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Asymmetric hydrophosphonylation of aldehydes catalyzed by bifunctional chiral Al(III) complexes

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Abstract

A new bifunctional chiral Al(III) complex of BINOL derivative, which contained *tert*-amine at 3,3′-position of the BINOL, has been developed for the effective enantioselective hydrophosphonylation of aldehydes. A variety of aromatic, heteroaromatic, condensed-ring, α,β-unsaturated, and aliphatic aldehydes were found to be suitable substrates for the reaction, and the desired α-hydroxy phosphonate were obtained in good to excellent yields (up to 99%) with moderate to good enantioselectivities (up to 87% ee) under mild conditions (at 0 °C). A possible catalytic cycle based on the experimental results was proposed.

Keywords: Aldehydes; Asymmetric catalysis; BINOL; Hydrophosphonylation; Al(III)

1. Introduction

In recent years, chiral α-hydroxy phosphoryl compounds (phosphonic acids and phosphonates) have attracted significant attentions owing to their biological activities.[1] To the best of our knowledge, the asymmetric hydrophosphonylation of aldehyde is probably the most effective methodology for their synthesis. However, in contrast to the hydrophosphonylation of imine compounds in which considerable progress has been made,[2,3] the asymmetric hydrophosphonylation of aldehydes is still less developed.[2a,4] Thus introduction of novel catalytic system that could show wide applicability for hydrophosphonylation of aldehydes has been strongly required.

Bifunctional catalysts have been tremendously developed for a broad range of asymmetric catalytic reactions.[5] Such catalysts could attach both electrophilic and nucleophilic substrates to the chiral catalyst in the transition state complex, thus could lead to a strong stereodiscrimination and catalyze the reaction with high enantioselectivity and reactivity. Just recently, we developed a BINOL based titanium(IV) complex in asymmetric cyano-ethoxycarbonylation of aldehydes, giving the desired products with good yields and enantioselectivities.[6] Enlightened by this, herein, we wish to report the asymmetric hydrophosphonylation of aldehydes using chiral Al(III) complex of BINOL derivative as the catalyst.

2. Results and discussion

2.1. Chiral ligand screening

In the preliminary studies, several BINOL derivatives were complexed in situ with $AlEt_2Cl$ to catalyze the asymmetric hydrophosphonylation of benzaldehyde in dry THF at 0 °C. As shown in Table 1, Al(III) complexes of BINOL and BINOL derivatives, which contained phosphorus, quinoline or sterically bulky β-naphthyl moieties only gave extremely poor results for the reaction (Table 1, entries 1–4), while the chiral aluminum species bearing two *tert*-amine moieties on the BINOL showed high reactivities (Table 1, entries 6–10), and the aluminum complex of (*R*,*S*)-**1j** gave the product with the

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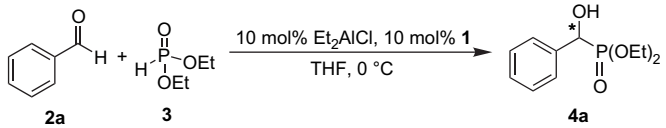
Table 1
Ligand screening for the hydrophosphonylation of benzaldehyde



Entry[a]	Ligand (10 mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	48	Trace	7 (*S*)
2	**1b**	24	ND[d]	—
3	**1c**	40	Trace	—
4	**1d**	24	NR	
5	**1e**	24	<19	0
6	**1f**	24	49	27 (*R*)
7	**1g**	40	71	46 (*S*)
8	**1h**	48	81	65 (*S*)
9	**1i**	48	68	56 (*S*)
10	**1j**	48	85	70 (*S*)

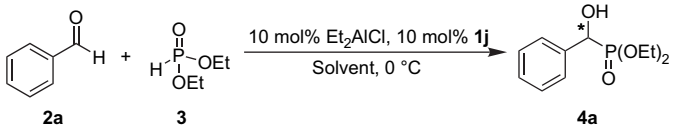
[a] The reactions were carried out under nitrogen, benzaldehyde (0.25 mmol), and diethyl phosphite (0.325 mmol) in 0.5 mL THF.
[b] Isolated yield.
[c] Determined by HPLC on Chiral AS-H column analysis, the absolute configuration of the major product was determined by the comparison with the reported value of optical rotation (Ref. 4h).
[d] Not determined.

best result (85% yield and 70% ee) (Table 1, entry 10). In contrast, ligand (*S*,*S*)-**1f** with an (*S*)-BINOL fragment displayed low enantioselectivity and favored the chiral α-hydroxy phosphonate with an opposite configuration as that produced by (*R*,*S*)-**1j** (Table 1, entry 6 vs entry 10). These results suggested that the axial chirality of the BINOL moieties had more influence in determining the absolute configuration of the hydrophosphonylation product, and the matched stereogenic elements are (*R*)-BINOL and (*S*)-1-phenylethanamine component (Fig. 1j).

2.2. Effect of reaction solvent

Solvent survey revealed that THF provided the product with the best reactivity and enantioselectivity (Table 2, entry 1).

Table 2
Effect of solvent in the asymmetric hydrophosphonylation of benzaldehyde



Entry[a]	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	THF	48	85	70
2	CH_2Cl_2	48	51	71
3	Et_2O	24	76	61
4	*t*-$BuOCH_3$	24	68	60
5	Anisole	30	26	12
6	1,2-Dimethoxyethane	15	66	2
7	2-Methoxypropane	15	88	43

[a] The reactions were carried out under nitrogen, benzaldehyde (0.25 mmol), and diethyl phosphite (0.325 mmol) in 0.5 mL solvent.
[b] Isolated yield.
[c] Determined by HPLC on Chiral AS-H column analysis.

Although CH_2Cl_2 gave a comparable enantioselectivity for the reaction, it led to a dramatic loss of reactivity (Table 2, entry 2). Further solvent studies focusing on ethers did not give any improvement for the reaction (Table 2, entries 3–7), especially for the anisole and 1,2-dimethoxyethane, only poor ee were obtained (Table 2, entries 5 and 6).

2.3. Effect of Lewis acids, concentration of benzaldehyde, and molecular sieves

The counterions of **1j**-Al(III) complexes showed a crucial effect on the enantioselectivity.[7] Upon changing the aluminum(III) reagent from $AlEt_2Cl$ through $AlEt_3$ to $Al(O^iPr)_3$, the enantioselectivities of the reaction decreased from 70% to 25% (Table 3, entries 1–3). Furthermore, increasing the concentration of the reaction led to slightly decreased reactivity and enantioselectivity (Table 3, entry 5), while only 53% yield and 42% ee were obtained when lowering the concentration of benzaldehyde from 0.5 M to 0.25 M (Table 3, entry 4), and

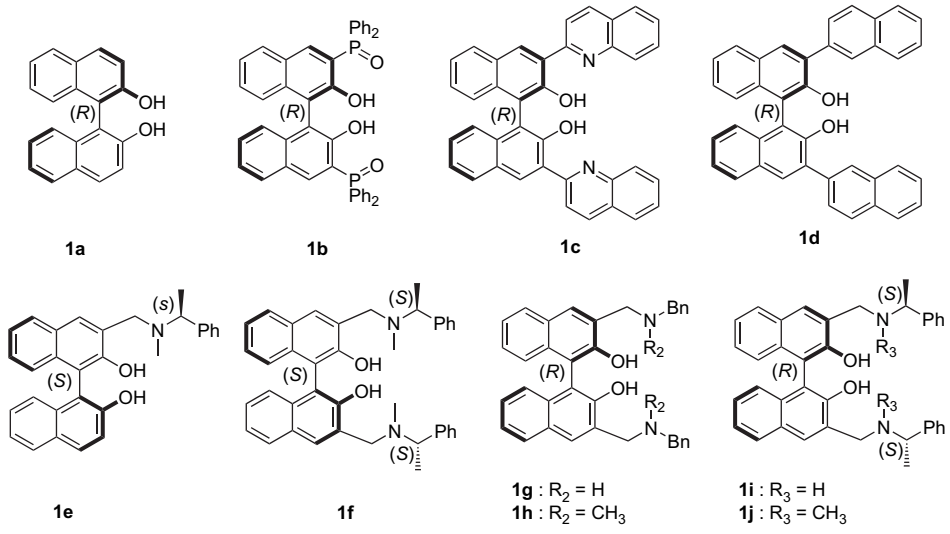
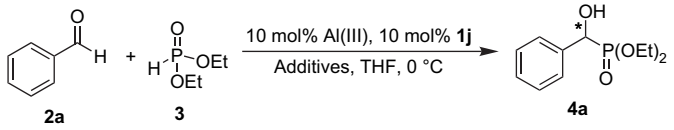


Figure 1. Structures of the ligands evaluated in this study.

Table 3
Effect of Lewis acid, concentration of benzaldehyde, and molecular sieves



Entry[a]	Metal	Concentration (M)	MS (mg)	Time (h)	Yield[b] (%)	ee[c] (%)
1	$AlEt_2Cl$	0.5	—	40	85	70
2	$Al(O^iPr)_3$	0.5	—	15	87	25
3	$AlEt_3$	0.5	—	15	98	52
4	$AlEt_2Cl$	0.25	—	40	53	42
5	$AlEt_2Cl$	0.75	—	30	83	67
6[d]	$AlEt_2Cl$	0.5	3 Å (10 mg)	24	88	75
7[d]	$AlEt_2Cl$	0.5	4 Å (10 mg)	24	33	37
8[d]	$AlEt_2Cl$	0.5	5 Å (10 mg)	24	51	36
9[d]	$AlEt_2Cl$	0.5	3 Å (5 mg)	20	71	57
10[d]	$AlEt_2Cl$	0.5	3 Å (15 mg)	24	76	46

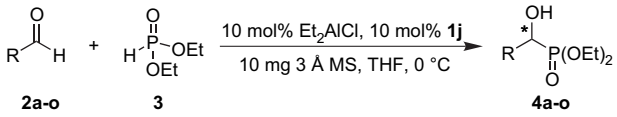
[a] The reactions were carried out under nitrogen, benzaldehyde (0.25 mmol), and diethyl phosphite (0.325 mmol) in THF.
[b] Isolated yield.
[c] Determined by HPLC on Chiral AS-H column analysis.
[d] THF was dried over $CaCl_2$, and used directly without distilling.

the concentration of benzaldehyde seemed to be appropriate at 0.5 M. To further improve the enantioselectivity of the reaction, molecular sieves were investigated. Compared with 4 Å and 5 Å molecular sieves, which showed unsatisfied results for the reaction (Table 3, entries 7 and 8 vs entry 1), the addition of 3 Å molecular sieves could improve the ee to 75% (Table 3, entry 6 vs entry 1). Further increasing or decreasing the amount of 3 Å molecular sieves would dramatically decrease the enantioselectivity of the reaction (Table 3, entries 9 and 10 vs entry 6). Hence, the optimized reaction conditions were as following: benzaldehyde (0.25 mmol), diethyl phosphite (0.325 mmol), 10 mmol % **lj**, 10 mmol % Et_2AlCl, and 10 mg 3 Å molecular sieves in 0.5 mL THF at 0 °C.

2.4. Substrate generality

Under the optimized conditions, various aldehydes were tested in the asymmetric hydrophosphonylation reaction, providing the corresponding products in good to excellent yield with moderate to good ee value. As shown in Table 4, the substituents of aromatic aldehydes impacted both reactivities and enantioselectivities of the reaction. In contrast to benzaldehyde, the electron-donating groups on the aromatic aldehydes had a beneficial effect on the enantioslectivities (Table 4, entries 1–5), and the aromatic aldehydes bearing electron-withdrawing groups gave the products with only moderate ee values (Table 4, entries 6–8). It was noteworthy that biphenyl-4-carbaldehyde, which was rarely studied previously, was also examined in the asymmetric hydrophosphonylation reaction, affording diethyl(4-phenyl)(hydroxy)methylphosphonate with 82% ee (Table 4, entry 9). While the condensed-ring aldehydes (1-naphthaldehyde and 2-naphthaldehyde) reacted smoothly with diethyl phosphite, giving the products with 78% and 74% ee, respectively (Table 4, entries 10 and 11), the reaction

Table 4
Asymmetric hydrophosphonylation of aldehydes catalyzed by **1j**–Al(III) complex



Entry[a]	Aldehyde	Time (h)	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde (**2a**)	24	88	75 (*S*)
2	4-Methoxybenzaldehyde (**2b**)	40	74	87 (*S*)
3	3-Methoxybenzaldehyde (**2c**)	40	71	81
4	Benzo[*d*][1,3]dioxole-5-carbaldehyde (**2d**)	24	73	83[d]
5	4-Methylbenzaldehyde (**2e**)	40	91	83 (*S*)
6	4-Chlorobenzaldehyde (**2f**)	40	88	65 (*S*)
7	4-Fluorobenzaldehyde (**2g**)	40	87	62
8	4-Nitrobenzaldehyde (**2h**)	20	88	67
9	Biphenyl-4-carbaldehyde (**2i**)	40	85	82
10	1-Naphthaldehyde (**2j**)	20	90	78 (*S*)[e]
11	2-Naphthaldehyde (**2k**)	20	82	74
12	(*E*)-Cinnamaldehyde (**2l**)	20	86	63 (*S*)
13	Thiophene-2-carbaldehyde (**2m**)	30	75	45 (*S*)
14	3-Phenylpropanal (**2n**)	30	99	75
15	Pentanal (**2o**)	20	85	77[f]

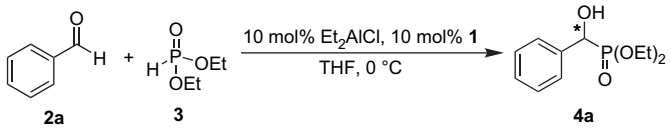
[a] The reactions were carried out under nitrogen, aldehyde (0.25 mmol), and diethyl phosphite (0.325 mmol) in 0.5 mL THF.
[b] Isolated yield.
[c] Unless indicated, the ee was determined by HPLC on Chiral AS-H column analysis, the absolute configuration of the major product was *S* compared with the reported value of optical rotation (Ref. 4h,i).
[d] Determined by Chiral OD-H column analysis.
[e] Determined by Chiral AD-H column analysis.
[f] Determined by HPLC analysis after conversion of the product into the corresponding benzoate.

of α,β-unsaturated aldehyde (cinnamaldehyde) showed a reduced enantioselectivity with good reactivity (Table 4, entry 12). For the heteroaromatic aldehyde (thiophene-2-carbaldehyde), a slightly higher ee was also obtained compared with the previous report (Table 4, entry 13).[4h] The enantioselective hydrophosphonylation of aliphatic aldehydes gave the corresponding α-hydroxy phosphonate in good to excellent yields with good ee values (Table 4, entries 14 and 15).

2.5. Catalytic cycle considerations

The phosphonate–phosphite tautomerism is common. The nonnucleophilic phosphonate form will shift to the reactive nucleophilic phosphite in the presence of a base or a Lewis acid.[3,4,8] And, it has been proved that the hydrophosphonylation could proceed smoothly using tertiary amines or aluminum(III) as the catalyst.[2–4] As to our catalytic system, the asymmetric hydrophosphonylation of aldehyde showed high reactivity in the presence of chiral Al(III) complex of BINOL derivative ($AlEt_2Cl$ as the aluminum(III) source), which contains two *tert*-amine moieties (Table 1, entries 8 and 10). However, using BINOL–$AlEt_2Cl$ complex as the catalyst, only trace amount of product was afforded (Table 1, entry 1). Thus, we considered that the *tert*-amine moiety of the BINOL derivative played a crucial role in the reaction. Indeed, the addition of a competing external base Et_3N (10 mol %) decreased the enantioselectivity of

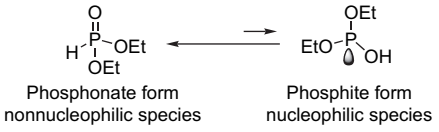
Table 5
Control experiments in the asymmetric hydrophosphonylation of benzaldehyde



Entry[a]	Ligand (10 mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	**1j**	48	>93	51
2	**1a**	48	Trace	7
3[d]	—	48	Trace	—
4[d]	**1a**	48	73	0
5[e]	**1a**	48	27	4
6[f]	**1a**	48	61	0

[a] The reactions were carried out under nitrogen, benzaldehyde (0.25 mmol), and diethyl phosphite (0.325 mmol) in 0.5 mL THF.
[b] Isolated yield.
[c] The ee was determined by HPLC on Chiral AS-H column analysis.
[d] Et_3N (10 mol %) was added.
[e] $Al(O^iPr)_3$ was used as the aluminum source.
[f] $AlEt_3$ was used as the aluminum source.

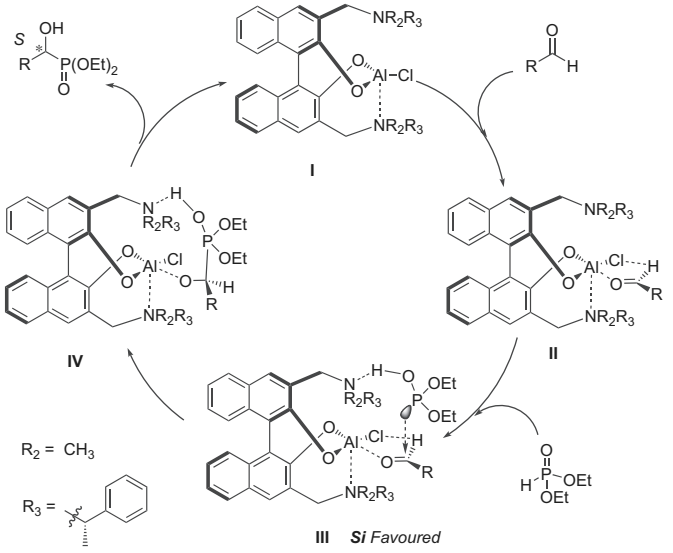
the reaction while the reactivity was improved (Table 5, entry 1). Furthermore, it was the *tert*-amine moiety and not the Lewis acid Al(III) center of the catalyst (**1j**−$AlEt_2Cl$) that shifted the phosphonate−phosphite equilibrium toward the phosphate form to undergo nucleophilic addition (Scheme 1). Based on the previous reports,[9] it is proposed that the complex **1j**−$AlEt_2Cl$ acted as a bifunctional catalyst for the reaction, which was also proved by the control experiments. While the BINOL−$AlEt_2Cl$ and Et_3N could not catalyze the reaction, respectively, the hydrophosphonylation of aldehyde proceed smoothly in the presence of BINOL−$AlEt_2Cl$ and Et_3N (Table 5, entries 2 and 3 vs entry 4).



Scheme 1. The equilibrium of phosphonate−phosphite.

Furthermore, the counterions of **1j**−Al(III) complexes played an important role for the asymmetric hydrophosponylation reaction (Table 3, entries 1−3). These disparate results were probably caused by the steric and electronic differences of the counterions (Cl, Et, and O^{i}Pr), which showed a different action in the catalytic cycles. In fact, using BINOL as the chiral ligand, $AlEt_3$ and $Al(O^iPr)_3$ provided the racemate products with 27% and 61% yield, respectively, while the reaction did not proceed using $AlEt_2Cl$ as the aluminum(III) source (Table 5, entries 5 and 6 vs entry 2). Thus, we suspected that the Lewis acid Al(III) moiety of the $AlEt_3$−**1j** and $Al(O^iPr)_3$−**1j** complexes may catalyze the reaction independently, and consequently the complex with $AlEt_3$ and $Al(O^iPr)_3$ shows high reactivity and low enantioselectivity in the reaction.

On the basis of the previous reports,[3,4,9,10] our experimental investigations and the absolute configuration of the products, a possible catalytic cycle containing the transition state has been proposed. As shown in Scheme 2, the Al(III) center of catalyst acted as a Lewis acid and activated the aldehyde to give the species **II**. The aldehyde was fixed on the catalyst and activated by two kinds of interactions: the strong one involving the coordination between Al(III) and the oxygen of the carbonyl group, and the weak one was the hydrogen bond effect between proton of aldehyde and chlorine atom.[9b,10] In addition, considering the steric effect of the bulk tertiary amine moiety as well as the diethyl phosphite, we envisage that the aldehyde seems to be not possible to approach the Al(III) center of catalyst along a vector trans to the coordinated nitrogen. In contrast, the carbonyl preferred to approach the catalyst along a vector trans to oxygen (the less hindered way, as shown in Scheme 2, species **II**), and led to a distorted square pyramidal configuration of aluminum(III) species. On the other hand, the tertiary amine moiety of the catalyst functioned as a Lewis base to activate the diethyl phosphite. The subsequent nucleophilic addition of phosphite to the aldehyde produced the chiral α-hydroxy phosphonate and regenerated the catalyst **I**.



Scheme 2. The proposed catalytic cycle for the asymmetric hydrophosponylation of aldehyde.

3. Conclusions

In summary, a new bifunctional chiral Al(III) complex of BINOL derivative **1j** has been developed for the asymmetric hydrophosphonylation of aldehyde, and showed a broad substrate generality. Based on previous reports and the experimental phenomena, a possible catalytic cycle has been proposed. The applications of the catalyst system in other asymmetric catalytic reactions are currently underway.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts were reported in parts per million from tetramethylsilane with the solvent resonance as the

internal standard ($CDCl_3$, δ=7.26). Spectra are reported as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (J, Hz), integration, and assignment. ^{13}C NMR spectra were collected on commercial instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ=77.0). The enantiomeric excesses were determined by HPLC analysis on chiral DAICEL CHIRALCEL AS-H, AD-H, OD-H, and AD column at 254 nm unless specially indicated. Optical rotations were measured on a commercial polarimeter and reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). Reagents obtained from commercial sources were used without further purification. Unless specially indicated, CH_2Cl_2 and THF were distilled over CaH_2 and Na, respectively, before use.

4.2. Typical procedure for the enantioselective hydrophosphonylation of aldehydes

$AlEt_2Cl$ (25%, w/w, 16 μL, 0.025 mmol) was added to a solution of **1j** (14.5 mg, 0.025 mmol) in 0.5 mL THF, and the mixture was stirred at 25 °C for 0.5 h under N_2 atmosphere, followed by the addition of the corresponding aldehyde (0.25 mmol) and diethyl phosphonate (40 μL, 0.325 mmol) at 0 °C. The contents were stirred for the indicated time as shown in Table 5, and the residue was purified by silica gel column chromatography (acetone/petroleum oil, 3:7–7:3 v/v) to afford the corresponding α-hydroxy phosphonate.

4.2.1. (S)-Diethyl hydroxy(phenyl)methylphosphonate (**4a**)

White solid, yield 88%. $[\alpha]_D^{25}$ −20.5 (c 2.0 in $CHCl_3$) (75% ee) [lit.[4h] $[\alpha]_D^{20}$ −6.6 (c 1.0, $CHCl_3$) for *S* enantiomer in 20% ee]. HPLC (AS-H column, 2-propanol/hexane 15/85, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.6 min, t_R (major)=10.8 min. ^1H NMR (300 MHz, $CDCl_3$): δ=7.46–7.49 (m, 2H), 7.25–7.37 (m, 3H), 5.00 (d, J=11.0 Hz, 1H), 3.94–4.08 (m, 4H), 1.14–1.27 (m, 6H) ppm.

4.2.2. (S)-Diethyl hydroxy(4-methoxyphenyl)methylphosphonate (**4b**)

White solid, yield 74%. $[\alpha]_D^{20}$ −34.7 (c 0.9 in $CHCl_3$) (87% ee) [lit.[4h] $[\alpha]_D^{20}$ −31.1 (c 1.0, $CHCl_3$) for *S* enantiomer in 82% ee]. HPLC (AS-H column, 2-propanol/hexane 20/80, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=10.5 min, t_R (major)=14.7 min. ^1H NMR (400 MHz, $CDCl_3$): δ=7.43 (d, J=6.8 Hz, 2H), 6.93 (t, J=8.8 Hz, 2H), 4.98 (d, J=9.6 Hz, 1H), 3.94–4.14 (m, 4H), 3.83 (s, 3H), 1.27 (dt, J=23.2, 7.2 Hz, 6H) ppm.

4.2.3. Diethyl hydroxy(3-methoxyphenyl)methylphosphonate (**4c**)

Colorless oil, yield 71%. $[\alpha]_D^{20}$ −18.14 (c 0.6 in $CHCl_3$) (81% ee). HPLC (AS-H column, 2-propanol/hexane 20/80, flow 1.0 mL/min, detection at 254 nm). t_R(minor)=10.0 min, t_R (major)=15.8 min. ^1H NMR (400 MHz, $CDCl_3$): δ=7.30 (t, J=7.6 Hz, 1H), 7.08 (d, J=8.0 Hz, 2H), 6.88 (d, J=8.4 Hz, 1H), 5.03 (d, J=10.8 Hz, 1H), 3.99–4.16 (m, 4H), 3.84 (s, 3H), 1.24–1.39 (dt, J=20.0, 6.8 Hz, 6H) ppm.

4.2.4. Diethyl benzo[d][1,3]dioxol-5-yl(hydroxy)methylphosphonate (**4d**)

Colorless oil, yield 73%. $[\alpha]_D^{20}$ +19.20 (c 0.5 in $CHCl_3$) (83% ee). HPLC (OD-H, 2-hexane/^{i}PrOH, 90/10, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.2 min, t_R (major)=9.6 min. ^1H NMR (400 MHz, $CDCl_3$): δ=6.94 (s, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.70 (d, J=8.0 Hz, 1H), 5.88 (s, 2H), 4.83 (d, J=10.0 Hz, 1H), 3.88–4.05 (m, 4H), 1.18 (dt, J=18.4, 7.2 Hz, 6H) ppm.

4.2.5. (S)-Diethyl hydroxy(4-methylphenyl)methylphosphonate (**4e**)

Colorless oil, yield 91%. $[\alpha]_D^{20}$ −37.96 (c 0.6 in $CHCl_3$) (83% ee) [lit.[4h] $[\alpha]_D^{20}$ −20.0 (c 1.0, $CHCl_3$) for *S* enantiomer in 58% ee]. HPLC (AS-H column, 2-propanol/hexane 20/80, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.7 min, t_R (major)=11.5 min. ^1H NMR (400 MHz, $CDCl_3$): δ=7.37 (dd, J=2.0, 8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 4.98 (dd, J=6.0, 10.4 Hz, 1H), 3.93–4.10 (m, 4H), 2.35 (d, J=1.6 Hz, 3H), 1.25 (dt, J=23.2, 7.2 Hz, 6H) ppm.

4.2.6. (S)-Diethyl (4-chlorophenyl)(hydroxy)methylphosphonate (**4f**)

White solid, yield 88%. $[\alpha]_D^{20}$ −31.51 (c 0.6 in $CHCl_3$) (65% ee) [lit.[4i] $[\alpha]_D^{20}$ +24.3 (c 1.0, $CHCl_3$) for *R* enantiomer in 52% ee]. HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=7.1 min, t_R (major)=9.1 min. ^1H NMR (400 MHz, $CDCl_3$): δ=7.33–7.44 (m, 4H), 5.00 (dd, J=4.8, 10.8 Hz, 1H), 3.99–4.17 (m, 4H), 1.22–1.30 (dt, J=6.8, 12.8 Hz, 6H) ppm.

4.2.7. Diethyl (4-fluorophenyl)(hydroxy)methylphosphonate (**4g**)

White solid, yield 87%. $[\alpha]_D^{20}$ −16.85 (c 0.2 in $CHCl_3$) (62% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=6.5 min, t_R (major)=7.9 min. ^1H NMR (400 MHz, $CDCl_3$): δ=6.95–6.98 (m, 2H), 6.56 (t, J=8.4 Hz, 2H), 4.50 (d, J=10.4 Hz, 1H), 3.47–3.61 (m, 4H), 0.72–0.79 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.5 (d, J=245 Hz), 132.6, 128.8, 115.1 (d, J=22 Hz), 70.1 (d, J=158 Hz), 63.4 (d, J=7 Hz), 63.0 (d, J=7 Hz), 16.4 (d, J=6 Hz) ppm. ESI–HRMS calcd for ($C_{11}H_{16}FO_4P+H^+$) 263.0843, found: 263.0844.

4.2.8. Diethyl hydroxy(4-nitrophenyl)methylphosphonate (**4h**)

White solid, yield 88%. $[\alpha]_D^{20}$ −31.2 (c 2.0 in $CHCl_3$) (67% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=9.9 min, t_R (major)=12.8 min. ^1H NMR (400 MHz, $CDCl_3$): δ=8.23 (d, J=8.4 Hz, 2H), 7.67 (dd, J=2.0, 8.8 Hz, 2H), 5.17 (d, J=12.0 Hz, 1H), 4.05–4.24 (m, 4H), 1.25–1.31 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.52, 144.45, 127.7 (d, J=5 Hz), 123.3, 70.1 (d, J=158 Hz), 64.0 (d, J=8 Hz), 63.3 (d, J=8 Hz) 16.4 ppm.

ESI–HRMS calcd for ($C_{11}H_{16}NO_6P+H^+$) 290.0788, found: 290.0785.

*4.2.9. Diethyl (4-phenyl)(hydroxy)methylphosphonate (**4i**)*

White solid, yield 85%. $[\alpha]_D^{20}$ −34.95 (*c* 2.0 in $CHCl_3$) (82% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.9 min, t_R (major)=12.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54–7.63 (m, 4H), 7.44 (t, *J*=7.6 Hz, 2H), 7.35 (t, *J*=7.6 Hz, 2H), 7.26 (s, 1H), 5.07 (d, *J*=10.8 Hz, 1H), 3.99–4.13 (m, 4H), 1.27 (dt, *J*=6.8, 16.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.8, 140.6, 135.7, 128.8, 127.5 (d, *J*=6 Hz), 127.4, 127.1, 126.9, 70.1 (d, *J*=158 Hz), 63.4 (d, *J*=7 Hz), 63.1 (d, *J*=7 Hz), 16.4 ppm. ESI–HRMS calcd for ($C_{17}H_{21}O_4P+Na^+$) 343.1070, found: 343.1065.

*4.2.10. (S)-Diethyl hydroxy(naphthalen-1-yl)methylphosphonate (**4j**)*

White solid, yield 90%. $[\alpha]_D^{20}$ −100.5 (*c* 0.6 in $CHCl_3$) (78% ee) [lit.[4h] $[\alpha]_D^{20}$ +19.4 (*c* 1.0, $CHCl_3$) for *R* enantiomer in 35% ee]. HPLC (AD-H, 2-hexane/^{i}PrOH, 90/10, flow 1.0 mL/min, detection at 254 nm). t_R (major)=10.8 min, t_R (minor)=12.0 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (d, *J*=8.4 Hz, 1H), 7.82–7.88 (m, 3H), 7.47–7.56 (m, 3H), 5.86 (d, *J*=11.6 Hz, 1H), 3.92–4.12 (m, 3H), 3.72–3.83 (m, 1H), 3.37 (s, 1H), 1.25 (t, *J*=7.2 Hz, 3H), 1.06 (t, *J*=7.2 Hz, 3H) ppm.

*4.2.11. Diethyl hydroxy(naphthalen-2-yl)methylphosphonate (**4k**)*

White solid, yield 82%. $[\alpha]_D^{20}$ −26.97 (*c* 0.5 in $CHCl_3$) (74% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.8 min, t_R (major)=11.2 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (s, 1H), 7.81–7.85 (m, 3H), 7.60 (d, *J*=8.8 Hz, 1H), 7.46–7.51 (m, 2H), 5.20 (d, *J*=11.2 Hz, 1H), 3.95–4.10 (m, 4H), 1.24 (dt, *J*=7.2, 21.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=134.2, 133.1 (d, *J*=2 Hz), 128.1 (d, *J*=1 Hz), 127.9, 127.7, 126.1 (d, *J*=7 Hz), 125.0, 71.0 (d, *J*=158 Hz), 63.4 (d, *J*=7 Hz), 63.1 (d, *J*=7 Hz), 16.4 ppm; ESI–HRMS calcd for ($C_{15}H_{19}O_4P+H^+$) 295.1094, found: 295.1091.

*4.2.12. (E)-Diethyl 1-hydroxy-3-phenylallylphosphonate (**4l**)*

White solid, yield 86%. $[\alpha]_D^{20}$ −12.37 (*c* 0.2 in $CHCl_3$) (63% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=9.9 min, t_R (major)=18.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24–7.42 (m, 5H), 6.78 (dd, *J*=4.8, 11.2 Hz, 1H), 6.28–6.36 (m, 1H), 4.64–4.69 (m, 1H), 4.16–4.24 (m, 4H), 1.34 (t, *J*=7.2 Hz, 6H) ppm.

*4.2.13. (S)-Diethyl hydroxy(thiophen-2-yl)methylphosphonate (**4m**)*

Colorless oil, yield 75%. $[\alpha]_D^{20}$ −6.09 (*c* 0.2 in $CHCl_3$) (45% ee) [lit.[4h] $[\alpha]_D^{20}$ −9.3 (*c* 1.0, $CHCl_3$) for *S* enantiomer in 41% ee]. HPLC (AS-H, 2-hexane/^{i}PrOH, 80/20, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=7.8 min, t_R (major)=9.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32 (dt, *J*=1.2, 5.2 Hz, 1H), 7.19 (t, *J*=7.2 Hz, 1H), 7.01 (dd, *J*=4.0, 5.2 Hz, 1H), 5.24 (d, *J*=10.8 Hz, 1H), 4.04–4.30 (m, 4H), 1.29 (dt, *J*=6.8, 20.0 Hz, 6H) ppm.

*4.2.14. Diethyl 1-hydroxy-3-phenylpropylphosphonate (**4n**)*

Colorless oil, yield 99%. $[\alpha]_D^{20}$ +14.65 (*c* 0.3 in $CHCl_3$) (75% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 90/10, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=6.1 min, t_R (major)=10.7 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.17–7.31 (m, 5H), 4.11–4.21 (m, 4H), 3.82–3.87 (m, 1H), 2.92–2.99 (m, 1H), 2.70–2.78 (m, 1H), 1.99–2.08 (m, 2H), 1.29–1.35 (m, 6H) ppm.

*4.2.15. Diethyl 1-hydroxypentylphosphonate (**4o**)*

Colorless oil, yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.13–4.21 (m, 4H), 3.85 (dt, *J*=5.6, 15.6 Hz, 1H), 1.58–1.80 (m, 3H), 1.32–1.41 (m, 9H), 0.82 (t, *J*=7.2 Hz, 3H) ppm. The product of **4o**: diethyl 1-(phenylperoxy)pentylphosphonate: colorless oil, yield 89%. $[\alpha]_D^{20}$ +14.67 (*c* 2.0 in $CHCl_3$) (77% ee). HPLC (AS-H, 2-hexane/^{i}PrOH, 90/10, flow 1.0 mL/min, detection at 254 nm). t_R (minor)=8.7 min, t_R (major)=14.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07–8.10 (m, 2H), 7.60 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=8.0 Hz 2H), 5.53 (dt, *J*=4.8, 12.4 Hz, 1H), 4.13–4.21 (m, 4H), 1.96–2.18 (m, 2H), 1.28–1.44 (m, 10H), 0.89 (t, *J*=7.2 Hz 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.6 (d, *J*=5 Hz), 133.3, 129.8, 129.5, 128.5, 68.4 (d, *J*=166 Hz), 62.8 (d, *J*=7 Hz), 62.6 (d, *J*=6 Hz), 29.2, 27.8, 22.2, 16.5 (d, *J*=5 Hz), 16.4 (d, *J*=6 Hz), 13.8 ppm. ESI–HRMS calcd for ($C_{16}H_{25}O_5P+H^+$) 329.1512, found: 329.1515.

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