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Diastereoselective synthesis of β-substituted α-hydroxyphosphinates through hydrophosphinylation of α-heteroatom-substituted aldehydes

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Abstract—The diastereoselective synthesis of β-substituted α-hydroxyphosphinates was achieved by hydrophosphinylation of α-oxy aldehydes and α-amino aldehydes with ethyl allylphosphinate catalyzed by lithium phenoxide.

β-Heteroatom-substituted α-hydroxyphosphinic acids are an interesting class of compounds from the viewpoint of medicinal chemistry, since these compounds serve as potentially useful components of a wide range of phosphinyl peptides[1] and phosphasugars.[2] However, few investigations have been taken on a chiral synthesis of these class of compounds. Patel reported a stereoselective synthesis of β-amino-α-hydroxyphosphinates, a chiral building block for the phosphinyl peptide showing good inhibitory activities against renin[3] and HIV protease,[4] through elongation of β-amino-α-hydroxyphosphonates whose stereochemistry was known.[1] α,β-Dihydroxyphosphinates, potentially useful compounds for the synthesis of phosphasugars of 2-deoxyglucose and 2-deoxyallose, were also prepared stereoselectively by the reaction of α-oxygenated aldehydes with isopropyl allylphosphinate in the presence of *tert*-butyldimethylchlorosilane and triethylamine.[2] We have recently established the methodology for a stereoselective synthesis of β-amino-α-hydroxyphosphinates through hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes by using AlLibis(binaphthoxide) (ALB)[5] as the catalyst.[6] In our reaction, the new synthesis of *syn*- and *anti*-β-amino-α-hydroxyphosphinate derivatives was achieved by tuning the chirality of ALB.[6a,b] The excellent ability of ALB for catalyzing diastereoselective hydrophosphinylation of α-amino aldehydes could be accounted for by simultaneous activation of aldehydes with aluminum metal as a Lewis acid, on the other hand, activation of phosphinic nucleophile with the lithium binaphthoxide moiety as a Brønsted base.[5] We have successively investigated a stereoselective hydrophosphinylation of α-heteroatom-substituted aldehydes to establish a new conventional methods for the synthesis of β-heteroatom-substituted α-hydroxyphosphinates. In the hydrophosphinylation of α-oxygenated aldehydes and α-amino derivatives, lithium phenoxide (PhOLi) was expected to activate the ethyl allylphosphinate[7] by converting to the corresponding phosphonite form (I) as shown in Scheme 1. The activated nucleophile would then react with aldehyde to give (II). Proton exchange between lithium alkoxide and phenol leads to the hydrophosphinylation product and regeneration of the catalyst.

In this paper, we describe a utility of PhOLi as an efficient catalyst for the hydrophosphinylation of α-heteroatom-substituted aldehydes (Scheme 2).

We first attempted reactions of (*S*)-α-*tert*-butyldiphenylsilyloxy aldehydes **1a**,[8] **1b**[9] and **1c**[10] with ethyl allylphosphinate in the presence of PhOLi (20 mol%), generated from *n*-BuLi and phenol, in THF at −40°C. As we expected, the reaction of **1a**–**c** proceeded catalytically affording *syn*-**2a**–**c** and *anti*-**2a**–**c** in the yields shown in Scheme 3. The ratio for *syn*- and *anti*-isomer could be determined by ^{31}P NMR (162 MHz, $CDCl_3$) analysis of crude products. The sterically less bulky substituent (R) in substrates enhanced the diastereoselectivity, in the case of **1c** (R=Me), a moderate *anti*-selectivity (*syn*/*anti*=23:77) was obtained. The observed selectivity favoring the formation of *anti*-adduct was realized by considering a Felkin–Anh transition state due to the absence of bidentate chelation with α-silyloxy aldehydes and metallic reagents.[11] The products

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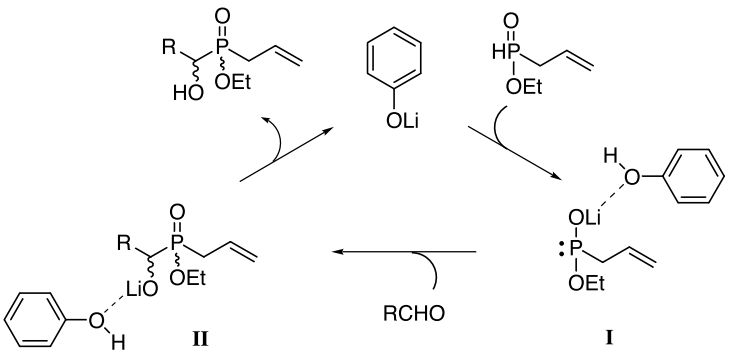
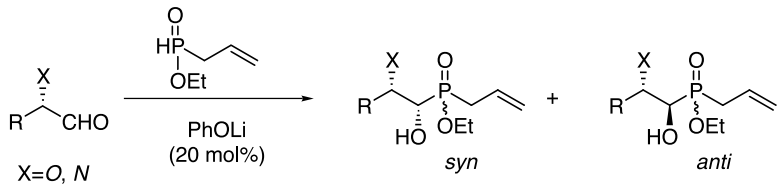
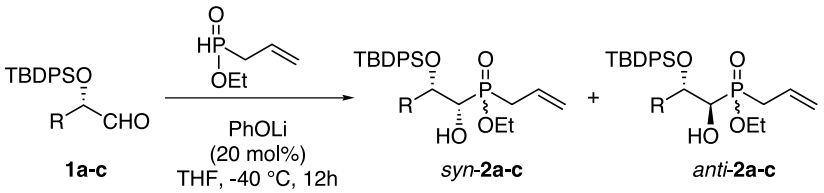


Scheme 1.

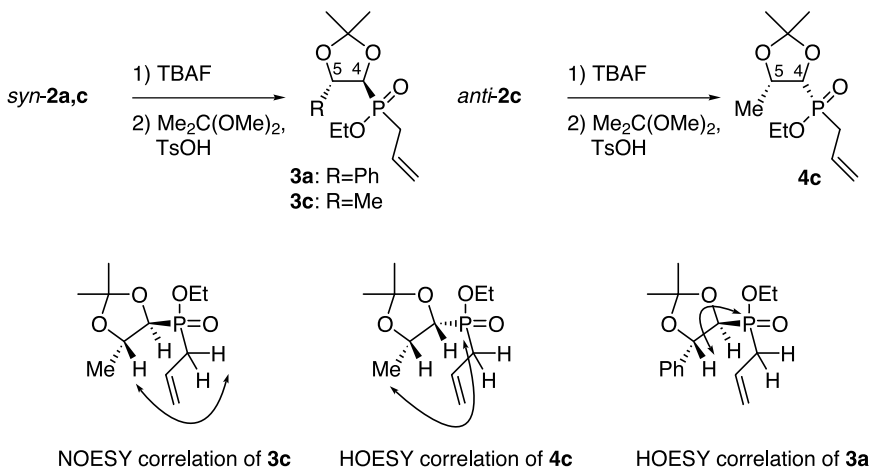


Scheme 2.



substrate	R	yield (%)	*syn*:*anti*
1a	Ph	63	44:56
1b	CH_2Ph	74	53:47
1c	Me	68	23:77

Scheme 3.



Scheme 4.

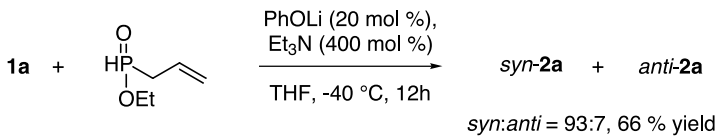
syn-**2a**–**c** and *anti*-**2a**–**c** were formed as mixtures of isomers arising from the chirality of the phosphinate group, respectively. Individual diastereomers of *syn*-**2a** and *anti*-**2a**,**c** were separated by preparative HPLC. No racemization took place during the hydrophosphinylation, which was verified by ^{31}P NMR analysis of MTPA esters derived from one of isomer of *anti*-**2c**.

The stereochemistry of one isomer of *syn*-**2a**,**c** and *anti*-**2c** was confirmed after converting to their corresponding dioxolanes **3a**,**c** and **4c**, respectively, through deprotection of the silyl group by TBAF, followed by treatment with 2,2-dimethoxypropane and TsOH (Scheme 4). In the ^{1}H NMR NOESY spectrum of **3c** and **4c**, the cross peak between H-5 and a proton at allylic position of **3c** was observed, while the no correlation was displayed between the corresponding ring protons of **4c**. Performing two-dimensional ^{31}P, ^{1}H heteronuclear NOE (HOESY) experiments provided important information concerning the relative stereochemistry of dioxolane derivatives.[12] In the HOESY spectra, phosphorus atom and Me group at C-5 of **4c** correlated, but no correlation was observed for **3c**. The correlation between phosphorus atom and H-5 was observed in the HOESY spectra of **3a**. On the basis of these results, **3a**,**c** and **4c** were assigned to be *trans* and *cis*, respectively.[13]

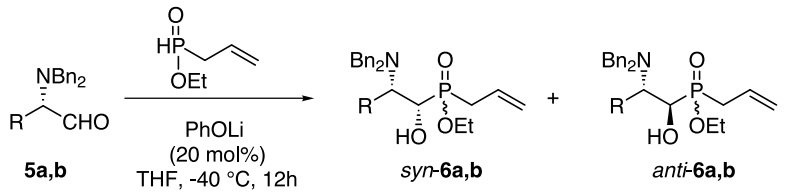
In view of the activity of catalysts, PhOLi was confirmed to be superior to ALB; that is, hydrophosphinylation of **1a** using (*R*)- and (*S*)-ALB (20 mol%) gave adducts in poor yields ((*R*)-ALB; 18% yield, *syn*/*anti*=48:52, (*S*)-ALB; 37% yield, *syn*/*anti*=54:46). The hydrophosphinylation of **1a** using other Brønsted base (20 mol%) Et_3N, *n*-BuLi and sodium phenoxide (PhONa), prepared from phenol and NaH, was also examined. It was found that only PhONa could promote the reaction to afford *syn*-**2a** and *anti*-**2a** in low yield (32%) in a ratio of 39:61. Above-mentioned results indicated PhOLi was relatively suitable catalyst for the hydrophosphinylation of α-silyloxy aldehydes.

In general, addition reactions of α-alkoxy aldehydes in the presence of Lewis acid are proceeded under chelation control to give products involving *syn* relative configuration.[14] Although we also examined hydrophosphinylation of α-benzyloxy aldehydes using Lewis acid ($LiClO_4$, $TiCl_4$, $ZnCl_2$ and $Yb(OTf)_3$) with and without PhOLi, any desired adduct was not obtained, most possibly due to a decomposition of phosphinic nucleophile with Lewis acid.[15] However, the reaction of α-silyloxy aldehyde **1a** in the presence of PhOLi (20 mol%) and Et_3N (400 mol%) gave products in 66% with high *syn*-selectivity (*syn*/*anti*=93:7) (Scheme 5).[16] To achieve the high *syn*-diastereoselectivity, premixing of **1a** with Et_3N was necessary before treating with phosphinic nucleophile. A low diastereoselectivity was observed without treatment of **1a** with Et_3N prior to the hydrophosphinylation (*syn*-**2a**/*anti*-**2a**=40:60). Reactions of other α-silyloxy aldehydes **1b**,**c** with ethyl allylphosphinate under the same condition resulted in moderate *anti*-selectivity (35% yield, *syn*/*anti*=23:77 for **1b**; 35% yield, *syn*/*anti*=30:70 for **1c**). The exact role of Et_3N is under investigation.

The present methodology was applied to a hydrophosphinylation of *N*,*N*-dibenzyl-L-phenylalanal **5a** and *N*,*N*-dibenzyl-L-leucinal **5b** (Scheme 6).[17] Hydrophosphinylation of **5a** and **5b** employing 20 mol% of PhOLi at −40°C afforded adducts in 69 and 78% yield, respectively. The ratio of *syn*-**6a** and *anti*-**6a** was determined to be 25:75. The similar selectivity was shown in the reaction of **5b** (*syn*/*anti*=24:76).[18] Products *syn*-**6a**,**b** and *anti*-**6a**,**b** were obtained as diastereomixture arising from the chirality of phosphinate group, respectively. Our previous reports revealed (*S*)-ALB-catalyzed reactions of **5a**,**b** with ethyl allylphosphinate at 0°C showing high *anti*-selectivity (**5a**; 63% yield, *syn*/*anti*=7:93, **5b**; 51% yield, *syn*/*anti*=5:95).[6c] Although the above-mentioned reactions provided moderate *anti*-selectivity compared to the case of ALB, PhOLi proved to possess sufficient catalytic activity to promote the reaction even at −40°C.



Scheme 5.



substrate	R	yield (%)	*syn*:*anti*
5a	CH_2Ph	69	25:75
5b	*i*-Bu	78	24:76

Scheme 6.

In conclusion, we have developed the procedure for the preparation of *anti*-β-substituted α-hydroxyphosphinates through hydrophosphinylation of α-oxy aldehydes and α-amino aldehydes with ethyl allylphosphinate using PhOLi as a catalyst. Applying Et_3N to the PhOLi-catalyzed hydrophosphinylation of α-oxy aldehydes afforded mono-protected *syn*-α,β-dihydroxyphosphinates with high selectivity. A further investigation to improve diastereo-selectivity is under progress.

1. Experimental

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 Bruker DPX400 NMR spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. The chemical shift data for each signal on ^1H NMR are given in units of δ relative to $CHCl_3$ (δ=7.26) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are reported relative to the $CDCl_3$ resonance (δ=77.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broad-band ^1H decoupling. Two-dimensional ^{31}P, ^1H HOESY spectra were recorded in $CDCl_3$ at 300 K. The mixing time was set to 1.5 s. Preparative HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-986; detector, UV-975, measured at 254 nm; column, GL Sciences Inertsil PREP SIL; mobile phase, EtOAc; flow rate, 15.0 mL/min. The aldehydes **1a**,[8] **1b**,[9] **1c**[10] and **5a**,**b**[17] were prepared by Swern oxidation of corresponding chiral alcohols and used without further purification.[17] Reactions were carried under nitrogen atmosphere.

1.1. The procedure for the hydrophosphinylation of 1a with ethyl allylphosphinate in the presence of PhOLi

A solution of phenol (37.6 mg, 0.4 mmol) in THF (8 mL) was added 1.56 M hexane solution of *n*-BuLi (0.3 mL, 0.4 mmol) at 0°C and stirred for 0.5 h at the same temperature. To this solution was added a solution of ethyl allylphosphinate (402 mg, 3.0 mmol) in THF (4 mL) and a solution of **1a** (2.0 mmol) in THF (4 mL) at −40°C. After stirring for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=2:1 to AcOEt) to give a mixture of *syn*-**2a** and *anti*-**2a** (671 mg, 63%). The mixture was separated into two isomers of *syn*-**2a** and two isomers of *anti*-**2a** by preparative HPLC.

1.1.1. Ethyl allyl((1*S*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxy-2-phenylethyl)phosphinate (*syn*-2a). White needles; mp 116–121°C; $[\alpha]_D^{28}$=+15.6 (*c* 0.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.27 (15H, m), 5.54–5.40 (1H, m), 5.17–4.90 (2H, m), 4.89–4.82 (1H, m), 4.12 (1H, dd, *J*=7.2, 14.3 Hz), 4.01–3.74 (2H, m), 2.21–2.08 (2H, m), 1.06 (9H, s), 1.03–0.97 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 129.9, 128.3, 127.9 (d, J_{PC}=10.4 Hz), 119.8 (d, J_{PC}=12.2 Hz), 74.7 (d, J_{PC}=9.6 Hz), 73.9 (d, J_{PC}=105.9 Hz), 60.7 (d, J_{PC}=7.0 Hz), 31.5 (d, J_{PC}=87.7 Hz), 27.0, 16.5 (d, J_{PC}=5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.77; IR (KBr) 3216, 1113, 1031 cm^{-1}; EIMS *m*/*z* 451 (M^+-t-Bu). HRMS calcd for $C_{25}H_{28}O_4PSi$ (M^+-t-Bu): 451.1494. Found: 451.1481.

1.1.2. Ethyl allyl((1*S*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxy-2-phenylethyl)phosphinate (*syn*-2a). Colorless oil; $[\alpha]_D^{28}$=+66.4 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.27 (15H, m), 5.75–5.70 (1H, m), 5.21–5.13 (2H, m), 5.05 (1H, dd, *J*=5.0, 14.5 Hz), 4.11 (1H, dd, *J*=5.7, 8.0 Hz), 3.86–3.50 (2H, m), 2.51–2.31 (2H, m), 1.10 (9H, s), 1.03–0.99 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 129.8, 128.2, 127.6 (d, J_{PC}=19.3 Hz), 120.2 (d, J_{PC}=12.0 Hz), 75.7 (d, J_{PC}=6.6 Hz), 74.3 (d, J_{PC}=107.6 Hz), 60.8, 33.3 (d, J_{PC}=86.8 Hz), 27.0, 19.4, 16.2 (d, J_{PC}=5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.27; IR (neat) 3241, 1110, 1038 cm^{-1}; EIMS *m*/*z* 451 (M^+-t-Bu). HRMS calcd for $C_{25}H_{28}O_4PSi$ (M^+-t-Bu): 451.1494. Found: 451.1508.

1.1.3. Ethyl allyl((1*R*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxy-2-phenylethyl)phosphinate (*anti*-2a). White needles; mp 98–103°C; $[\alpha]_D^{28}$=+35.5 (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.32 (15H, m), 5.67–5.62 (1H, m), 5.11–5.00 (2H, m), 4.97 (1H, dd, *J*=5.8, 8.0 Hz), 4.02 (1H, dd, *J*=3.3, 8.0 Hz), 3.77–3.39 (2H, m), 2.47–2.17 (2H, m), 1.02 (9H, s), 0.94–0.91 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.8, 133.4, 129.9, 129.7, 128.3, 128.1, 127.8, 127.6, 127.3 (d, J_{PC}=22.8 Hz), 120.0 (d, J_{PC}=12.3 Hz), 75.5 (d, J_{PC}=71.6 Hz), 74.6 (d, J_{PC}=6.7 Hz), 61.6 (d, J_{PC}=6.9 Hz), 33.4 (d, J_{PC}=85.9 Hz), 27.0, 16.5 (d, J_{PC}=5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.54; IR (KBr) 3239, 1112, 1052 cm^{-1}; EIMS *m*/*z* 451 (M^+-t-Bu). HRMS calcd for $C_{25}H_{28}O_4PSi$ (M^+-t-Bu): 451.1494. Found: 451.1480.

1.1.4. Ethyl allyl((1*R*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxy-2-phenylethyl)phosphinate (*anti*-2a). Colorless oil; $[\alpha]_D^{27}$=+37.4 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.27 (15H, m), 5.49–5.46 (1H, m), 5.17–4.98 (2H, m), 4.88–4.83 (1H, m), 4.08 (1H, d, *J*=10.3 Hz), 3.84–3.78 (2H, m), 2.72–2.12 (2H, m), 1.20–1.10 (3H, m), 1.06–0.89 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8, 128.2, 128.0, 127.7, 127.4 (d, J_{PC}=13.7 Hz), 120.1 (d, J_{PC}=12.3 Hz), 75.5 (d, J_{PC}=72.0 Hz), 74.6 (d, J_{PC}=6.6 Hz), 61.5 (d, J_{PC}=7.1 Hz), 33.4 (d, J_{PC}=85.9 Hz), 27.0, 16.4 (d, J_{PC}=5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.75; IR (neat) 3224, 1110, 1033 cm^{-1}; EIMS *m*/*z* 451 (M^+-t-Bu). HRMS calcd for $C_{25}H_{28}O_4PSi$ (M^+-t-Bu): 451.1494. Found: 451.1485.

1.1.5. Ethyl allyl((1*S*,2*S*)- and (1*R*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-hydroxy-3-phenylpropyl)phosphinate (*syn*-2b and *anti*-2b). Compounds *syn*-**2b** and *anti*-**2b** were prepared from **1b** (2.0 mmol) in accordance with the procedure described for **1a**. Purification of the residue by column chromatography (hexane/EtOAc=2:1 to AcOEt) to give a mixture of *syn*-**2a** and *anti*-**2a** (770 mg, 74%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–6.85 (15H, m), 5.75–5.60 (1H, m), 5.29–4.93 (2H, m), 4.31–3.97 (3H, m), 3.66–3.47 (1H, m), 3.00–2.51 (4H, m), 1.34–0.99 (12H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.90, 49.39, 48.82, 48.26; IR (neat) 3263, 1111, 1037 cm^{-1}; EIMS *m/z* 522 (M^+). HRMS calcd for $C_{30}H_{39}O_4PSi$ (M^+): 522.2355. Found: 522.2306.

1.1.6. Ethyl allyl((1*S*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxypropyl)phosphinate (*syn*-2c). Compounds *syn*-**2c** and *anti*-**2c** were prepared from **1c** (10 mmol) in accordance with the procedure described for **1a**. Purification of the residue by column chromatography (hexane/EtOAc=2:1 to AcOEt) to give a mixture of *syn*-**2c** and *anti*-**2c** (3.03 g, 68%). The mixture was separated into a mixture of two isomers of *syn*-**2c** and individual isomers of *anti*-**2c** by preparative HPLC. This compound was obtained as a mixture of diastereomers in a ratio of 1:3.8. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.35 (10H, m), 5.78–5.72 (1H, m), 5.17–5.12 (2H, m), 4.29–4.21 (1H, m), 4.18–4.02 (2H, m), 3.97 (1H, d, J=4.3 Hz), 2.75–2.59 (2H, m), 1.29 (3H, t, J=7.0 Hz), 1.17 (3H, d, J=6.2 Hz), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.7, 133.7, 132.8, 130.1, 129.9, 127.7, 127.2 (d, J_{PC}=9.8 Hz), 120.1 (d, J_{PC}=12.1 Hz), 73.9 (d, J_{PC}=108.8 Hz), 69.3 (d, J_{PC}=5.9 Hz), 60.8 (d, J_{PC}=6.9 Hz), 32.2 (d, J_{PC}=85.9 Hz), 26.9, 19.5, 16.5 (d, J_{PC}=5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.12, 49.29; IR (neat) 3289, 1110, 1037 cm^{-1}; EIMS *m/z* 389 (M^+-t-Bu). HRMS calcd for $C_{20}H_{26}O_4PSi$ (M^+-t-Bu): 389.1338. Found: 389.1323.

1.1.7. Ethyl allyl((1*R*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxypropyl)phosphinate (*anti*-2c). Colorless oil; $[\alpha]_D^{28}$=+2.9 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.38 (10H, m), 5.76–5.71 (1H, m), 5.26–5.14 (2H, m), 4.25–4.19 (1H, m), 4.05–3.89 (2H, m), 3.83 (1H, dd, J=3.2, 4.5 Hz), 2.75–2.61 (2H, m), 1.28 (3H, d, J=6.4 Hz), 1.20 (3H, t, J=7.0 Hz), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 133.6, 129.9, 127.8, 127.2 (d, J_{PC}=10.3 Hz), 120.3 (d, J_{PC}=12.0 Hz), 73.4 (d, J_{PC}=104.9 Hz), 69.7 (d, J_{PC}=5.8 Hz), 61.1 (d, J_{PC}=7.0 Hz), 33.3 (d, J_{PC}=85.2 Hz), 27.0, 19.2, 16.5 (d, J_{PC}=5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.73; IR (neat) 3278, 1110, 1037 cm^{-1}; EIMS *m/z* 389 (M^+-t-Bu). HRMS calcd for $C_{24}H_{35}O_4PSi$ (M^+): 446.2042. Found: 446.2010.

1.1.8. Ethyl allyl((1*R*,2*S*)-2-{[*tert*-butyl(diphenyl)silyl]-oxy}-1-hydroxypropyl)phosphinate (*anti*-2c). Colorless oil; $[\alpha]_D^{28}$=+0.7 (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.37 (10H, m), 5.85–5.75 (1H, m), 5.29–5.16 (2H, m), 4.35–4.18 (1H, m), 4.16–3.93 (2H, m), 3.75–3.64 (1H, m), 2.71–2.62 (2H, m), 1.39–1.23 (6H, m), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.7, 133.6, 129.9, 127.8, 127.6, 127.1 (d, J_{PC}=9.4 Hz), 120.4 (d, J_{PC}=12.0 Hz), 73.7 (d, J_{PC}=107.1 Hz), 68.9, 61.3 (d, J_{PC}=7.3 Hz), 33.0 (d, J_{PC}=84.9 Hz), 26.9, 19.2 (d, J_{PC}=8.6 Hz), 16.4 (d, J_{PC}=5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.74; IR (neat) 3278, 1110, 1036 cm^{-1}; EIMS *m/z* 389 (M^+-t-Bu). HRMS calcd for $C_{20}H_{26}O_4PSi$ (M^+-t-Bu): 389.1338. Found: 389.1328.

1.1.9. Ethyl allyl[(4*S*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]phosphinate (3a). To a stirred solution of one isomer of *syn*-**2a** (198 mg, 0.39 mmol) in THF (2.0 mL) was added 1 M THF solution of TBAF (0.47 mL, 0.47 mmol) at 0°C. After stirring for 1.5 h at the same temperature, the mixture was poured into cold water and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue. A mixture of the residue, 2,2-dimethoxypropane (0.19 mL, 1.56 mmol) and *p*-toluenesulfonic acid monohydrate (7.4 mg, 0.039 mmol) in benzene (2.0 mL) was heated under reflux for 1.5 h. After being cooled, the mixture was poured into sat. $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=3:1 to 1:2) to give **3a** (35 mg, 29%). Colorless oil; $[\alpha]_D^{27}$=−1.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.29 (5H, m), 5.10–5.05 (2H, m), 4.87 (1H, dd, J=9.3, 11.4 Hz), 4.24–4.13 (3H, m), 2.57–2.31 (2H, m), 1.61–1.55 (6H, m), 1.36–1.29 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.2, 127.8, 126.8 (d, J_{PC}=10.7 Hz), 126.0, 120.0 (d, J_{PC}=11.9 Hz), 112.1 (d, J_{PC}=3.9 Hz), 84.3 (d, J_{PC}=110.6 Hz), 71.5, 61.9 (d, J_{PC}=7.3 Hz), 31.0 (d, J_{PC}=87.2 Hz), 25.9, 25.7, 16.7 (d, J_{PC}=5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.84; IR (neat) 1061, 1032 cm^{-1}; EIMS *m/z* 310 (M^+). HRMS calcd for $C_{15}H_{20}O_4P$ (M^+-Me): 295.1099. Found: 295.1095.

1.1.10. Ethyl allyl[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]phosphinate (3c). The compound **3c** was prepared from a mixture of *syn*-**2c** (178 mg, 0.40 mmol) in an analogous manner to that for preparation of **3a**. Purification of the residue by column chromatography (hexane/EtOAc=3:1 to 1:2) gave **3c** (8.7 mg, 11%). Colorless oil; $[\alpha]_D^{27}$=+4.0 (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.83 (1H, m), 5.30–5.23 (2H, m), 4.43–4.11 (2H, m), 3.68 (1H, dd, J=3.2, 9.3 Hz), 2.80–2.73 (2H, m), 1.43–1.40 (9H, m), 1.34 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.8 (d, J_{PC}=9.7 Hz), 120.5 (d, J_{PC}=12.4 Hz), 110.4 (d, J_{PC}=9.9 Hz), 77.8 (d, J_{PC}=113.2 Hz), 72.6 (d, J_{PC}=4.3 Hz), 61.1 (d, J_{PC}=6.9 Hz), 32.1 (d, J_{PC}=87.6 Hz), 26.8, 26.2, 18.3 (d, J_{PC}=1.8 Hz), 16.5 (d, J_{PC}=5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.76; IR (neat) 1088, 1032 cm^{-1}; EIMS *m/z* 249 (MH^+). HRMS calcd for $C_{11}H_{21}O_4P$ (M^+): 248.1177. Found: 248.1152.

1.1.11. Ethyl allyl[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]phosphinate (4c). The compound **4c** was prepared from one isomer of *anti*-**2c** (548 mg, 1.23 mmol) in an analogous manner to that for preparation of **3a**. Purification of the residue by column chromatography (hexane/EtOAc=3:1 to 1:2) gave **4c** (30 mg, 10%). Colorless oil; $[\alpha]_D^{27}$=+14.0 (*c* 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.82 (1H, m), 5.31–5.23 (2H, m), 4.42–4.11 (3H, m), 3.74 (1H, dd, J=8.5, 9.0 Hz), 2.79–2.67 (2H, m), 1.43–1.40 (9H, m), 1.34 (3H, t, J=3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.4 (d, J_{PC}=9.2 Hz), 120.4 (d, J_{PC}=12.1 Hz), 109.8 (d, J_{PC}=4.4 Hz), 74.9 (d, J_{PC}=114.0 Hz), 73.2, 61.4 (d, J_{PC}=7.3 Hz), 34.1 (d, J_{PC}=85.8 Hz), 27.0, 25.1, 18.7, 16.6 (d, J_{PC}=5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.52; IR (neat) 1087, 1031 cm^{-1}; EIMS *m/z* 219 (M^+-Et). HRMS calcd for $C_{10}H_{18}O_4P$ (M^+-Me): 233.0942. Found: 233.0937.

1.2. The procedure for the hydrophosphinylation of 1a with ethyl allylphosphinate in the presence of PhOLi and Et_3N

To a solution of PhOLi (0.4 mmol) in THF (4 mL), prepared from phenol (37.6 mg, 0.4 mmol) and 1.56 M hexane solution of *n*-BuLi (0.26 mL, 0.4 mmol), was added a solution of ethyl allylphosphinate (402 mg, 3.0 mmol) in THF (4 mL) and a solution of **1a** (2.0 mmol) and Et_3N (1.1 mL, 8.0 mmol) in THF (8 mL), which were mixed at room temperature before 2 h in prior to use, at −40°C under stirring. After stirring for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=5:1 to EtOAc) to give a mixture of *syn*-**2a** and *anti*-**2a** (670 mg, 66%).

1.3. General procedure for the hydrophosphinylation of 5a,b with ethyl allylphosphinate in the presence of PhOLi

To a solution of PhOLi (0.8 mmol) in THF (8 mL), prepared from phenol (75 mg, 0.8 mmol) and 0.98 M hexane solution of *n*-BuLi (0.82 mL, 0.8 mmol), was added a solution of ethyl allylphosphinate (804 mg, 6.0 mmol) in THF (4 mL) and a solution of **5a**,**b** (4.0 mmol) in THF (8 mL) at −40°C under stirring. After stirring for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (hexane/EtOAc=2:1 to EtOAc) to give *syn*-**6a**,**b** and *anti*-**6a**,**b**.

1.3.1. Ethyl allyl[(1*S*,2*S*)-2-(dibenzylamino)1-hydroxy-3-phenylpropyl]phosphinate (*syn*-6a). This compound was obtained as a mixture of diastereomers in a ratio of 1:2.0. Yield (333 mg, 18%); white plates; mp 83–85°C. The ^1H and ^{31}P NMR spectra were identical to those of the authentic sample reported in the literature.[6c]

1.3.2. Ethyl allyl[(1*R*,2*S*)-2-(dibenzylamino)1-hydroxy-3-phenylpropyl]phosphinate (*anti*-6a). This compound was obtained as a mixture of diastereomers in a ratio of 1:1.5. Yield (945 mg, 51%); white plates; mp 130–133°C. The ^1H and ^{31}P NMR spectra were identical to those of the authentic sample reported in the literature.[6c]

1.3.3. Ethyl allyl[(1*S*,2*S*)-2-(dibenzylamino)1-hydroxy-4-methylpentyl]phosphinate (*syn*-6b). This compound was obtained as a mixture of diastereomers in a ratio of 1:1.2. Yield (326 mg, 19%); colorless oil. The ^1H and ^{31}P NMR spectra were identical to those of the authentic sample reported in the literature.[6c]

1.3.4. Ethyl allyl[(1*R*,2*S*)-2-(dibenzylamino)1-hydroxy-4-methylpentyl]phosphinate (*anti*-6b). This compound was obtained as a mixture of diastereomers in a ratio of 1:1.5. Yield (1.01 g, 59%); white plates; mp 141–143°C. The ^1H and ^{31}P NMR spectra were identical to those of the authentic sample reported in the literature.[6c]

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18. Although the hydrophosphinylation of **5a**,**b** in the presence of PhOLi (20 mol%) and Et_3N (400 mol%) were examined, the diastereoselectivity were analogous to those of PhOLi-catalyzed reactions (33% yield, *syn*/*anti*=23:77 for **5a**; 81% yield, *syn*/*anti*=36:64 for **5b**).