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# First asymmetric Abramov-type phosphonylation of aldehydes with trialkyl phosphites catalyzed by chiral Lewis bases

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ABSTRACT

Chiral phosphine oxides (Lewis bases) catalyze silicon tetrachloride-mediated, enantioselective phosphonylation of aldehydes with trialkyl phosphites (Abramov-type reaction), which leads to optically active α-hydroxyphosphonates with moderate enantioselectivities. $^{31}P$ NMR analysis of the phosphonylation of benzaldehyde with triethyl phosphite supports the assumed reaction mechanism.



## 1. Introduction

α-Hydroxyphosphonates are an attractive class of biologically active compounds as well as useful synthetic intermediates of α-substituted phosphonyl compounds.[1] Because their biological activities usually depend on the absolute configuration, catalytic enantioselective synthesis of these compounds has been explored. Although a few successful asymmetric metal catalysts have been developed for phosphonylation of aldehydes with *dialkyl* phosphites (Pudovik-type reaction[2]),[3,4] asymmetric catalysis of the alternative reaction with *trialkyl* phosphites (Abramov-type reaction[5]) has yet to be achieved.

Recently, Denmerk et al. have reported that weakly Lewis acidic silicon tetrachloride ($SiCl_4$) can be activated by coordination of Lewis bases and that the resulting Lewis base/$SiCl_4$ complex promotes ring-opening of epoxides[6] or addition of nucleophiles (allyl/propargyltin,[7] enoxysilanes,[8] isocyanides,[9] or silyl ketene imines[10]) to aldehydes or ketones.

In our continuous efforts to develop chiral Lewis base-catalyzed asymmetric reactions,[11] we envisioned that a chiral Lewis base (LB*)/$SiCl_4$ complex could activate prochiral aldehydes and facilitate enantioselective attack of trialkyl phosphites to yield trichlorosilylated α-hydroxyphosphonates after Arbuzov-type[12] liberation of the corresponding alkyl chloride (Fig. 1). Herein, we report first catalytic enantioselective Abramov-type phosphonylation of aldehydes.

## 2. Results and discussion

At the onset, we investigated phosphonylation of benzaldehyde (**1a**) with triethyl phosphite under various conditions using (*S*)-BINAP dioxide (BINAPO) as a chiral Lewis base catalyst (Table 1). We selected BINAPO catalyst because of its effectiveness in asymmetric aldol reactions,[11e,f] allylations,[11c,f] and epoxide ring-opening reactions.[11d] When $SiCl_4$ was added dropwise to a solution of **1a**, the phosphite, and $^{i}Pr_2NEt$[13] in $CH_2Cl_2$ at −78 °C, desired hydroxyphosphonate **2a** was obtained in a good yield with a moderate enantioselectivity (entry 1). On the other hand, when the addition order of the silane and the phosphite was reversed, enantioselectivity was not observed (entry 2). We reasoned that $SiCl_4$ itself promoted the non-selective reaction. Therefore, the rate of silane addition was investigated. It was found that adding the silane over 2 h improved the enantioselectivity (entry 3). In the absence of the amine, both the yield and selectivity decreased (entry 4). Furthermore, the addition of 2-methyl-2-butene, a non-basic proton scavenger did not improve the result (entry 5). This observation implies that the role of the amine is not only to capture concomitant acid, but also to promote the catalyst turnover. Next, the amount of the amine was investigated (entries 6 and 7). A substoichiometric amount (0.5 equiv) resulted in low yield, while an excess amount (5.0 equiv) gave a result comparable to that using 1.5 equiv. In addition, the loading of the BINAPO catalyst had a negligible effect on the selectivity (entries 9 and 10). It should be noted that the catalyst turnover of BINAPO was sufficient under the conditions, considering the reaction proceeded even in the absence of the catalyst (entry 8).

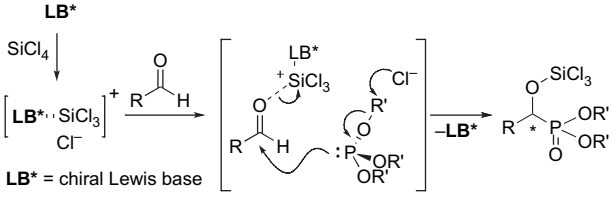


**Figure 1.** Assumed reaction mechanism.

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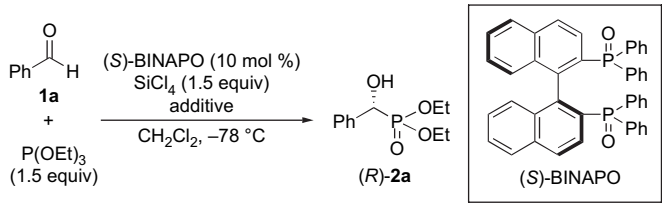
**Table 1**
Phosphonylation of benzaldehyde catalyzed by (*S*)-BINAPO




| Entry | Additive (equiv) | Method[a] | **2a** (%) | % ee (config.) |
|---|---|---|---|---|
| 1 | $^{i}Pr_2NEt$ (1.5) | **A** | 73 | 31 (*R*) |
| 2 | $^{i}Pr_2NEt$ (1.5) | **B** | 57 | 0 |
| 3 | $^{i}Pr_2NEt$ (1.5) | **C** | 91 | 41 (*R*) |
| 4 | — | **C** | 30 | 15 (*R*) |
| 5 | 2-Methyl-2-butene (1.5) | **C** | 18 | 29 (*R*) |
| 6 | $^{i}Pr_2NEt$ (0.5) | **C** | 28 | 37 (*R*) |
| 7 | $^{i}Pr_2NEt$ (5.0) | **C** | 86 | 41 (*R*) |
| 8[b] | $^{i}Pr_2NEt$ (1.5) | **C** | 75 | — |
| 9[c] | $^{i}Pr_2NEt$ (1.5) | **C** | 67 | 40 (*R*) |
| 10[d] | $^{i}Pr_2NEt$ (1.5) | **C** | 60 | 40 (*R*) |

[a] (**A**) Addition of $SiCl_4$ at usual rate to a solution of **1a**, (*S*)-BINAPO (10 mol %), $P(OEt)_3$, and additive in $CH_2Cl_2$ at −78 °C. (**B**) Addition of $P(OEt)_3$ over 5 h to a solution of **1a**, (*S*)-BINAPO (10 mol %), $SiCl_4$, and additive in $CH_2Cl_2$ at −78 °C. (**C**) Addition of $SiCl_4$ over 2 h to a solution of **1a**, (*S*)-BINAPO (10 mol %), $P(OEt)_3$, and additive in $CH_2Cl_2$ at −78 °C.
[b] Without BINAPO.
[c] (*S*)-BINAPO (30 mol %).
[d] (*S*)-BINAPO (5 mol %).

Using toluene or THF instead of dichloromethane afforded reactions with inferior results. Although a high reactivity was observed in propionitrile (90% yield), the enantioselectivity decreased to 7% ee, presumably because propionitrile served as an achiral Lewis base.

As summarized in Figure 2, chiral Lewis bases other than BINAPO were examined for the phosphonylation of benzaldehyde (**1a**) with triethyl phosphite under optimized conditions (Table 1, entry 3). Triarylphosphine oxides showed high activities, whereas alkylarylphosphine oxides or bisquinoline *N*,*N*′-dioxides provided inferior results.

Next, the effect of varying the phosphites on reaction of **1a** was investigated (Table 2). For trialkyl phosphites, smaller alkyl groups tended to give higher yields (entries 1–4), whereas triphenyl phosphite did not react at all (entry 5). These findings are consistent with the assumed mechanism, which involves an Arbuzov-type attack of the chloride anion on the alkyl group of phosphite. Among the trialkyl phosphites tested, triethyl phosphite gave the highest enantioselectivity. On the other hand, it was found that Pudovik-type reactions with dialkyl phosphites were also promoted by silicon tetrachloride and the BINAPO catalyst (entries 6–9). However, the selectivities were lower than those with trialkyl phosphites.

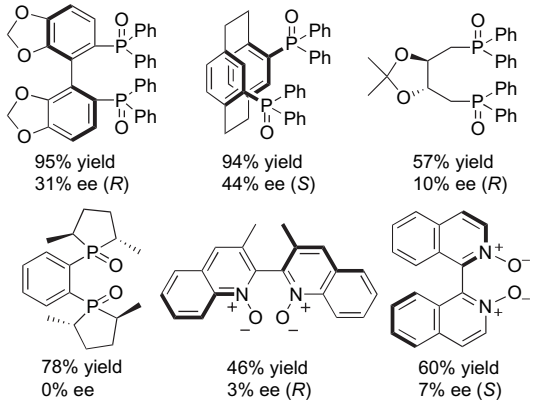
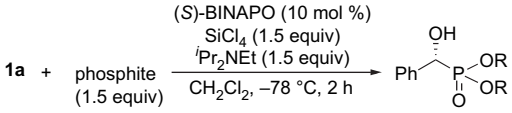



**Figure 2.** Screening of Lewis base catalyst; conditions: **1a** (0.5 mmol), $P(OEt)_3$ (1.5 equiv), $^{i}Pr_2NEt$ (1.5 equiv), and $SiCl_4$ (1.5 equiv slowly added over 2 h) at −78 °C.

**Table 2**
BINAPO-catalyzed reaction of **1a** with various phosphites[a]

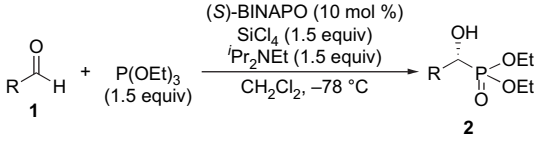



| Entry | Phosphite | R | Yield (%) | % ee (config.) |
|---|---|---|---|---|
| 1 | $P(OR)_3$ | Me | 97 | 28 (*R*) |
| 2 | | Et | 91 | 41 (*R*) |
| 3 | | $^{i}Pr$ | 84 | 40 (*R*) |
| 4 | | Bu | 84 | 33 |
| 5 | | Ph | 0 | — |
| 6 | $HP(O)(OR)_2$ | Me | 57 | 27 (*R*) |
| 7 | | Et | 82 | 18 (*R*) |
| 8 | | $^{i}Pr$ | 72 | 19 (*R*) |
| 9 | | Bn | 51 | 8 (*R*) |

[a] All reactions were carried out using **1a** (0.5 mmol), (*S*)-BINAPO (10 mol %), a phosphite (1.5 equiv), $^{i}Pr_2NEt$ (1.5 equiv), and $SiCl_4$ (1.5 equiv slowly added over 2 h) at −78 °C.

Then the scope and limitations of aldehyde substrates were examined (Table 3). The reactions were performed under optimized conditions using triethyl phosphite. *p*-Anisaldehyde, an electron-donating benzaldehyde derivative, and benzaldehyde provided comparable results (entry 1), but that with *p*-bromobenzaldehyde gave a lower selectivity (entry 2). Aldehydes with a low Lewis basicity may loosen the transition state structure for the enantio-determining step (vide infra), leading to a decreased selectivity. Although sterically congested 1-naphthaldehyde gave a low selectivity (entry 3), 2-naphthaldehyde afforded a moderate selectivity (entry 4). Cinnamaldehyde, an even less congested conjugate aldehyde, afforded an improved enantioselectivity (entry 5), and the 1,4-adduct was not observed. The enantioselectivity was slightly improved by using (*S*)-PHANEPHOS dioxide as a catalyst, but the yield remained moderate (entry 6). Aliphatic aldehydes exhibited good reactivities, albeit with their low selectivities, despite low reactivity due to chlorohydrin formation with chlorosilane reagents[14] (entries 7 and 8).

**Table 3**
Asymmetric phosphonylation of various aldehydes with triethyl phosphite catalyzed by BINAPO[a]




| Entry | R | Product | Yield (%) | % ee (config.) |
|---|---|---|---|---|
| 1 | *p*-$MeOC_6H_4$ | **2b** | 90 | 40 (*R*) |
| 2 | *p*-$BrC_6H_4$ | **2c** | 87 | 22 |
| 3 | 1-Naphthyl | **2d** | 83 | 9 |
| 4[b] | 2-Naphthyl | **2e** | 98 | 33 |
| 5 | (*E*)-PhCH=CH | **2f** | 89 | 49 (*R*) |
| 6[c] | (*E*)-PhCH=CH | **2f** | 64 | 52 (*S*) |
| 7[d] | $PhCH_2CH_2$ | **2g** | 65 | 17[f] |
| 8[e] | Cyclohexyl | **2h** | 49 | 23[f] |

[a] Reactions were carried out using an aldehyde (0.5 mmol), (*S*)-BINAPO (10 mol %), $P(OEt)_3$ (1.5 equiv), $^{i}Pr_2NEt$ (1.5 equiv), and $SiCl_4$ (1.5 equiv slowly added over 2 h) at −78 °C otherwise noted.
[b] Reaction was performed at −78 °C for 1 h after addition of $SiCl_4$.
[c] (*S*)-PHANEPHOS dioxide (10 mol %) was used instead of (*S*)-BINAPO.
[d] Reaction was performed at −78 °C for 10 h after addition of $SiCl_4$.
[e] Reaction was performed at −78 °C for 12 h after addition of $SiCl_4$.
[f] The ee was determined by $^{31}P$ NMR analysis using quinine.[15]

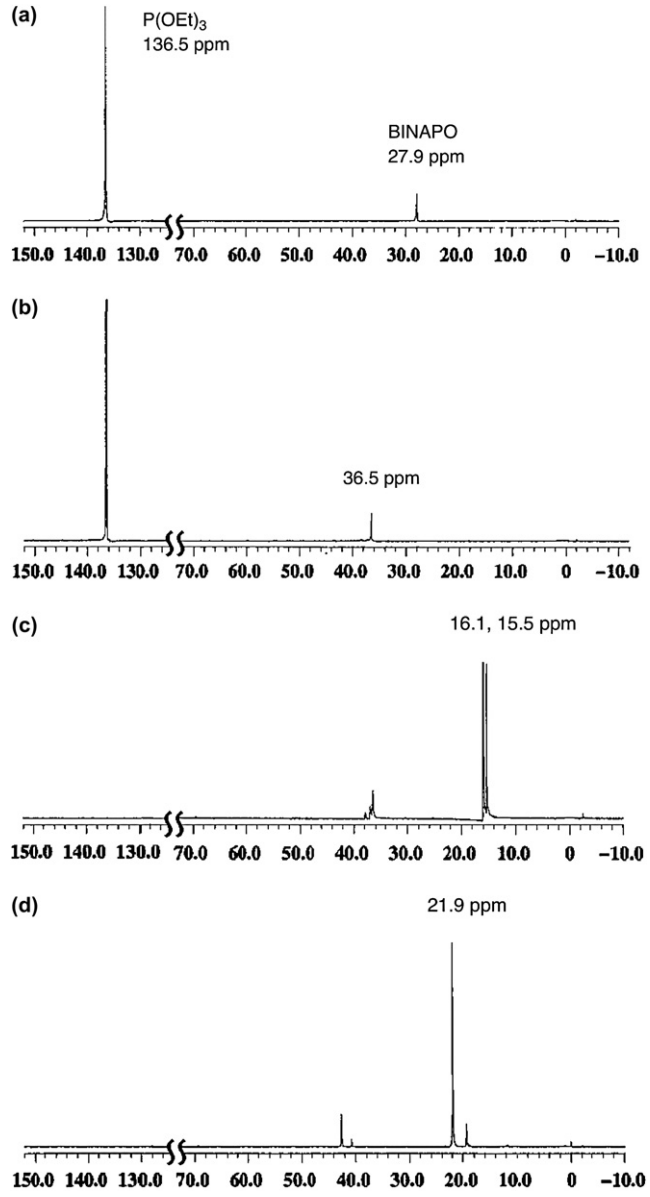



**Chart 1.** $^{31}P\{^{1}H\}$ NMR analysis of phosphonylation of benzaldehyde with triethyl phosphite in $CD_2Cl_2$ at −78 °C. (a) $P(OEt)_3$ and BINAPO; (b) (a)+$SiCl_4$; (c) (b)+PhCHO; (d) quenched with ethanol.

In order to gain mechanistic insights, the reaction of benzaldehyde with triethyl phosphite in deuterated dichloromethane at −78 °C was monitored by $^{31}P\{^{1}H\}$ NMR analysis (Chart 1). First, the signals of BINAPO (10 mol %) and $P(OEt)_3$ appeared at 27.9 and 136.5 ppm, respectively (spectrum a). Upon the addition of $SiCl_4$, the BINAPO signal shifted to 36.5 ppm, whereas that of $P(OEt)_3$ did not shift (spectrum b). These observations support the formation of a $SiCl_4$/BINAPO complex and deny the possibility that a new phosphonylating agent is generated from $P(OEt)_3$ and $SiCl_4$. Next, when benzaldehyde was added to the mixture, the $P(OEt)_3$ signal disappeared completely, but signals near 16 ppm emerged (spectrum c). This observation supports that trivalent $P(OEt)_3$ is transformed into pentavalent phosphonate products, which is consistent with the assumed mechanism shown in Figure 1. Finally, α-hydroxyphosphonate **2a** was liberated at 21.9 ppm after quenching with ethanol (spectrum d). According to this mechanism, the enantio-determining step is the attack of phosphites to the aldehyde/$SiCl_4$/BINAPO complex. However, a detailed projection of the transition state for this step remains unclear.

## 3. Conclusion

We have demonstrated that chiral Lewis bases catalyze asymmetric phosphonylation of aldehydes with trialkyl phosphites. Although the selectivity is not yet satisfactory, this is the first catalytic enantioselective Abramov-type phosphonylation of aldehydes. Further improvement of the selectivity by developing new Lewis base catalysts is currently under investigation.

## 4. Experimental

### 4.1. General

Melting points were uncorrected. $^{1}H$, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were measured in $CDCl_3$ with JEOL JNM-ECX400 spectrometer otherwise noted. Tetramethylsilane (TMS) ($\delta$=0 ppm), $CDCl_3$ ($\delta$=77.0 ppm), and aq phosphoric acid sealed in a glass capillary ($\delta$=0 ppm) were used for internal standards for $^{1}H$, $^{13}C$, and $^{31}P$ NMR analyses, respectively. Infrared spectra were recorded on JIR-6500W. Mass spectra were measured with JEOL JMS-DX303HF mass spectrometer. Optical rotations were recorded on JASCO P-1010 polarimeter. High pressure liquid chromatography (HPLC) was performed with JASCO P-980 and UV-1575. Thin-layer chromatography (TLC) analysis was carried out using Merk silica gel plates. Visualization was accomplished with UV light and/or phosphomolybdic acid. Column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, neutral, 63–210 μm). All reactions were performed under argon atmosphere using oven- and heating gun-dried glassware equipped with a rubber septum and a magnetic stirring bar.

Dichloromethane (dehydrated) was purchased from Kanto Chemical and stored over 4 Å MS prior to use. All other solvents were purified based on standard procedures. Silicon tetrachloride was purchased from Tokyo Kasei Kogyo (TCI) and used without further purification. (*S*)-BINAP dioxide was prepared by oxidation of (*S*)-BINAP with hydrogen peroxide in acetone.[11f] Triethyl phosphite was distilled from sodium. Diisopropylethylamine was distilled from calcium hydride. All other chemicals were purified based on standard procedures.

### 4.2. General procedure for phosphonylation of aldehydes catalyzed by BINAPO

A phosphite (0.75 mmol) was added to a solution of an aldehyde (0.5 mmol), $^{i}Pr_2NEt$ (0.75 mmol), and (*S*)-BINAPO (10 mol %) in dichloromethane (2 mL) at −78 °C and then silicon tetrachloride (0.75 M dichloromethane solution, 1.0 mL) was introduced over 2 h using a syringe pump. After checking completion of the reaction by TLC analysis, deionized water (2 mL), satd aq $NaHCO_3$ (5 mL), and ethyl acetate (5 mL) were added in turn to the reaction mixture. After being stirred for 1 h, the mixture was filtered via a Celite pad and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified with silica gel column chromatography (silica gel 15 g, hexane/acetone 2/1 then 1/1) to give the corresponding α-hydroxyphosphonate. After separation of the product, BINAPO could be recovered quantitatively by eluting with dichloromethane/ethanol (10/1) without loss of the optical activity.

### 4.3. Physical data of products

*4.3.1. (R)-Diethyl 1-hydroxy-1-phenylmethylphosphonate (**2a**)*[16]

TLC: $R_f$ 0.41 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{27}$ +14.8 (*c* 1.01, $CHCl_3$) for 41% ee (*R*). [lit.[3a] $[\alpha]_D^{20}$ +19.1 (*c* 1.0, $CHCl_3$) for 53% ee (*R*)]; $^{1}H$ NMR ($CDCl_3$): $\delta$ 1.22 (t, 3H, *J*=7.3 Hz), 1.27 (t, 3H, *J*=7.3 Hz), 3.20 (br s, 1H), 3.22–4.09 (m,

4H), 5.03 (dd, 1H, $J$=5.0, 10.5 Hz), 7.28–7.40 (m, 3H), 7.48–7.50 (m, 2H); $^{31}$P NMR ($CDCl_3$): $\delta$ 21.4; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=19/1, UV detection at 254 nm): $t_R$=17.2 min (*R*, major), 22.5 min (*S*, minor).

#### 4.3.2. (R)-Dimethyl 1-hydroxy-1-phenylmethylphosphonate[3e]

TLC: $R_f$ 0.23 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{20}$ +21.5 (*c* 0.80, $CHCl_3$) for 28% ee (*R*). [lit.[17] $[\alpha]_D^{20}$ −45 (*c* 0.80, $CHCl_3$) for 90% ee (*S*)]; mp: 91.0–92.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 3.22–3.27 (m, 1H), 3.67 (d, 3H, $J$=10.1 Hz), 3.72 (d, 3H, $J$=10.5 Hz), 5.06 (dd, 1H, $J$=5.0, 11.0 Hz), 7.31–7.40 (m, 3H), 7.49–7.50 (m, 2H); $^{31}$P NMR ($CDCl_3$): $\delta$ 23.5; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=9/1, UV detection at 254 nm): $t_R$=15.7 min (*R*, major), 19.9 min (*S*, minor).

#### 4.3.3. (R)-Diisopropyl 1-hydroxy-1-phenylmethylphosphonate[17]

TLC: $R_f$ 0.57 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{19}$ +12.2 (*c* 1.01, $CHCl_3$) for 40% ee (*R*). [lit.[18] $[\alpha]_D^{20}$ −17.3 (*c* 1.0, $CHCl_3$) for 65% ee (*S*)]; mp: 85.0–86.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.13 (d, 3H, $J$=6.0 Hz), 1.24 (d, 3H, $J$=6.0 Hz), 1.276 (d, 3H, $J$=6.4 Hz), 1.281 (d, 3H, $J$=6.0 Hz), 3.19 (br s, 1H), 4.57–4.67 (m, 2H), 4.96 (d, 1H, $J$=11.0 Hz), 7.28–7.38 (m, 3H), 7.48–7.50 (m, 2H); $^{31}$P NMR ($CDCl_3$): $\delta$ 19.9; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=39/1): $t_R$=12.1 min (*R*, major), 14.5 min (*S*, minor).

#### 4.3.4. Di-n-butyl 1-hydroxy-1-phenylmethylphosphonate

TLC: $R_f$ 0.35 (hexane/acetone=2/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{20}$ +8.8 (*c* 1.05, $CHCl_3$) for 33% ee; IR (neat): 3282, 2960, 1454, 1236, 1058, 734 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 0.87 (t, 3H, $J$=7.3 Hz), 0.90 (t, 3H, $J$=7.3 Hz), 1.24–1.39 (m, 4H), 1.50–1.63 (m, 4H), 3.34 (dd, 1H, $J$=5.0, 10.3 Hz), 3.88–4.11 (m, 4H), 5.02 (dd, 1H, $J$=5.0, 11.0 Hz), 7.27–7.38 (m, 3H), 7.47–7.49 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.8, 18.8 ($J_{cp}$=4.8 Hz), 32.7 ($J_{cp}$=4.8 Hz), 66.8 ($J_{cp}$=7.6 Hz), 67.7 ($J_{cp}$=7.6 Hz), 71.0 ($J_{cp}$=158.3 Hz), 127.4 ($J_{cp}$=5.7 Hz), 128.1 ($J_{cp}$=3.0 Hz), 128.3, 137.1; $^{31}$P NMR ($CDCl_3$): $\delta$ 21.3; MS (FAB): $m/z$ 107, 173, 227, 301 $[M+H]^+$; HRMS: calcd for $C_{15}H_{26}O_4P$ 301.1569, found 301.1588; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=39/1, UV detection at 254 nm): $t_R$=12.0 min (major), 16.9 min (minor).

#### 4.3.5. (R)-Dibenzyl 1-hydroxy-1-phenylmethylphosphonate[19]

TLC: $R_f$ 0.27 (hexane/acetone=2/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{18}$ +0.4 (*c* 1.01, MeOH) for 8% ee (*R*). [lit.[19] $[\alpha]^{19}$ −16.3 (*c* 1.0, MeOH) for 99% ee (*S*)]; mp: 103.0–104.0 °C; $^1$H NMR ($CDCl_3$): $\delta$ 3.33 (dd, 1H, $J$=5.0, 9.8 Hz), 4.84–4.97 (m, 4H), 5.07 (dd, 1H, $J$=4.1, 10.3 Hz), 7.19–7.22 (m, 2H), 7.26–7.36 (m, 11H), 7.44–7.46 (m, 1H); $^{31}$P NMR ($CDCl_3$): $\delta$ 22.1; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=4/1, UV detection at 254 nm): $t_R$=9.2 min (*R*, major), 15.5 min (*S*, minor).

#### 4.3.6. (R)-Diethyl 1-hydroxy-1-(4-methoxyphenyl)-methylphosphonate (**2b**)[20]

TLC: $R_f$ 0.34 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{18}$ +14.1 (*c* 1.01, $CHCl_3$) for 40% ee (*R*). [lit.[20] $[\alpha]_D^{20}$ +29.8 (*c* 1.49, $CHCl_3$) for 74% ee (*R*)]; mp: 119.0–120.0 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.23 (t, 3H, $J$=6.9 Hz), 1.29 (t, 3H, $J$=6.9 Hz), 2.68–2.74 (m, 1H), 3.82 (s, 3H), 3.92–4.11 (m, 4H), 4.95 (dd, 1H, $J$=5.0, 10.1 Hz), 6.91 (d, 2H, $J$=8.2 Hz), 7.26–7.43 (m, 2H); $^{31}$P NMR ($CDCl_3$): $\delta$ 21.8; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=4/1, UV detection at 254 nm): $t_R$=11.0 min (*R*, major), 14.7 min (*S*, minor).

#### 4.3.7. Diethyl 1-hydroxy-1-(4-bromophenyl)methyl-phosphonate (**2c**)

TLC: $R_f$ 0.48 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{22}$ +7.2 (*c* 0.99, $CHCl_3$) for 22% ee; IR (KBr): 3259, 2979, 1578, 1486, 1230, 733 cm$^{-1}$; mp: 69.0–71.0 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.25 (t, 3H, $J$=6.9 Hz), 1.28 (t, 3H, $J$=6.9 Hz), 1.71 (br s, 1H), 4.00–4.11 (m, 4H), 4.99 (d, 1H, $J$=11.0 Hz), 7.35–7.38 (m, 2H), 7.49–7.51 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.32, 16.37, 63.1 ($J_{cp}$=7.6 Hz), 63.5 ($J_{cp}$=6.7 Hz), 70.1 ($J_{cp}$=159.2 Hz), 121.9 ($J_{cp}$=3.81 Hz), 128.7 ($J_{cp}$=4.77 Hz), 131.3, 135.8; $^{31}$P NMR ($CDCl_3$): $\delta$ 20.6; MS (FAB): $m/z$ 121, 185, 305, 307, 323, 325 $[M+H]^+$; HRMS: calcd for $C_{11}H_{17}O_4BrP$ 323.0048 (100), 325.0029(99), found 323.0043; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=9/1, UV detection at 254 nm): $t_R$=11.0 min (major), 14.8 min (minor).

#### 4.3.8. Diethyl 1-hydroxy-1-(1-naphthyl)methylphosphonate (**2d**)[20]

TLC: $R_f$ 0.13 (hexane/acetone=2/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{19}$ +11.5 (*c* 1.01, $CHCl_3$) for 9% ee. [lit.[20] $[\alpha]_D^{20}$ +19.4 (*c* 1.19, $CHCl_3$) for 35% ee]; mp: 114.0–115.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.05 (t, 3H, $J$=6.9 Hz), 1.25 (t, 3H, $J$=6.9 Hz), 3.32 (dd, 1H, $J$=5.5, 11.5 Hz), 3.72–3.82 (m, 1H), 3.92–4.12 (m, 3H), 5.86 (dd, 1H, $J$=5.5, 11.5 Hz), 7.48–7.56 (m, 3H), 7.82–7.88 (m, 3H), 8.10 (d, 1H, $J$=8.2 Hz); $^{31}$P NMR ($CDCl_3$): $\delta$ 21.7; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=9/1, UV detection at 254 nm): $t_R$=12.4 min (major), 42.3 min (minor).

#### 4.3.9. Diethyl 1-hydroxy-(2-naphthyl)methylphosphonate (**2e**)

TLC: $R_f$ 0.21 (hexane/acetone=2/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{22}$ +11.9 (*c* 1.0, $CHCl_3$) for 33% ee (*R*); IR (KBr): 3273, 2981, 1630, 1600, 1234, 1016, 762 cm$^{-1}$; mp: 88.0–89.0 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.21 (t, 3H, $J$=6.9 Hz), 1.26 (t, 3H, $J$=6.9 Hz), 3.89–4.18 (m, 5H), 5.20 (dd, 1H, $J$=4.1, 11.0 Hz), 7.46–7.50 (m, 2H), 7.60 (d, 1H, $J$=8.7 Hz), 7.82–7.85 (m, 3H), 7.96 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.31, 16.35, 63.1 ($J_{cp}$=6.7 Hz), 63.4 ($J_{cp}$=7.6 Hz), 70.9 ($J_{cp}$=158.3 Hz), 124.9 ($J_{cp}$=3.8 Hz), 126.05, 126.11, 127.6, 127.8, 128.0, 133.0, 134.16, 134.20; $^{31}$P NMR ($CDCl_3$): $\delta$ 21.4; MS (FAB): $m/z$ 157, 277, 295 $[M+H]^+$; HRMS: calcd for $C_{15}H_{20}O_4P$ 295.1099, found 295.1100; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=4/1, UV detection at 254 nm): $t_R$=8.3 min (major), 9.9 min (minor).

#### 4.3.10. (1R,2E)-Diethyl 1-hydroxy-3-phenylprop-2-enyl-phosphonate (**2f**)[21]

TLC: $R_f$ 0.34 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{18}$ +7.7 (*c* 0.92, $CHCl_3$) for 49% ee (*R*). [lit.[20] $[\alpha]_D^{20}$ +4.7 (*c* 0.59, $CHCl_3$) for 41% ee (*R*)]; mp: 99.0–99.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.34 (t, 6H, $J$=7.1 Hz), 2.66 (dd, 1H, $J$=3.6, 5.5 Hz), 4.16–4.24 (m, 4H), 4.64–4.70 (m, 1H), 6.32 (ddd, 1H, $J$=5.5, 5.7, 16.0 Hz), 6.78 (dd, 1H, $J$=4.6, 16.0 Hz), 7.25–7.42 (m, 5H); $^{31}$P NMR ($CDCl_3$): $\delta$ 21.9; HPLC (Daicel Chiralpak AS, flow rate: 1.0 mL/min, hexane/$^i$PrOH=9/1, UV detection at 254 nm): $t_R$=14.0 min (*R*, major), 23.0 min (*S*, minor).

#### 4.3.11. (R)-Diethyl 1-hydroxy-3-phenylpropylphosphonate (**2g**)[20]

TLC: $R_f$ 0.39 (hexane/acetone=1/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{20}$ −3.7 (*c* 1.0, $CHCl_3$) for 17% ee; $^1$H NMR ($CDCl_3$): $\delta$ 1.30–1.35 (m, 6H), 1.95–2.14 (m, 2H), 2.67–2.78 (m, 2H), 2.92–2.99 (m, 1H), 3.82–3.89 (m, 1H), 4.12–4.19 (m, 4H), 7.18–7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.4 (d, $J_{cp}$=4.8 Hz), 16.5 (d, $J_{cp}$=4.8 Hz), 31.6 (d, $J_{cp}$=14.3 Hz), 32.9, 62.5 (d, $J_{cp}$=7.7 Hz), 62.8 (d, $J_{cp}$=7.7 Hz), 66.8 (d, $J_{cp}$=160.2 Hz), 125.9, 128.4, 128.6, 141.3; $^{31}$P NMR ($CDCl_3$): $\delta$ 25.3. The enantiomeric excess was determined by $^{31}$P NMR analysis of a solution of the phosphonate (5 mg) and quinine (40 mg) in $CDCl_3$ (0.6 mL).[15]

#### 4.3.12. Diethyl 1-hydroxy-1-cyclohexylmethylphosphonate (**2h**)[22]

TLC: $R_f$ 0.35 (hexane/acetone=2/1, stained blue with phosphomolybdic acid/EtOH); $[\alpha]_D^{21}$ −1.5 (*c* 1.16, $CHCl_3$) for 23% ee; $^1$H NMR ($CDCl_3$): $\delta$ 1.35 (t, 3H, $J$=6.9 Hz), 1.35 (t, 3H, $J$=6.9 Hz), 1.09–1.35 (m, 5H), 1.66 (br d, 1H, $J$=11.4 Hz), 1.72–1.82 (m, 4H), 2.00 (br d, 1H,

$J$=12.8 Hz), 2.17 (t, 1H, $J$=6.9 Hz), 3.64–3.69 (m, 1H), 4.13–4.21 (m, 4H); $^{31}$P NMR ($CDCl_3$): $\delta$ 25.9. The enantiomeric excess was determined as **2g**.

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