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Enantioselective Synthesis of α-Hydroxyphosphinic Acid Derivatives through Hydrophosphinylation of Aldehydes Catalyzed by Al-Li-BINOL Complex

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Abstract: The first catalytic asymmetric synthesis of (*S*)-α-hydroxy-H-phosphinates and (*S,S*)-α,α′-dihydroxyphosphinates were achieved by the reaction of methyl phosphinate with aldehydes in the presence of Al-Li-BINOL complex.

In the last decade, α-substituted phosphinic acid derivatives have attracted significant attentions due to their usefulness both in the development of catalytic antibodies[1] and protease inhibitors.[2] Especially, some chiral α-hydroxyphosphinyl peptides functioned as a good transition state mimic of peptide hydrolysis[3] and showed significant inhibitory activity for HIV protease.[4] Our interest is to search the efficient method for the synthesis of chiral α-hydroxyphosphinic acid derivatives. Previously, chiral α-hydroxyphosphinate derivatives have been synthesized by the Grignard alkylation of suitable protected α-hydroxyphosphinyl chlorides, prepared from the corresponding chiral α-hydroxyphosphonates via sequential deesterification and chlorination.[3] Alternative synthesis of α-hydroxyphosphinates was achieved by applying hydrophosphinylation of aldehydes with methyl phosphinate under thermal conditions, generated from anhydrous phosphinic acid and trimethyl orthoformate *in situ*.[5] In this synthesis, concomitant hydrophosphinylation of aldehydes with the transiently produced α-hydroxy-H-phosphinates readily occured to give α,α′-dihydroxyphosphinates as a mixture of diastereomers.[6,7] The method has not been applied to chiral synthesis of the α-hydroxy-H-phosphinates and α,α′-dihydroxyphosphinates. We have studied the catalytic asymmetric hydrophosphinylation of aldehydes with methyl phophinate as an extension of our previous works on asymmetric hydrophosphonylation of aldehydes catalyzed by chiral metal alkoxides.[8,9] We now disclose a new method for the enantioselective synthesis of α-hydroxy-H-phosphinates, which were amenable intermediates for the synthesis of several chiral α-hydroxyalkylphosphinates including symmetrical and pseudo symmetrical α,α′-dihydroxyphosphinates as well as closely related compounds (Scheme 1). In this paper, we describe the experimental details of our study.

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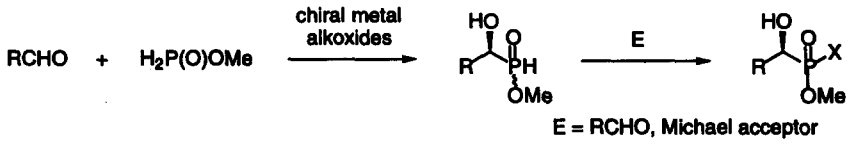
Scheme 1



The binaphtol-modified heterobimetallic complexes such as La-Li-BINOL (LLB),[8b,c,9] Al-Li-BINOL (ALB),[8d,10] and La-K-BINOL (LPB)[11] have been shown to be efficient catalysts for asymmetric addition of dialkyl phosphite to aldehydes or imines. We attempted to apply the heterobimetallic catalysts to the asymmetric hydrophosphinylation of aldehydes. First, benzaldehyde was treated with methyl phosphinate in the presence of the binaphtol-modified heterobimetallic complexes in THF under several representative conditions to verify an effective catalytic system for the reaction. To isolate the desired α-hydroxy-H-phosphinate **1a**, a large excess (5.0 equiv.) of methyl phosphinate was used. The results of this exploratory study are summarized in Table 1.

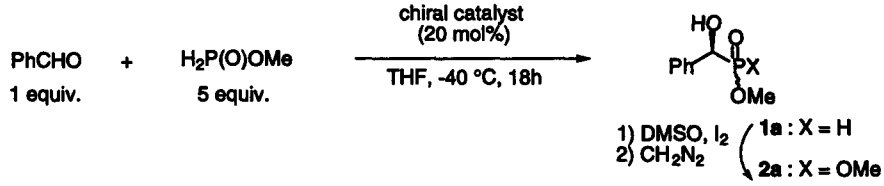
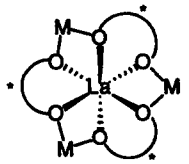


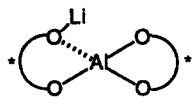
Table 1 Hydrophosphinylation of benzaldehyde catalyzed by heterobimetallic complexes

entry	chiral catalyst (mol%)	temp (°C)	yield (%) of **1a**[a]	ee (%) of **2a**[b]
1	LLB (20)	-40	0	
2	LPB (20)	-40	76	1
3	ALB (20)	-40	62	85
4	ALB (20)	0	54	51
5	ALB (5)	-40	0	

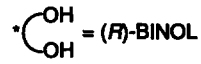
[a] Isolated yield. [b] Determined by HPLC analysis.



LLB: M = Li
LPB: M = K



ALB

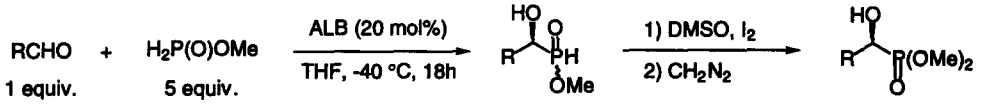


No hydrophosphinylation products were detected when the reaction was carried out in the presence of LLB (entry 1). However, the hydrophosphinylation proceeded in a desired manner to give **1a** as a 1:1 mixture of

the diastereomers, upon conducting the reaction under the influence of a catalytic amount (20 mol%) of LPB or ALB at -40 °C (entries 2 and 3). The optical purity of **1a** was determined by HPLC analysis on a chiral phase (DAICEL CHIRALPAK AS column, hexane:EtOH = 9:1) after leading to known α-hydroxyphosphonate **2a** through oxidation with DMSO in the presence of iodine,[12] followed by methylation with CH_2N_2.[13] While the phosphonate **2a** derived from the reaction with LPB was almost racemic (entry 2), the optical purity of **2a** obtained from the reaction catalyzed by ALB was determined to be 85 %ee (entry 3). The results show that ALB is a good catalyst for the hydrophosphinylation among the heterobimetallic complexes examined. The catalytic activity of ALB for the hydrophosphinylation seems to work effectively at -40 °C in the presence of 20 mol% of the catalyst. Significant decrease in the enantioselectivity (51 %ee) was observed when the reaction was carried out at 0 °C under the influence of 20 mol% of ALB (entry 4). No hydrophosphinylation products were obtained when the reaction was carried out with 5 mol% of ALB (entry 5).

The hydrophosphinylation of *p*-tolualdehyde and isobutyraldehyde also proceeded enantioselectively to give **1b** and **1c** in 81 % and 37 % yield, respectively, under the conditions using 20 mol% of ALB at -40 °C (Scheme 2). The optical purity of **1b** and **1c** was determined to be 79 %ee and 43 %ee, respectively, as analyzing the derived phosphonates **2b** and **2c**. The hydrophosphonylation of aromatic aldehydes using ALB was reported to proceed with good enantioselectivity, but low for the reaction of aliphatic aldehydes.[10a] The reactivity of methyl phosphinate to aldehydes promoted by ALB was found to be similar to that of dimethyl phosphite. The absolute configuration of **2a-c** was determined to be *S* by chiroptical comparison with those reported.[10a,14]

Scheme 2

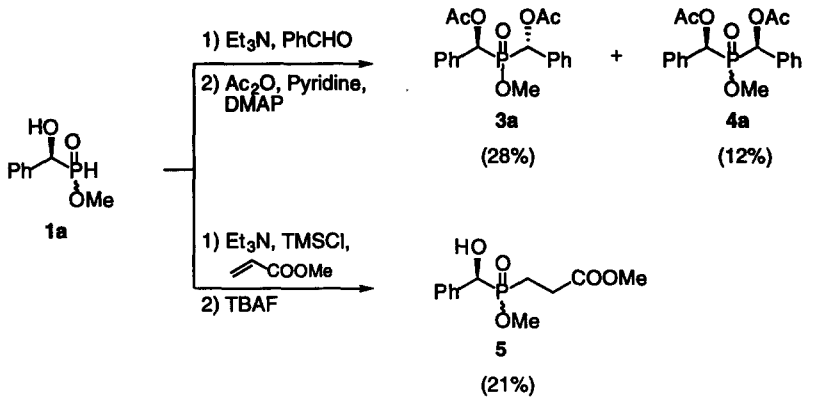


1b: R = 4-Me-C_6H_4, 81 %yield, 79 %ee
1c: R = *i*-Pr, 37 %yield, 43 %ee

2b,c

We next examined the reactions of **1a** with electrophiles. Treatment of **1a** with 1.2 equiv. of benzaldehyde in the presence of 1.2 equiv. of Et_3N, followed by acetylation of the reaction products gave α,α′-dihydroxyphosphinate derivatives **3a** (28%) and **4a** (12%) in a low diastereoselectivity (Scheme 3). The Michael reaction of **1a** with methyl acrylate in the presence of Et_3N gave only trace amount of the adduct **5**. However, when the acrylate was treated with **1a** in the presence of both Et_3N and TMSCl,[15] the Michael adduct **5** was isolated in 21% yield, after desilylation of the resulting reaction product with Bu_4NF. Although a further optimization for these reactions is needed, the results suggest that the hydrophosphinylation and the Michael reaction with α-hydroxy-H-phosphinate **1a** would be potentially useful for the synthesis of both symmetrical and unsymmetrical chiral α-hydroxyphosphinate derivatives.[16]

Scheme 3



Next, we examined straightfoward methodology for the preparation of α,α′-dihydroxyphosphinates by the reaction of methyl phosphinate with excess amounts of aldehydes catalyzed by ALB. In these reactions, we expected the diastereoselectivity might be improved by double asymmetric induction arising from the chiral α-hydroxy-H-phosphinate and ALB. Treatment of methyl phosphinate with 2.2 equiv. of aldehydes and 20 mol% ALB in THF at -40 °C for 18 h, followed by acetylation, gave α,α′-dihydroxyphosphinate derivatives **3a-d** and **4a-d** in yields shown in Table 2.[17]

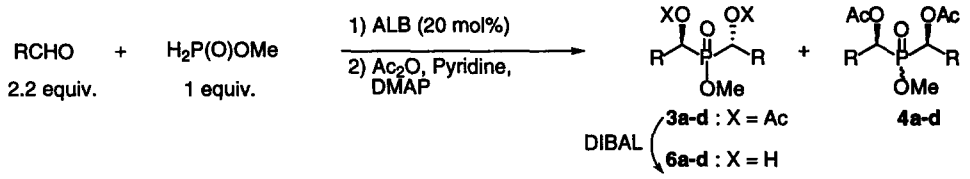


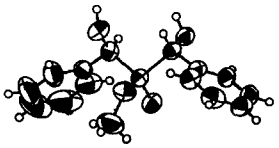
Table 2 The reactions of methyl phosphinate with 2.2 equiv. of aldehydes catalyzed by ALB

			3		4
entry[a]	R	product	ee (%)[b]	yield (%)[c]	yield (%)[c]
1	Ph	**a**	80[d]	43	20
2	4-Me-C_6H_4	**b**	82	35	20
3	4-Cl-C_6H_4	**c**	61	34	32
4	(*E*)-PhCH:CH	**d**	67	14	20

[a] All reactions were carried out for 18 h at -40 °C. [b] Determined by ^{31}P NMR analysis of the corresponding MTPA ester. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the corresponding MTPA ester.

In all cases, α-hydroxy-H-phosphinates were not observed by the TLC monitoring. While the preferable diastereoselection for *anti* stereochemistry regarding the stereogenic centers were observed in some cases (entries 1 and 2), the extent of diastereoselectivities was low. These results indicated that double asymmetric induction did

not take place in the second hydroxyalkylation step. The acetyl group of **3a-d** could be removed by treatment with DIBAL to give corresponding α,α'-dihydroxyphosphinates **6a-d**. The optical purity of **3a** and **3b** was determined to be 80 %ee and 82 %ee respectively, by ^{1}H or ^{31}P NMR analysis of the corresponding Mosher esters (entries 1 and 2). The slight decrease of enantioselectivity was observed in the reaction of the aromatic aldehyde posessing an electron-withdrawing group and the α,β-unsaturated aldehyde (entries 3 and 4). The absolute configuration of **6a** was determined to be *S,S* by X-ray crystallographic analysis. The stereochemistry of **6b-d** was assigned to be *S,S* configuration by similarity in ^{31}P NMR spectrum of (*R*)-MTPA esters to that derived from **6a** (Table 3). In all cases, ^{31}P signals due to (*R*)-MTPA-(*S,S*)-**6a-d** were observed at lower field than those arising from (*R*)-MTPA-(*R,R*)-**6a-d**.[18]



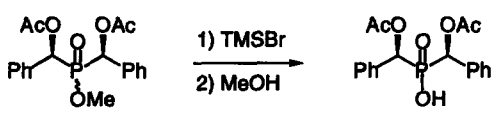
ORTEP drawing of **6a**

Table 3 ^{31}P NMR (162 MHz, $CDCl_3$) data of (*R*)-MTPA esters of **6a-d**

6	(*R*)-MTPA-(*S,S*)-**6a-d** (δ ppm)	(*R*)-MTPA-(*R,R*)-**6a-d** (δ ppm)
6a	36.40	35.72
6b	35.10	34.43
6c	35.24	34.70
6d	36.16	35.82

The relative configuration of **4a** was estimated to be *syn* stereochemistry after converting to the free acid **7** by transesterification with TMSBr, followed by methanolysis (Scheme 4).[19] The signals for ^{31}P NMR spectrum of **4a** were observed at 38.97 and 37.29 ppm in a ratio of 1.8:1, indicating **4a** would be a mixture of diastereomers arising from the chirality of the phosphinate group. The only one signal could be observed at 32.65 ppm in that of **7**. The optical rotation of **7** showed almost zero; this fact also supported the assignment. On the basis of these data, the relative configuration of **4a** was determined to be *syn* stereochemistry.

Scheme 4



4a **7**

4a: ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.97, 37.29

7: ^{31}P NMR (162 MHz, CD_3OD) δ 32.65 $[\alpha]_D^{20}$ = -1.6 (c 0.5, MeOH)

In conclusion, we have developed hydrophosphinylation of aldehydes catalyzed by ALB to give α-hydroxy-H-phosphinates, which allowed conversion to chiral α-hydroxyphosphinates by the reaction with electrophile such as aldehydes or Michael acceptors. Moreover, straightforward synthesis of α,α′-dihydroxyphosphinates could be achieved through the hydrophosphinylation using excess amounts of aldehydes albeit with low diastereoselectivities.

Acknowledgements

The authors wish to thank Mr. Haruhiko Fukaya (the analytical center of this university) for his help in carrying out the X-ray crystallographic analysis.

Experimental Section

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on a Finnigan TSQ-700 or a VG Auto Spec E. Elemental analysis were recorded on an Elemental Vavio EL. NMR spectra were obtained on a Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ = 7.26) for $CDCl_3$ solution or CH_3OH (δ = 4.78) for CD_3OD solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ or CD_3OD are reported relative to the $CDCl_3$ resonance (δ = 77.0) and CD_3OD resonance (δ = 49.0), respectively. The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ = 0) with broad-band ^{1}H decoupling. All reactions were conducted under nitrogen.

General procedure for the synthesis of α-hydroxy-H-phosphinate 1a-c using ALB at -40 °C. A mixture of anhydrous phosphinic acid (2.64 g, 40.0 mmol) and trimethyl orthoformate (21.9 mL, 200 mmol) was stirred for 1.5h at room temperature. To this solution was added 0.1 M THF solution of ALB (16.0 mL, 1.60 mmol), prepared from (*R*)-BINOL (916 mg, 3.20 mmol) and $LiAlH_4$ (60.7 mg, 1.60 mmol) *in situ* according to Shibasaki's method,[10] and a solution of aldehyde (8.00 mmol) in THF (20 mL) at -40 °C under stirring. After stirring for 18h at the same temperature, the mixture was diluted with 1N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue which was chromatographed on silica gel (EtOAc to $CHCl_3$:MeOH = 20:1) to give **1a-c**.

Hydrophosphinylation of benzaldehyde catalyzed by LLB and LPB. The reactions with LLB and LPB were carried out in an identical fashion to that described for the ALB catalyzed reaction except for the use of a THF solution of LLB and LPB prepared as follows.

THF solution of LLB. Prepared from $LaCl_3 \cdot 7H_2O$ (780 mg, 2.10 mmol), (*R*)-BINOL (1.62g, 5.68 mmol), 1.25 M hexane solution of *n*-BuLi (9.08 mL, 11.4 mmol), and NaOBu^t (60.5 mg, 0.63 mmol) in THF (54 mL) according to Shibasaki's method.[9b]

THF solution of LPB. Prepared from $La(OPr^i)_3$ (446 mg, 1.41 mmol), (*R*)-BINOL (1.21 g, 4.20 mmol), 0.5 M toluene solution of KHMDS (8.40 mL, 4.20 mmol), and water (25.5 mg, 1.41 mmol) in THF (28.2 mL) according to Shibasaki's method.[11a]

(*S*,R_P)- and (*S*,S_P)-Methyl phenylhydroxymethylphosphinate 1a. Yield (923 mg, 62%); oil; $[\alpha]_D^{20}$ -31.4 (c 1.0, MeOH) for a sample of 85 %ee; ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.25 (5H, m), 6.81 (0.5H, d, *J* = 556.8 Hz), 6.75 (0.5H, d, *J* = 557.8 Hz with small splits), 4.97 (0.5H, d, *J* = 7.7 Hz), 4.94 (0.5H, d, *J* = 11.7 Hz), 3.75 (1.5H, d, *J* = 11.4 Hz), 3.62 (1.5H, d, *J* = 11.4 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 41.04, 40.67; IR (neat) 3259, 1223 cm^{-1}; EIMS *m/z* 186 (M^+). High resolution MS calcd for $C_8H_{11}O_3P$ (M^+): 186.0446. Found: 186.0451. $[\alpha]_D^{20}$ -13.5 (c 0.9, MeOH) for a sample of 51 %ee. $[\alpha]_D^{20}$ -1.43 (c 0.8, MeOH) for a sample of 1 %ee.

(*S*,R_P)- and (*S*,S_P)-Methyl (4-methylphenyl)hydroxymethylphosphinate 1b. Yield (1.29 g, 81%); mp 44-46 °C; $[\alpha]_D^{20}$ -29.9 (c 1.4, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.26 (2H, d, *J* = 8.1 Hz), 7.15 (2H, d, *J* = 7.8 Hz), 6.78 (0.5H, d, *J* = 555.0 Hz), 6.74 (0.5H, d, *J* = 556.3 Hz with small splits), 4.91 (0.5H, d, *J* = 7.3 Hz), 4.89 (0.5H, d, *J* = 12.3 Hz), 3.74 (1.5H, d, *J* = 11.4 Hz), 3.62 (1.5H, d, *J* = 11.4 Hz), 2.28 (3H, s); ^{31}P NMR (162 MHz, CD_3OD) δ 41.45, 40.83; IR (neat) 3188, 1225 cm^{-1}; EIMS *m/z* 200 (M^+). High resolution MS calcd for $C_9H_{13}O_3P$ (M^+): 200.0602. Found: 200.0608.

(*S*,R_P)- and (*S*,S_P)-Methyl 1-hydroxy-2-methylpropylphosphinate 1c. Yield (445 mg, 37%); oil; $[\alpha]_D^{20}$ +2.32 (c 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (0.5H, d, *J* = 542.1 Hz), 6.80 (0.5H, d, *J* = 545.3 Hz with small splits), 3.80 (1.5H, d, *J* = 11.4 Hz), 3.77 (1.5H, d, *J* = 11.5 Hz), 3.57-3.50 (1H, m), 2.10-1.96 (1H, m), 1.02-0.99 (6H, m); ^{31}P NMR (162 MHz, CD_3OD) δ 45.74, 43.96; IR (neat) 3289, 1200 cm^{-1}; EIMS *m/z* 153 (MH^+). High resolution MS calcd for $C_5H_{14}O_3P$ (MH^+): 153.0681. Found: 153.0678.

General procedure for conversion of 1a-c to α-hydroxyphosphonates 2a-c. A solution of **1a-c** (1.84 mmol), DMSO (0.13 mL, 1.84 mmol), and iodine (5.1 mg, 0.02 mmol) in THF (5 mL) was stirred at 60 °C for 5h. The mixture was evaporated to give a residue. To a stirred Et_2O solution of CH_2N_2 (12 mL), prepared from 77% *N*-nitroso-*N*-methylurea (492 mg, 3.68 mmol), was added a solution of the residue in Et_2O:MeOH = 10:1 (7.7 mL) at 0 °C and the solution was stirred for 30 minutes at the same temperature. After decomposition of excess CH_2N_2 with AcOH (0.05 mL), the mixture was diluted with sat. $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue which was chromatographed on silica gel (EtOAc) to give **2a-c**.

(*S*)-Dimethyl phenylhydroxymethylphosphonate 2a. Yield (127 mg, 32%); mp 82-84 °C; $[\alpha]_D^{20}$ -42.7 (c 1.0, $CHCl_3$) for a sample of 85 %ee. mp 87-89 °C; $[\alpha]_D^{20}$ -17.5 (c 0.9, $CHCl_3$) for a sample of 51 %ee. mp 92-94 °C; $[\alpha]_D^{20}$ -0.68 (c 0.9, $CHCl_3$) for a sample of 1 %ee. The ^{1}H NMR spectrum was identical to that of the authentic sample reported in the literature.[10a,14]

(*S*)-Dimethyl (4-methyl)phenylhydroxymethylphosphonate 2b. Yield (199 mg, 47%); mp 75-77 °C; $[\alpha]_D^{20}$ -41.0 (c 1.0, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of the authentic sample reported in the literature.[10a,14b]

(*S*)-Dimethyl 1-hydroxy-2-methylpropylphosphonate 2c. Yield (38 mg, 11%); oil; $[\alpha]_D^{20}$ -1.83 (c 0.2, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of the authentic sample reported in the literature.[10a]

Reaction of 1a with benzaldehyde. To a stirred solution of **1a** (186 mg, 1.00 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.17 mL, 1.20 mmol) and a solution of benzaldehyde (127 mg, 1.20 mmol) in CH_2Cl_2 (1 mL) at 0 °C and then mixture was stirred for 12h at room temperature. The mixture was diluted with sat. $KHSO_4$ and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of

solvent gave a residue. Acetylation of this residue with Ac_2O (0.33 mL, 3.00 mmol) in CH_2Cl_2 (3 mL) in the presence of pyridine (0.29 mL, 3.60 mmol) and DMAP (24.4 mg, 0.20 mmol) followed by a usual work-up gave a residue which was chromatographed on silica gel (hexane:EtOAc = 2:1 to 1:1) to give **3a** (104 mg, 28%) and **4a** (46 mg, 12%).

(*S*,*S*)-Methyl di(phenylacetyloxymethyl)phosphinate 3a. Mp 114-116 °C; $[\alpha]_D^{20}$ -3.5 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.33 (10H, m), 6.38 (1H, d, J = 6.1 Hz), 6.24 (1H, d, J = 6.8 Hz), 3.17 (3H, d, J = 10.1 Hz), 2.21 (3H, s), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (d, J_{PC} = 9.3 Hz), 169.1 (d, J_{PC} = 8.5 Hz), 132.1, 132.0, 129.0, 128.7, 128.6, 128.5 (2 carbons), 127.2, 70.2 (d, J_{PC} = 109.6 Hz), 69.8 (d, J_{PC} = 117.6 Hz), 53.4 (d, J_{PC} = 7.3 Hz), 20.8, 20.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.37; IR (KBr) 1766, 1224 cm^{-1}; EIMS *m/z* 377 (MH^+). Anal. calcd. for $C_{19}H_{21}O_6P$: C, 60.63; H, 5.62. Found: C, 60.61; H, 5.65.

(S,R,R_P)- and (S,R,S_P)-Methyl di(phenylacetyloxymethyl)phosphinate 4a. This compound was obtained as a mixture of diastereomer in a ratio of 2.3:1. Mp 93-96 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.33 (10H, m), 6.21 (0.6H, d, J = 8.8 Hz), 6.02 (1.4H, d, J = 6.5 Hz), 3.55 (2.1H, d, J = 10.3 Hz), 3.37 (0.9H, d, J = 10.1 Hz), 2.14 (4.2H, s), 2.04 (1.8H, s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.97, 37.29; EIMS *m/z* 377 (MH^+).

(S,R_P)- and (S,S_P)-Methyl (phenylhydroxymethyl)methoxycarbonylethylphosphinate 5. To a stirred solution of **1a** (279 mg, 1.50 mmol) in CH_2Cl_2 (1.5 mL) was added Et_3N (0.46 mL, 3.30 mmol), TMSCl (0.42 mL, 3.30 mmol) and a solution of methyl acrylate (194 mg, 2.25 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C and then mixture was stirred for 19h at room temperature. The mixture was diluted with sat. $KHSO_4$ and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue. Desilylation of this residue with 1M THF solution of Bu_4NF (1.60 mL, 1.60 mmol) in THF (3 mL) followed by a usual work-up gave a residue which was chromatographed on silica gel (hexane:EtOAc = 1:1 to EtOAc) to give **5** (85 mg, 21%) as a mixture of diastereomer in a ratio of 1.3:1. Oil; $[\alpha]_D^{20}$ -6.48 (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.32 (5H, m), 5.02 (0.6H, dd, J = 5.1, 9.1 Hz), 4.97 (0.4H, dd, J = 6.2, 6.2 Hz), 3.67 (1.3H, s), 3.66 (1.7H, s), 3.62 (1.7H, d, J = 10.1 Hz), 3.58 (1.3H, d, J = 10.1 Hz), 2.63-2.44 (2H, m), 2.11-1.83 (2H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.29, 51.83; IR (neat) 3249, 1737, 1240 cm^{-1}; EIMS *m/z* 272 (M^+). High resolution MS calcd for $C_{12}H_{17}O_5P$ (M^+): 272.0814. Found: 272.0814.

General procedure for the reaction of methyl phosphinate with 2.2 equiv. of aldehyde catalyzed by ALB. A mixture of anhydrous phosphinic acid (528 mg, 8.00 mmol) and trimethyl orthoformate (4.38 mL, 40.0 mmol) was stirred for 1.5h at room temperature. To this solution was added 0.1 M THF solution of ALB (16.0 mL, 1.60 mmol), prepared from (*R*)-BINOL (916 mg, 3.20 mmol) and $LiAlH_4$ (60.7 mg, 1.60 mmol) *in situ*, and a solution of aldehyde (17.6 mmol) in THF (20 mL) at -40 °C under stirring. After stirring for 18h at the same temperature, the mixture was diluted with 1N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue. Acetylation of this residue with Ac_2O (2.70 mL, 24.0 mmol) in CH_2Cl_2 (24 mL) in the presence of pyridine (2.30 mL, 28.8 mmol) and DMAP (195 mg, 1.60 mmol) followed by a usual work-up gave a residue which was chromatographed on silica gel (hexane:EtOAc = 2:1 to 1:1) to give **3a-d** and **4a-d**.

(*S*,*S*)-Methyl di(phenylacetyloxymethyl)phosphinate 3a. Yield (1.29 g, 43%); $[\alpha]_D^{20}$ -4.5 (c 1.0, $CHCl_3$). The ^1H NMR spectrum was identical with that of the authentic sample prepared by the reaction of **1a** with benzaldehyde.

(*S*,*R*,R_P)- and (*S*,*R*,S_P)-Methyl di(phenylacetyloxymethyl)phosphinate 4a. This compound was obtained as a mixture of diastereomer in a ratio of 1.8:1. Yield (602 mg, 20%). The ^1H NMR spectrum was identical with that of the authentic sample prepared by the reaction of **1a** with benzaldehyde.

(*S*,*S*)-Methyl di[1-acetyloxy-1-(4-methylphenyl)methyl]phosphinate 3b. Yield (1.14 g, 35%); mp 111-113 °C; $[\alpha]_D^{20}$ -16.9 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (4H, m), 7.18 (4H, d, J = 7.9 Hz), 6.32 (1H, d, J = 5.2 Hz), 6.19 (1H, d, J = 6.4 Hz), 3.20 (3H, d, J = 10.1 Hz), 2.34 (6H, s), 2.19 (3H, s), 2.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (d, J_{PC} = 9.4 Hz), 169.2 (d, J_{PC} = 8.5 Hz), 139.0, 138.6, 129.3 (4 carbons), 128.5, 127.3, 69.7 (d, J_{PC} = 110.2 Hz), 69.3 (d, J_{PC} = 117.9 Hz), 53.4 (d, J_{PC} = 7.3 Hz), 21.2, 21.1, 20.8, 20.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.54; IR (KBr) 1746, 1232 cm^{-1}; EIMS *m/z* 406 (M^+). Anal. calcd. for $C_{21}H_{25}O_6P$: C, 62.37; H, 6.23. Found: C, 62.39; H, 6.18.

(*S*,*R*,R_P)- and (*S*,*R*,S_P)-Methyl di[1-acetyloxy-1-(4-methylphenyl)methyl]phosphinate 4b. This compound was obtained as a mixture of diastereomer in a ratio of 2.6:1. Yield (650 mg, 20%); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1.1H, d, J = 8.0 Hz), 7.30 (2.9H, d, J = 8.0 Hz), 7.16 (4H, d, J = 7.4 Hz), 6.14 (0.6H, d, J = 8.1 Hz), 5.97 (1.4H, d, J = 6.1 Hz), 3.56 (2.2H, d, J = 10.3 Hz), 3.37 (0.8H, d, J = 10.1 Hz), 2.33 (6H, s), 2.13 (4.3H, s), 2.03 (1.7H, s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.35, 36.53; EIMS *m/z* 405 (M^+-H).

(*S*,*S*)-Methyl di[1-acetyloxy-1-(4-chlorophenyl)methyl]phosphinate 3c. Yield (1.21 g, 34%); mp 115-117 °C; $[\alpha]_D^{20}$ -10.5 (c 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.34 (8H, m), 6.32 (1H, d, J = 6.2 Hz), 6.19 (1H, d, J = 7.1 Hz), 3.22 (3H, d, J = 10.1 Hz), 2.20 (3H, s), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (d, J_{PC} = 9.4 Hz), 169.0 (d, J_{PC} = 8.4 Hz), 135.3, 134.9, 130.5, 130.3, 129.8, 128.9 (2 carbons), 128.6, 69.0 (d, J_{PC} = 109.9 Hz), 68.6 (d, J_{PC} = 117.9 Hz), 53.6 (d, J_{PC} = 7.4 Hz), 20.7 (2 carbons); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.87; IR (KBr) 1757, 1229 cm^{-1}; EIMS *m/z* 445 (M^+). Anal. calcd. for $C_{19}H_{19}Cl_2O_6P$: C, 51.25; H, 4.30. Found: C, 51.51; H, 4.56.

(*S*,*R*,R_P)- and (*S*,*R*,S_P)-Methyl di[1-acetyloxy-1-(4-chlorophenyl)methyl]phosphinate 4c. This compound was obtained as a mixture of diastereomer in a ratio of 2.2:1. Yield (1.14 g, 32%); mp 132-135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (8H, m), 6.17 (0.6H, d, J = 8.9 Hz), 5.98 (1.4H, d, J = 6.4 Hz), 3.61 (2.1H, d, J = 10.3 Hz), 3.43 (0.9H, d, J = 10.2 Hz), 2.15 (4.1H, s), 2.04 (1.9H, s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.06, 35.86; EIMS *m/z* 445 (M^+).

(*S*,*S*)-Methyl di(1-acetyloxy-3-phenyl-2*E*-propenyl)phosphinate 3d. Yield (479 mg, 14%); mp 88-90 °C; $[\alpha]_D^{20}$ -8.9 (c 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (10H, m), 6.83-6.72 (2H, m), 6.30-6.25 (2H, m), 6.06 (1H, dd, J = 7.2, 7.2 Hz), 5.93 (1H, dd, J = 8.3, 8.3 Hz), 3.81 (3H, d, J = 10.1 Hz), 2.18 (3H, s), 2.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (d, J_{PC} = 8.0 Hz), 169.2 (d, J_{PC} = 8.0 Hz), 137.0, 136.9, 135.5, 135.3, 128.7 (2 carbons), 128.5 (2 carbons), 126.9, 126.8, 118.9 (d, J_{PC} = 5.0 Hz), 118.6 (d, J_{PC} = 4.0 Hz), 69.5 (d, J_{PC} = 116.3 Hz), 69.1 (d, J_{PC} = 111.3 Hz), 53.8 (d, J_{PC} = 7.5 Hz), 20.8 (2 carbons); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.94; IR (KBr) 1751, 1223 cm^{-1}; EIMS *m/z* 428 (M^+). High resolution MS calcd for $C_{21}H_{22}O_4P$ (M^+-OAc): 369.1256. Found: 369.1240.

(*S*,*R*,*R*$_P$)- and (*S*,*R*,*S*$_P$)-Methyl di(1-acetyloxy-3-phenyl-2*E*-propenyl)phosphinate 4d. This compound was obtained as a mixture of diastereomer in a ratio of 7.6:1. Yield (685 mg, 20%); mp 82-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (10H, m), 6.71-6.66 (2H, m), 6.31-6.24 (2H, m), 5.98-5.94 (2H, m), 3.89 (2.7H, d, *J* = 10.2 Hz), 3.77 (0.3H, d, *J* = 11.0 Hz), 2.15 (5.3H, s), 2.14 (0.7H, s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.90, 37.85; EIMS *m/z* 428 (M^+).

General procedure for reductive deacetylation of 3a-d. To a stirred solution of **3a-d** (1.72 mmol) in CH_2Cl_2 (5.50 mL) was added 1 M solution of DIBAL in toluene (6.02 mL, 6.02 mmol) at -78 °C and the mixture was stirred for 1h at the same temperature. The mixture was then diluted with 1N HCl. The resulting gel was filtered and the filtrate was extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue which was chromatographed on silica gel (hexane:EtOAc = 1:1 to EtOAc) to give **6a-d.**

(*S*,*S*)-Methyl di(phenylhydroxymethyl)phosphinate 6a. Yield (246 mg, 49%); mp 160-162 °C; $[\alpha]_D^{20}$ -28.3 (c 0.8, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.45-7.20 (10H, m), 5.29 (1H, d, *J* = 7.2 Hz), 5.27 (1H, d, *J* = 6.3 Hz), 3.04 (3H, d, *J* = 9.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 138.2, 138.1, 129.2, 129.0, 128.8, 128.7, 128.3 (2 carbons), 70.9 (d, J_{PC} = 104.6 Hz), 70.0 (d, J_{PC} = 110.7 Hz), 53.4 (d, J_{PC} = 7.9 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 46.98; IR (KBr) 3402, 1171 cm^{-1}; EIMS *m/z* 277 (M^+-CH_3). Anal. calcd. for $C_{15}H_{17}O_4P$: C, 61.64; H, 5.86. Found: C, 61.87; H, 5.90.

(*S*,*S*)-Methyl di[1-hydroxy-1-(4-methylphenyl)methyl]phosphinate 6b. Yield (237 mg, 43%); mp 171-174 °C; $[\alpha]_D^{20}$ -40.1 (c 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (4H, d, *J* = 7.8 Hz), 7.11 (4H, d, *J* = 7.8 Hz), 5.22 (1H, d, *J* = 6.5 Hz), 5.21 (1H, d, *J* = 5.4 Hz), 3.05 (3H, d, *J* = 9.7 Hz), 2.26 (6H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 139.0, 135.1, 129.9 (4 carbons), 129.0, 128.3, 70.5 (d, J_{PC} = 104.8 Hz), 69.9 (d, J_{PC} = 110.4 Hz), 53.5 (d, J_{PC} = 7.7 Hz), 21.3 (2 carbons); ^{31}P NMR (162 MHz, CD_3OD) δ 46.98; IR (KBr) 3351, 1147 cm^{-1}; API (Atmospheric Pressure Ionization) MS *m/z* 321 (MH^+). Anal. calcd. for $C_{17}H_{21}O_4P$: C, 63.74; H, 6.61. Found: C, 63.66; H, 6.75.

(*S*,*S*)-Methyl di[1-hydroxy-1-(4-chlorophenyl)methyl]phosphinate 6c. Yield (229 mg, 37%); mp 166-171 °C; $[\alpha]_D^{20}$ -29.8 (c 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.43-7.28 (8H, m), 5.29 (1H, d, *J* = 5.4 Hz), 5.27 (1H, d, *J* = 4.1 Hz), 3.11 (3H, d, *J* = 9.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 137.0 (2 carbons), 135.0, 134.8, 130.4, 129.8, 129.3 (2 carbons), 69.8 (d, J_{PC} = 105.1 Hz), 69.3 (d, J_{PC} = 111.4 Hz), 53.6 (d, J_{PC} = 7.7 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 46.56; IR (KBr) 3362, 1154 cm^{-1}; APIMS *m/z* 361 (MH^+). Anal. calcd. for $C_{15}H_{15}Cl_2O_4P$: C, 49.88; H, 4.19. Found: C, 50.10; H, 4.39.

(*S*,*S*)-Methyl di(1-hydroxy-3-phenyl-2*E*-propenyl)phosphinate 6d. Yield (237 mg, 40%); mp 142-144 °C; $[\alpha]_D^{20}$ -17.6 (c 0.8, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.32-7.16 (10H, m), 6.76-6.72 (2H, m), 6.39-6.29 (2H, m), 4.92 (1H, dd, *J* = 7.0, 7.0 Hz), 4.85-4.78 (1H, m), 3.73 (3H, d, *J* = 9.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 137.8 (2 carbons), 134.3 (d, J_{PC} = 11.2 Hz), 133.6 (d, J_{PC} = 10.8 Hz), 130.3 (2 carbons), 129.6, 129.5, 128.2 (2 carbons), 125.2 (d, J_{PC} = 3.8 Hz), 125.0 (d, J_{PC} = 3.4 Hz), 70.0 (d, J_{PC} = 108.2 Hz), 69.9 (d, J_{PC} = 103.5 Hz), 54.0 (d, J_{PC} = 8.1 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 47.80; IR (KBr) 3340, 1184 cm^{-1}; EIMS *m/z* 344 (M^+). Anal. calcd. for $C_{19}H_{21}O_4P$: C, 66.27; H, 6.15. Found: C, 65.95; H, 6.16.

General procedure for preparation of (*R*)-MTPA esters of 6a-d. To a stirred suspension of (*R*)-MTPA (137 mg, 0.539 mmol), DCC (111 mg, 0.539 mmol), and DMAP (2.8 mg, 0.02 mmol) in CH_2Cl_2 (1

ml) was added a solution of **6a-d** (0.077 mmol) in CH_2Cl_2 (3 mL) and pyridine (0.1 mL) at 0 °C. After stirring at room temperature until the starting material disappeared as evidenced by TLC, the mixture was diluted with 1N HCl and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue which was diluted with Et_2O and passed through silica gel. The filtrate was evaporated to leave (*R*)-MTPA esters of **6a-d**, which were analyzed by NMR spectroscopy. ^{31}P NMR data of (*R*)-MTPA-**6a-d** were listed in Table 3.

Determination of the absolute configuration of 6a. X-ray crystal data of **6a** were collected by Mac-Science MXC18 diffarectometers. The structure was solved by direct methods using SIR 92 (Giacovazzo, 1994)[20] and refined with a full matrix least-squares method. Crystal data of **6a**: $C_{15}H_{17}O_4P$, Mr = 292.30, monoclinic, space group $P2_1$, a = 14.797(4) Å, b = 8.370(3) Å, c = 13.234(3) Å, V = 1518.9(7) Å^3, T = 298 K, Z = 4, D_x = 1.278 mgm^{-3}, (Cu-Kα) = 1.54178 Å, μ = 16.909 mm^{-1}, R = 0.043 over 3053 independent reflections.

(*S*,*R*)-di(phenylacetyloxymethyl)phosphinic acid 7. To a stirred solution of **4a** (564 mg, 1.50 mmol) in CH_2Cl_2 (4.5 mL) was added TMSBr (0.79 mL, 6.00 mmol) at 0 °C and the mixture was stirred for 12h at room temperature. After the mixture was concentrated, residue was dissolved in MeOH (4 mL) and stirred for 2h at room temperature. Evaporation of the mixture gave a residue which was purified by ion-exchange chromatography on DOWEX 50 resin (H^+ form) (H_2O) to give **7** (506 mg, 93%). Mp 213-215 °C; $[\alpha]_D^{20}$ -1.6 (c 0.5, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.34-7.25 (10H, m), 5.96 (2H, d, *J* = 7.8 Hz), 1.99 (6H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 170.8 (d, J_{PC} = 8.9 Hz), 134.6, 129.7, 129.5, 129.0, 72.7 (d, J_{PC} = 113.9 Hz), 20.7; ^{31}P NMR (162 MHz, CD_3OD) δ 32.65; IR (KBr) 1749, 1229, 1031 cm^{-1}; FABMS *m/z* 363 (MH^+).

References and Notes

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