8.3, J_{H-H} = 7.0 Hz, 2H), 4.243 (dq, J_{P-H} = 8.3, J_{H-H} = 7.0 Hz, 2H), 7.1—7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 16.41 (d, J_{P-C} = 5.6 Hz) (q), 16.43 (d, J_{P-C} = 5.6 Hz) (q), 19.25 (d, J_{P-C} = 5.4 Hz) (q), 24.41 (d, J_{P-C} = 9.1 Hz) (t), 31.23 (t), 33.88 (d, J_{P-C} = 3.9 Hz) (t), 35.58 (t), 35.84 (d, J_{P-C} = 146.0 Hz) (s), 64.03 (d, J_{P-C} = 7.4 Hz) (t), 64.05 (d, J_{P-C} = 7.4 Hz) (t), 119.74 (d, J_{P-C} = 7.8 Hz) (s), 125.83 (d), 128.33 (4C) (d), 141.93 (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 22.62; IR (neat) 2240, 1258 cm^{-1}; Anal. Found: C, 62.96; H, 8.28; N, 4.21%. Calcd for $C_{17}H_{26}NO_3P$: C, 63.14; H, 8.10; N, 4.33%.

Methyl 2-(Dimethoxyphosphinoyl)-2-methyl-6-phenylhexanoate (5). (1-Cyanopentyl)phosphonate (−)-**4** (748 mg, 2.31 mmol) and 47% HBr (2.5 mL) were mixed and refluxed for 24 h. The mixture was evaporated, and the residue was dissolved in ether (2.5 mL). Diazomethane solution in ether was added at 0 °C until the yellow color did not disappear. Preparative thin-layer chromatography [Silica gel (Merck 7747), EtOAc/THF = 7/1] gave the product **5** (302 mg, 40%) and **4** (303 mg, 45%). The latter can be subjected to hydrolysis. **5**: Oil; $[\alpha]_D^{20}$ −2.9 (*c* 4.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.1—1.8 (m, 5H), 1.43 (d, J_{P-H} = 16.6 Hz, 3H), 2.0—2.2 (m, 1H), 2.61 (m, 2H), 3.74 (s, 3H), 3.78 (d, J_{P-H} = 10.8 Hz, 3H), 3.80 (d, J_{P-H} = 10.6 Hz, 3H), 7.1—7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 17.33 (d, J_{P-C} = 4.8 Hz) (q), 23.96 (d, J_{P-C} = 11.7 Hz) (t), 31.47 (t), 33.78 (d, J_{P-C} = 4.2 Hz) (t), 35.51 (t), 48.39 (d, J_{P-C} = 134.7 Hz) (s), 52.62 (q), 53.49 (d, J_{P-C} = 7.3

Hz) (q), 53.74 (d, J_{P-C} = 7.1 Hz) (q), 125.67 (d), 128.23 (2C) (d), 128.32 (2C) (d), 142.22 (s), 171.98 (d, J_{P-C} = 3.5 Hz) (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 29.84; IR (neat) 1738, 1254 cm^{-1}; HRMS (EI): Found: *m/z* 328.1441. Calcd for $C_{16}H_{25}O_5P$: M, 328.1440.

Dimethyl [1-(*N*-Benzyloxycarbonylamino)-1-methyl-5-phenylpentyl]phosphonate (6). Ester (−)-**5** (302 mg, 0.92 mmol) was dissolved in the mixture of 1 mL of 10% aqueous KOH and 1 mL of EtOH, and this solution was hydrolyzed at 50 °C for 2 h. This reaction mixture was cooled and concentrated, then acidified with 6 mol dm^{-3} HCl. The aqueous solution was extracted three times with ether, washed with saturated NaCl, dried over Na_2SO_4 and evaporated to give 284 mg of 2-(dimethoxyphosphinoyl)-2-methyl-6-phenylhexanoic acid. In an argon atmosphere, to an ice-cooled solution of the carboxylic acid in 1,4-dioxane (1 mL) were added diphenyl phosphoroazidate (782 mg, 2.84 mmol) and triethylamine (0.3 mL). The mixture was stirred at room temperature for 6.5 h. The product was isolated by silica gel column chromatography to give 277 mg of an oil. At this stage, an IR spectrum of the product indicated that it was a mixture of the corresponding acyl azide (2144, 1708 cm^{-1}) and isocyanate (2260 cm^{-1}). It was dissolved in 1,2-dichloroethane (1 mL), benzyl alcohol (0.2 mL) was added, and the mixture was refluxed for 40 h. After the mixture was allowed to cool to room temperature, MPLC purification (EtOAc/THF = 7/1) gave 313 mg (81%) of **6**: Oil; $[\alpha]_D^{20}$ −5.9 (*c* 5.01, $CHCl_3$); 88% ee by HPLC [Daicel Chiralpak AD (4.6 mm×250 mm), hexane/2-propanol = 80/20]; ^{1}H NMR ($CDCl_3$) δ = 1.3—2.2 (m, 6H), 1.57 (d, J_{P-H} = 16.4 Hz, 3H), 2.61 (m, 2H), 3.75 (d, J_{P-H} = 10.4 Hz, 3H), 3.76 (d, J_{P-H} = 10.6 Hz, 3H), 4.90 (br d, 1H), 5.06 (s, 2H), 7.1—7.4 (m, 10H); ^{13}C NMR ($CDCl_3$) δ = 20.40 (q), 22.56 (d, J_{P-C} = 7.6 Hz) (t), 31.46 (t), 34.86 (d, J_{P-C} = 1.6 Hz) (t), 35.67 (t), 53.35 (d, J_{P-C} = 7.3 Hz) (q), 53.46 (d, J_{P-C} = 7.4 Hz) (q), 55.34 (d, J_{P-C} = 156.0 Hz) (s), 56.89 (q), 66.50 (t), 125.63 (d), 128.09 (2C) (d), 128.12 (d), 128.22 (2C) (d), 128.33 (2C) (d), 128.47 (2C) (d), 136.33 (s), 142.34 (s), 154.55 (d, J_{P-C} = 7.9 Hz) (s); ^{31}P NMR (81 MHz, $CDCl_3$) δ = 30.31; IR ($CHCl_3$) 3448, 1734, 1248 cm^{-1}; HRMS (EI): Found: *m/z* 419.1889. Calcd for $C_{22}H_{30}NO_5P$: M, 419.1862.

References

1 For reviews, see: a) B. Dhawan and D. Redmore, *Phosphorus and Sulfur*, **32**, 119 (1987). b) K. Yamauchi, *Yuki Gosei Kagaku Kyokaishi*, **46**, 654 (1988). c) V. P. Kukhar, V. A. Soloshonok, and V. A. Solodenko, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **92**, 239 (1994). d) T. Yokomatsu, T. Yamagishi, and S. Shibuya, *Yuki Gosei Kagaku Kyokaishi*, **53**, 881 (1995).

2 a) U. Schöllkopf and R. Schütze, *Liebigs Ann. Chem.*, **1987**, 45. b) S. Hanessian and Y. L. Bennani, *Tetrahedron Lett.*, **31**, 6465 (1990). c) U. Groth, L. Richter, and U. Schöllkopf, *Tetrahedron*, **48**, 117 (1992). d) S. Laschat and H. Kunz, *Synthesis*, **1992**, 90. e) K. M. Yager, C. M. Taylor, and A. B. Smith, III., *J. Am. Chem. Soc.*, **116**, 9377 (1994). f) I. M. Lefebvre and S. A. Evans, Jr., *J. Org. Chem.*, **62**, 7532 (1997).

3 a) U. Schöllkopf, I. Hoppe, and A. Thiele, *Liebigs Ann. Chem.*, **1985**, 555. b) A. Togni and S. D. Pastor, *Tetrahedron Lett.*, **30**, 1071 (1989). c) M. Sawamura, Y. Ito, and T. Hayashi, *Tetrahedron Lett.*, **30**, 2247 (1989). d) J. P. Genet, S. Juge, I. Besnier, J. Uziel, D. Ferroud, N. Kardos, S. Achi, J. Ruiz-Montes, and S. Thorimbert, *Bull. Soc. Chim. Fr.*, **127**, 781 (1990). e) I. C. Baldwin and J. M. J. Williams, *Tetrahedron: Asymmetry*, **6**, 679 (1995). f) M. Kitamura, M. Tokunaga, T. Pham., W. D. Lubell, and R. Noyori, *Tetrahedron Lett.*, **36**, 5769 (1995). g) H. Sasai, S. Arai, Y. Tahara, and M. Shibasaki, *J. Org. Chem.*, **60**, 6656 (1995). h) H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, and M. Shibasaki, *J. Am. Chem. Soc.*, **120**, 3089 (1998).

4 For stoichiometric reaction, see: a) A. Studer and D. Seebach, *Heterocycles*, **40**, 357 (1995). For catalytic reaction, see: b) R. Kuwano, R. Nishio, and Y. Ito, *Org. Lett.*, **1**, 837 (1999).

5 For resolution of α-alkylated α-amino phosphonic acid derivatives, see: a) Y. P. Belov, V. A. Davankov, and S. V. Rogozhin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1977**, 1596. b) A. N. Chekhlov, Y. P. Belov, I. V. Martynov, and A. Y. Aksinenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1986**, 2821.

6 a) M. Sawamura, H. Hamashima, M. Sugawara, R. Kuwano, and Y. Ito, *Organometallics*, **14**, 4549 (1995). b) R. Kuwano, M. Sawamura, S. Okuda, T. Asai, Y. Ito, M. Redon, and A. Krief, *Bull. Chem. Soc. Jpn.*, **70**, 2807 (1997).

7 a) M. Sawamura, H. Hamashima, and Y. Ito, *J. Am. Chem. Soc.*, **114**, 8295 (1992). b) M. Sawamura, H. Hamashima, and Y. Ito, *Tetrahedron*, **50**, 4439 (1994). c) M. Sawamura, H. Hamashima, H. Shinoto, and Y. Ito, *Tetrahedron Lett.*, **36**, 6479 (1995).

8 M. Sawamura, M. Sudoh, and Y. Ito, *J. Am. Chem. Soc.*, **118**, 3309 (1996).

9 J. P. Albarella, *J. Org. Chem.*, **42**, 2009 (1977).