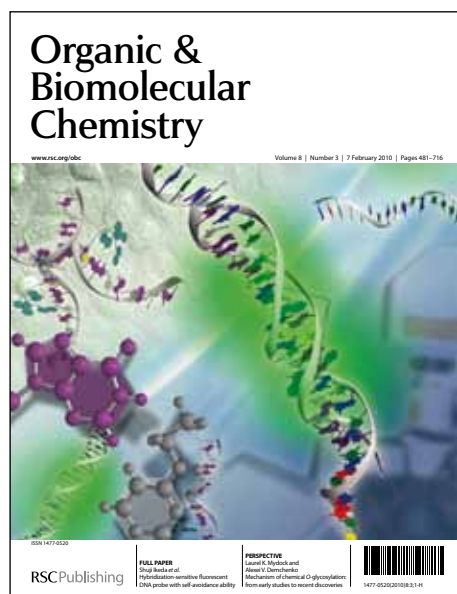


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ARTICLE

Organocatalytic Enantioselective Hydrophosphonylation of Aldehydes

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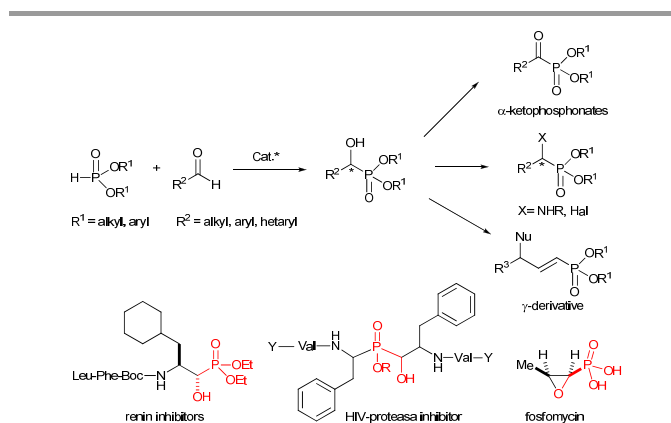
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We report our results concerning the first squaramide-catalysed hydrophosphonylation of aldehydes. In all cases, the reactions proceeded smoothly and cleanly under mild reaction conditions rendering final α -hydroxy phosphonates in very good yields and high enantioselectivities. It is one of the scarce organocatalytic examples of this reaction using aldehydes. It is the first time that diphenylphosphite **1e** has been successfully employed in a chiral Pudovik reaction with aldehydes, in contrast to the dialkylphosphites used in previously published procedures, extending the generality of this asymmetric methodology.

Introduction

Addition of dialkyl- and diphenylphosphites to carbonyl compounds (Pudovik reaction)¹ is a powerful and widely applied strategy for the construction of C-P bonds, and a straightforward tool for providing efficient access to chiral α -hydroxy phosphonates and their corresponding phosphonic acids.² Interestingly, compounds bearing this motif have shown remarkable biological activities and are currently employed in the pharmaceutical industry (Scheme 1).³ The absolute configuration of these phosphonyl compounds could strongly influence their biological activities,⁴ and a growing interest in their asymmetric synthesis has been promoted during the last two decades. Several efficient enantioselective catalytic methods of hydrophosphonylation of aldehydes have been reported in the presence of a chiral metal complex giving access to α -hydroxy phosphonates with good outcomes.^{5,6}

In addition to the extensive spectrum of biological properties exhibited by this kind of compounds (antibacterial, antiviral, antibiotic and pesticidal activities, as well as a potent antitumor agent),⁷ α -hydroxy phosphonates have also attracted attention as synthetic intermediates for preparing further α -⁸ and γ -functionalised⁹ phosphonates (Scheme 1).

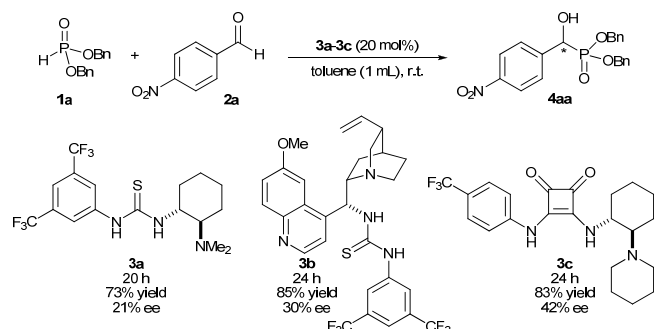


Scheme 1 Direct approach to appealing phosphonate derivatives

Although the Pudovik reaction with aldehydes has been the focus of intensive studies using chiral metal catalysts,^{2,5,6} the organocatalytic version of this appealing strategy has been overlooked in the literature. After the pioneering chiral organocatalytic example appeared in 1983,¹⁰ in which a scarce number of aldehydes (only two) was disclosed, requiring successive recrystallizations to improve the enantioselectivities, only a pivotal example of an organocatalysed approach has been published in 2009 by Ooi's group.¹¹ Our experience in the organocatalysed Pudovik reaction with imines^{12,13} and hydrazones,¹⁴ and the lack of background information on aldehydes encouraged us to explore the feasibility of catalysing this process with hydrogen bonding based catalysts, due to their well-known capacity to activate carbonyl compounds.^{15,16} In this communication, we report our appealing results concerning the first asymmetric squaramide-organocatalysed Pudovik reaction using aldehydes.

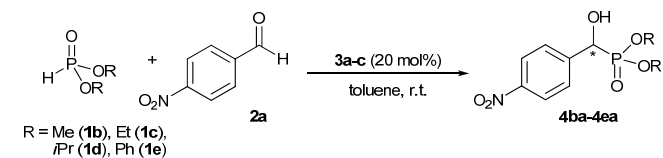
Results and discussion

We started our investigation examining the viability of the addition of dibenzylphosphite (**1a**) to aldehyde **2a** catalysed by chiral catalysts **3a-3c** acting through hydrogen bonding (Scheme 2). Based on our own experience in the hydrophosphonylation reaction,^{12,14} we foresaw the importance of comprising a basic functionality in the catalyst structure, favouring a plausible bifunctional catalysis, since only model catalysts **3a-c** afforded promising results, compared with simple thioureas.¹⁷



Scheme 2 Model hydrophosphonylation reaction tested

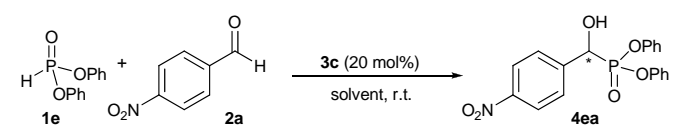
To our delight, the initial screening of catalysts revealed squaramide **3c** to be the best compromise in terms of both enantioselectivity and reactivity. However, before discarding thioureas **3a** and **3b**, we continued exploring these catalysts to verify if they worked better with other phosphites **1b-1e** (Table 1).

Table 1. Screening of different phosphites **1b-e** with catalysts **3a-c**.^a

Entry	R	Cat.	time (h)	yield (%) ^b	ee(%) ^c
1 ^d	Me	3a	20	83	8
2 ^d	Et	3a	18	90	14
3 ^d	<i>i</i> Pr	3a	48	83	14
4 ^d	Ph	3a	72	30	18
5	Me	3c	20	86	38
6	Et	3c	24	n.d. ^e	n.d. ^e
7	<i>i</i> Pr	3c	24	n.d. ^e	n.d. ^e
8	Ph	3c	20	83	46
9	Ph	3b	48	57	25

^a Experimental conditions: To a mixture of catalyst **3a-c** (0.02 mmol) and aldehyde **2a** (0.1 mmol) in toluene (0.5 mL), phosphite **1b-e** (0.2 mmol) was further added in a test tube at room temperature. After the reaction time, adducts **4** were isolated by flash chromatography. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Reaction performed using 0.2 mmol of aldehyde. ^e Not determined.

After examining the influence of diverse phosphites **1b-e** in our reaction model, and although we did not observe reactivity with some of the phosphites investigated while using catalyst **3c** (entries 6 and 7), we found that diphenylphosphite (**1e**) led to the best results in terms of enantioselectivity and reactivity (entry 8). Subsequent to this exploration, we continued the study with squaramide **3c** as the catalyst of choice and phosphite **1e** for testing different key parameters such as type of solvent, temperature and concentration (Table 2).

Table 2 Screening of the reaction conditions.^a

Entry	Solvent (mL)	Cat. (%)	T (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	Xylene (0.5)	20	r.t.	24	92	50
2	CH ₂ Cl ₂ (0.5)	20	r.t.	24	97	62
3	CH ₃ Cl (0.5)	20	r.t.	24	81	60
4	THF (0.5)	20	r.t.	24	94	62
5	CH ₃ CN (0.5)	20	r.t.	24	70	70
6	1,4-Dioxane (0.5)	20	r.t.	24	n.r. ^d	n.r. ^d
7	Et ₂ O (0.5)	20	r.t.	24	n.r. ^d	n.r. ^d
8	CH ₂ Cl ₂ (0.5)	20	5	19	83	68
9	CH ₂ Cl ₂ (0.5)	20	-27	19	75	72
10	CH ₃ CN (0.5)	20	-27	72	80	79
11	CH ₃ CN (1)	20	-27	96	98	82
12 ^e	CH ₃ CN (1)	20	-27	83	71	82
13	CH ₃ CN (1)	10	-27	95	85	80
14 ^f	CH ₃ CN (0.5)	20	-38	52	85	87
15	CH ₃ CN (0.5)	20	-38	96	88	76
16 ^f	CH ₃ CN (0.5)	30	-38	52	97	86
17	CH ₃ CN (0.5)	10	-38	99	62	52

^a Experimental conditions: To a mixture of catalyst **3c** (0.02 mmol) and aldehyde **2a** (0.1 mmol) in the corresponding solvent, phosphite **1e** (0.2 mmol) was further added in a test tube at the temperature indicated. After the reaction time, adduct **4ea** was isolated by flash chromatography. ^b Isolated yield. ^c Determined by chiral HPLC analysis (Chiralpak IA, flow hexane/AcOEt 70:30, 1 mL/min). ^d No reaction. ^e Reaction performed with 1 equiv. of phosphite **1e**. ^f Reaction performed in absence of stirring.

Among all the studied solvents, we found CH₃CN to be the best choice for this procedure in terms of enantioselectivity (entry 5), whereas no reaction was observed with some ethereal solvents such as 1,4-dioxane (entry 6) or Et₂O (entry 7), having a negative influence on the activity of the catalyst. Furthermore, we were pleased to find that cooling the reaction mixture to -38 °C had a remarkable positive effect on the enantioselectivity of the process, without impairing the levels of reactivity (entry 14). We did not decrease the temperature of the reaction any further since we were close to the m.p. of the solvent (-44 °C). The dilution of the reaction also had a positive effect at -27 °C on the enantioselectivity of the products (entry 9). Lowering the catalyst loading did not afford better results (entries 13 and 17) and although better yields are attained with a higher catalytic charge as expected (entry 16), we continued with a reasonable 20 mol%. Surprisingly, we observed that performing the reaction at -38 °C in absence of stirring afforded the best results in terms of enantioselectivity and reactivity (compare entries 14 and 15). It seems that the insolubility of the product at this temperature is the driving force of the reaction, since in absence of stirring a big precipitate is observed at the bottom of the reaction tube. This fact resulted in better yields when compared with the same reaction performed at higher temperatures and it also had a clear positive effect on the enantioselectivity. With the optimised reaction conditions in hand, we extended our methodology to a broad range of different substituted aldehydes as shown in Table 3.

Table 3. Scope of the squaramide-catalysed hydrophosphonylation reaction.

Entry	R	Product	time (h)	yield (%) ^a	ee (%) ^b
1 ^c	4-NO ₂ Ph, 2a	4ea	95	98	88
2	4-MePh, 2b	4eb	96	81	80
3	1-Naphthyl, 2c	4ec	92	92	80
4	Ph, 2d	4ed	92	82	81
5	4-BrPh, 2e	4ee	92	72	84
6	4-CIPh, 2f	4ef	88	80	82
7	3-CIPh, 2g	4eg	88	98	80
8 ^c	4-CNPh, 2h	4eh	90	98	85
9	PhCH ₂ CH ₂ , 2i	4ei	90	77	68
10	Cy, 2j	4ej	92	98	75
11	<i>t</i> Bu, 2k	4ek	94	73	85

^a Isolated yield. ^b Determined by chiral HPLC. ^c Reaction performed in 1 mL of solvent.

The addition reaction took place smoothly giving rise to the desired α -hydroxy phosphonates **4** in excellent yields (up to 98%) and high enantioselectivities (up to 88%). The efficiency of the developed methodology is well accounted since it was successfully applied to all the aldehydes examined **2a-k**. We could reach 88% and 85% of ee using aldehydes **2a** and **2h**, respectively, simply through slight modifications of the reaction conditions, using 1 mL of solvent instead of 0.5 mL (entries 1 and 8). The electronic effects on the enantioselectivity and reactivity were explored using different *meta*- and *para*-substituted benzaldehydes (entries 1-8). Neither the reactivity nor the enantioselectivity suggested a dependence on the electronic environment in the aromatic ring, as excellent results were accomplished with all of them. On the other hand, using aliphatic aldehydes, a clear dependence on steric hindrance could be observed (compare entries 9, 10 and 11), since better enantioselectivities were achieved with bulkier groups, that is from primary < secondary < tertiary carbon, although no correlation with the yield was revealed. In the case of aldehyde **2k**, it was necessary to cool the aldehyde before its addition in order to avoid its evaporation. Its volatility could justify the yield reached with this substrate (entry 11).

Since these final adducts have not been previously reported in the chiral version, in order to determine the absolute configuration of our products, single crystals were grown from adducts **4ee** and **4eg**. The stereochemical outcome was determined to be *R* for both final products (Figure 1).¹⁸ The same absolute configuration was assumed for all products **4**.

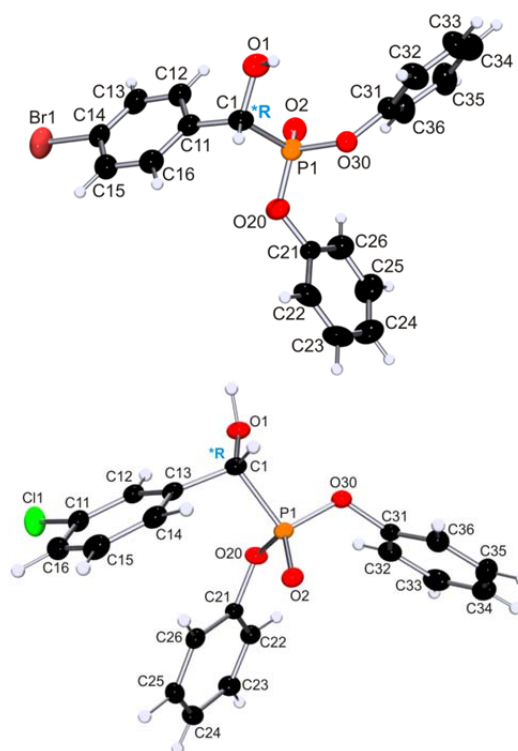


Fig. 1 X-ray crystal structures of (*R*)-**4ee** and (*R*)-**4eg**.

Having demonstrated the capacity of squaramide **3c** to efficiently catalyse the addition of diphenylphosphite **1e** to aldehydes **2a-k**, we propose the following reasonable transition state to explain the role of the catalyst based on previous modes of activation by this kind of structure (Figure 2).¹⁹ On the basis of the experimental results, we envisioned that the chiral squaramide **3c** could act in a bifunctional fashion.²⁰ On one hand, the aldehyde could be activated by the squaramide moiety through double hydrogen bonding with the NH groups. Simultaneously, the basic nitrogen atom on the pyrrolidine ring would activate the phosphonate form in the tautomeric equilibrium,²¹ driving the attack of the active phosphite form over the *Re*-face of the fixed aldehyde. This would afford the *R* absolute configuration in all final products, which is consistent with the observed results in our products.

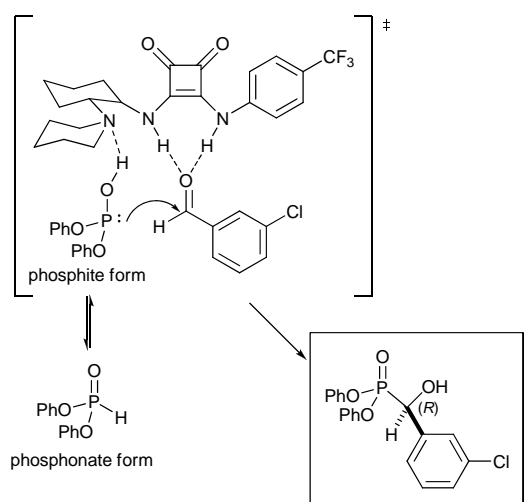


Fig. 2 Proposed mechanistic hypothesis

Our developed methodology, if compared with the pioneering protocol described by Wynberg and co-workers,^{10,22} has broader applicability. It is evident by the fact that our strategy is tolerant towards various functional groups including halides, nitro, cyano, naphthyl and alkyl groups. Additionally, the herein described method is a more straightforward protocol achieving the final goal in a simplest manner, without the necessity of subsequent derivatization or recrystallization in order to obtain high enantioselectivities. Further, our most accessible catalyst **3c** compared with that used by Ooi and co-workers and the development of the reaction at $-38\text{ }^{\circ}\text{C}$ instead of at $-98\text{ }^{\circ}\text{C}$ makes our procedure an attractive alternative.^{11a}

Conclusions

In conclusion, we have demonstrated the ability of the chiral squaramide **3c** to accomplish the addition of diphenylphosphite **1e** to a variety of aromatic **2a-h** and aliphatic aldehydes **2i-k** through a simple and general approach, with very good results in terms of enantioselectivity and reactivity. This protocol represents an additional extended organocatalytic procedure of hydrophosphonylation of aldehydes, with all reagents and

catalyst being commercially available. Moreover, tedious or hazardous conditions, anhydrous solvents or reagents and inert atmosphere are not required as they are in the organometallic version. The potential of this methodology is demonstrated by its simplicity and generality which could become a key work in this area of research. Moreover, it is the first time, to the best of our knowledge, that diphenylphosphite **1e** has been successfully employed in a chiral Pudovik reaction of aldehydes in contrast to the other dialkylphosphites used in previously published procedures,² extending the generality of this asymmetric methodology.²³

Experimental Section

General Experimental Methods. Purification of reaction products was carried out by flash chromatography using silical-gel (0.063-0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silical gel 60-F plates. ESI ionization method and mass analyser type MicroTof-Q were used for the HRMS measurements. $^1\text{H-NMR}$ spectra were recorded at 300 MHz and 400 MHz; $^{13}\text{C-NMR}$ spectra were recorded at 75 MHz and 100 MHz; CDCl_3 as the solvent. Chemical shifts were reported in the δ scale relative to residual CHCl_3 (7.26 ppm) for $^1\text{H-NMR}$ and to the central line of CDCl_3 (77 ppm) for $^{13}\text{C-NMR}$.

Materials. All commercially available solvents and reagents were used as received. The ^1H and ^{13}C NMR spectra for compounds **4eb**,²⁴ **4ec**,²⁵ **4ee**,²⁵ **4eg**,²⁵ are consistent with values previously reported in the literature

Representative procedure for squaramide-organocatalysed hydrophosphonylation reaction of aldehydes

To a mixture of catalyst **3c** (0.02 mmol), and aldehyde **2a-k** (0.1 mmol) in CH_3CN (0.5 mL), phosphite **1e** (0.2 mmol) was further added in a test tube at $-38\text{ }^{\circ}\text{C}$. After the reaction time (see Table 3), adducts **4** were isolated by flash chromatography or medium pressure liquid chromatography (SiO_2 , hexane/EtOAc 7:3). Yields and enantioselectivities are reported in Table 3.

(*R*)-Diphenyl hydroxy(4-nitrophenyl)methylphosphonate (**4ea**)

Following the general procedure, compound **4ea** was obtained after 95 h of reaction at $-38\text{ }^{\circ}\text{C}$ as a white solid in 98% yield (37.7 mg). The ee of the product was determined to be 88% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/AcOEt = 70:30, flow rate 1 mL/min, $\lambda = 268.3\text{ nm}$): $\tau_{\text{major}} = 23.7\text{ min}$; $\tau_{\text{minor}} = 20.7\text{ min}$. M.p. $137\text{--}140\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{26} = +47$ (*c* 0.40, CHCl_3 , 80% ee). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.1\text{ Hz}$, 2H), 7.76 (dd, $J = 2.4, 8.4\text{ Hz}$, 2H), 7.27-7.31 (m, 4H), 7.16-7.20 (m, 2H), 7.03-7.08 (m, 4H), 5.44 (dd, $J = 4.8, 11.0\text{ Hz}$, 1H), 4.02 (dd, $J = 5.3, 7.8\text{ Hz}$, 1H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 150.0 (d, $J = 10.1\text{ Hz}$, 1C), 149.9 (d, $J = 10.6\text{ Hz}$, 1C), 147.7 (d, $J = 4.0\text{ Hz}$, 1C), 143.0 (d, $J = 1.8\text{ Hz}$, 1C), 129.9 (d, $J = 6.6\text{ Hz}$, 4C), 128.0 (d, $J = 1.8\text{ Hz}$, 2C), 125.7 (d, $J = 7.6\text{ Hz}$, 2C),

123.4 (d, $J = 2.8$ Hz, 2C), 120.5 (d, $J = 9.3$ Hz, 2C), 120.4 (d, $J = 9.3$ Hz, 2C), 69.8 (d, $J = 160.3$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3306, 2923, 2853, 1588, 1513, 1488, 1377, 1215, 1182, 945, 761, 690. HRMS (ESI+) calcd $\text{C}_{19}\text{H}_{16}\text{NNaO}_6\text{P}$ 408.0613; found 408.0607 [M+Na].

(R)-Diphenyl hydroxy(*p*-tolyl)methylphosphonate (4eb)²⁴

Following the general procedure, compound **4eb** was obtained after 96 h of reaction at -38 °C as a white solid in 81% yield (28.7 mg). The ee of the product was determined to be 80% by HPLC using a Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 262$ nm): $\tau_{\text{major}} = 18.9$ min; $\tau_{\text{minor}} = 16.8$ min. $[\alpha]_{\text{D}}^{28} = +27$ (c 0.87, CHCl_3 , 74% ee). IR (KBr film) (cm^{-1}) ν 3337, 2924, 2854, 1590, 1489, 1456, 1377, 1260, 1241, 1212, 1190, 1163, 1071, 1022, 1040, 940, 800, 764, 689. HRMS (ESI+) calcd $\text{C}_{20}\text{H}_{19}\text{NaO}_4\text{P}$ 377.0919; found 377.0913 [M+Na].

(R)-Diphenyl hydroxy(naphthalen-1-yl)methylphosphonate (4ec)

Following the general procedure, compound **4ec** was obtained after 92 h of reaction at -38 °C as a white solid in 92% yield (35.9 mg). The ee of the product was determined to be 80% by HPLC using a Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 283.7$ nm): $\tau_{\text{major}} = 21.5$ min; $\tau_{\text{minor}} = 17.3$ min. M.p. 110-112 °C. $[\alpha]_{\text{D}}^{26} = +98$ (c 0.61, CHCl_3 , 80% ee). ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.5$ Hz, 1H), 7.97 (dd, $J = 3.4, 7.2$ Hz, 1H), 7.85-7.90 (m, 2H), 7.49-7.56 (m, 3H), 7.04-7.27 (m, 8H), 6.88-6.90 (m, 2H), 6.20 (dd, $J = 3.8, 10.5$ Hz, 1H), 3.56 (br s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.3 (d, $J = 10.3$ Hz, 1C), 150.3 (d, $J = 9.9$ Hz, 1C), 133.7 (d, $J = 1.7$ Hz, 1C), 131.5 (d, $J = 1.8$ Hz, 1C), 130.9 (d, $J = 6.8$ Hz, 1C), 129.6 (d, $J = 14.5$ Hz, 4C), 129.4 (d, $J = 3.5$ Hz, 1C), 128.8 (d, $J = 0.7$ Hz, 1C), 126.5 (1C), 126.1 (d, $J = 6.4$ Hz, 1C), 125.8 (1C), 125.4 (d, $J = 3.5$ Hz, 1C), 125.2 (d, $J = 14.9$ Hz, 2C), 123.4 (1C), 120.4 (d, $J = 22.4$ Hz, 2C), 120.3 (d, $J = 22.4$ Hz, 2C), 67.2 (d, $J = 163.7$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3252, 2924, 2854, 1590, 1513, 1488, 1463, 1377, 1250, 1186, 1161, 942, 804, 767, 688. HRMS (ESI+) calcd $\text{C}_{23}\text{H}_{19}\text{NaO}_4\text{P}$ 413.0919; found 413.0913 [M+Na].

(R)-Diphenyl hydroxy(phenyl)methylphosphonate (4ed)²⁵

Following the general procedure, compound **4ed** was obtained after 92 h of reaction at -38 °C in 82% yield (27.9 mg). The ee of the product was determined to be 81% by HPLC using a Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 261.2$ nm): $\tau_{\text{major}} = 16.9$ min; $\tau_{\text{minor}} = 14.4$ min. $[\alpha]_{\text{D}}^{28} = +21$ (c 0.35, CHCl_3 , 79% ee).

(R)-Diphenyl (4-bromophenyl)(hydroxy)methylphosphonate (4ee)

Following the general procedure, compound **4ee** was obtained after 92 h of reaction at -38 °C as a white solid in 72% yield (30.2 mg). The ee of the product was determined to be 84% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 260.7$ nm): $\tau_{\text{major}} = 21.1$ min;

$\tau_{\text{minor}} = 19.3$ min. M.p. 128-130 °C. $[\alpha]_{\text{D}}^{23} = +29$ (c 0.47, CHCl_3 , 83% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.51 (m, 2H), 7.42-7.46 (m, 2H), 7.25-7.30 (m, 4H), 7.13-7.19 (m, 2H), 7.06-7.08 (m, 2H), 7.01-7.03 (m, 2H), 5.25 (d, $J = 9.3$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.2 (d, $J = 10.4$ Hz, 1C), 150.1 (d, $J = 11.1$ Hz, 1C), 134.8 (1C), 131.5 (d, $J = 2.6$ Hz, 2C), 129.7 (d, $J = 8.3$ Hz, 4C), 129.0 (d, $J = 6.1$ Hz, 2C), 125.3 (d, $J = 10.4$ Hz, 2C), 122.5 (d, $J = 4.3$ Hz, 2C), 120.5 (d, $J = 4.6$ Hz, 2C), 120.5 (d, $J = 4.8$ Hz, 2C), 69.9 (d, $J = 161.9$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3319, 2924, 2854, 1730, 1589, 1511, 1487, 1462, 1403, 1377, 1242, 1212, 1189, 1163, 1101, 1070, 1043, 1025, 1010, 942, 823, 766, 730, 689, 616, 581, 442. HRMS (ESI+) calcd $\text{C}_{19}\text{H}_{16}\text{BrNaO}_4\text{P}$ 440.9867; found 440.9862 [M+Na].

(R)-Diphenyl (4-chlorophenyl)(hydroxy)methylphosphonate (4ef)²⁵

Following the general procedure, compound **4ef** was obtained after 88 h of reaction at -38 °C as a white solid in 80% yield (30 mg). The ee of the product was determined to be 82% by HPLC using a Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, $\lambda = 261.3$ nm): $\tau_{\text{major}} = 12.2$ min; $\tau_{\text{minor}} = 10.3$ min. $[\alpha]_{\text{D}}^{28} = +18$ (c 0.32, CHCl_3 , 78% ee). IR (KBr film) (cm^{-1}) ν 3313, 2924, 2853, 1589, 1489, 1457, 1377, 1185, 1162, 1014, 759, 687.

(R)-Diphenyl (3-chlorophenyl)(hydroxy)methylphosphonate (4eg)

Following the general procedure, compound **4eg** was obtained after 88 h of reaction at -38 °C as a white solid in 98% yield (36.7 mg). The ee of the product was determined to be 80% by HPLC using a Daicel Chiralpak IC column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1 mL/min, $\lambda = 272.6$ nm): $\tau_{\text{major}} = 21.7$ min; $\tau_{\text{minor}} = 16.5$ min. M.p. 154-156 °C. $[\alpha]_{\text{D}}^{28} = +26$ (c 0.33, CHCl_3 , 77% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.61 (m, 1H), 7.46-7.51 (m, 1H), 7.26-7.35 (m, 6H), 7.15-7.21 (m, 2H), 7.04-7.11 (m, 4H), 5.35 (dd, $J = 5.0, 9.6$ Hz, 1H), 3.46 (dd, $J = 5.1, 10.0$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 150.2 (d, $J = 10.0$ Hz, 1C), 150.1 (d, $J = 10.2$ Hz, 1C), 137.4 (d, $J = 2.2$ Hz, 1C), 134.4 (d, $J = 3.0$ Hz, 1C), 129.7 (d, $J = 4.4$ Hz, 4C), 129.7 (1C), 128.7 (d, $J = 3.4$ Hz, 1C), 127.5 (d, $J = 6.3$ Hz, 1C), 125.5 (d, $J = 5.8$ Hz, 1C), 125.4 (d, $J = 5.3$ Hz, 2C), 120.5 (d, $J = 6.6$ Hz, 2C), 120.5 (d, $J = 6.6$ Hz, 2C), 70.1 (d, $J = 160.8$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3343, 2924, 2853, 1723, 1589, 1490, 1456, 1377, 1252, 1240, 1208, 1196, 1184, 1166, 1099, 1071, 1010, 960, 938, 808, 769, 759, 690. HRMS (ESI+) calcd $\text{C}_{19}\text{H}_{16}\text{ClNaO}_4\text{P}$ 397.0372; found 397.0367 [M+Na].

(R)-Diphenyl (4-cyanophenyl)(hydroxy)methylphosphonate (4eh)

Following the general procedure, compound **4eh** was obtained after 90 h of reaction at -38 °C as a white solid in 98% yield (35.8 mg). The ee of the product was determined to be 85% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 236.4$ nm): $\tau_{\text{major}} = 31.7$ min; $\tau_{\text{minor}} = 27.8$ min. M.p. 124-126 °C. $[\alpha]_{\text{D}}^{30} = +51$ (c 1.31, CHCl_3 ,

82% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.70 (m, 4H), 7.26-7.31 (m, 4H), 7.15-7.20 (m, 2H), 7.01-7.06 (m, 4H), 5.34 (dd, $J = 5.1, 10.7$ Hz, 1H), 4.52 (t, $J = 6.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.0 (d, $J = 13.4$ Hz, 1C), 149.9 (d, $J = 13.9$ Hz, 1C), 140.8 (d, $J = 2.4$ Hz, 1C), 132.1 (d, $J = 2.9$ Hz, 2C), 129.8 (d, $J = 7.2$ Hz, 4C), 127.9 (d, $J = 5.7$ Hz, 2C), 125.6 (d, $J = 9.8$ Hz, 2C), 120.4 (d, $J = 4.2$ Hz, 2C), 120.4 (d, $J = 4.1$ Hz, 2C), 118.5 (d, $J = 2.2$ Hz, 1C), 112.2 (d, $J = 3.8$ Hz, 1C), 70.0 (d, $J = 159.8$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3319, 2924, 2854, 2225, 1641, 1529, 1491, 1462, 1377, 1245, 1208, 1184, 1069, 940, 757, 685. HRMS (ESI+) calcd $\text{C}_{20}\text{H}_{16}\text{NNaO}_4\text{P}$ 388.0715; found 388.0709 [M+Na].

(R)-Diphenyl 1-hydroxy-3-phenylpropylphosphonate (4ei)

Following the general procedure, compound **4ei** was obtained as a white solid after 90 h of reaction at -38 °C as a white solid in 77% yield (28.4 mg). The ee of the product was determined to be 68% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, $\lambda = 261.2$ nm): $\tau_{\text{major}} = 13.1$ min; $\tau_{\text{minor}} = 14.7$ min. M.p. 108-110 °C. $[\alpha]_{\text{D}}^{25} = -6.8$ (c 1.02, CHCl_3 , 67% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.12-7.32 (m, 15H), 4.15-4.19 (m, 1H), 3.16 (br s, 1H), 2.98-3.04 (m, 1H), 2.77-2.85 (m, 1H), 2.17-2.32 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.3 (d, $J = 9.1$ Hz, 1C), 150.2 (d, $J = 10.0$ Hz, 1C), 140.9 (1C), 129.8 (4C), 128.6 (d, $J = 13.0$ Hz, 4C), 126.2 (1C), 125.3 (d, $J = 5.0$ Hz, 1C), 125.3 (d, $J = 4.9$ Hz, 1C), 120.7 (d, $J = 5.9$ Hz, 2C), 120.7 (d, $J = 5.9$ Hz, 2C), 66.8 (d, $J = 160.6$ Hz, 1C), 33.0 (d, $J = 2.0$ Hz, 1C), 31.6 (d, $J = 15.0$ Hz, 1C). IR (KBr film) (cm^{-1}) ν 3338, 3062, 3026, 2926, 2856, 2225, 1591, 1490, 1454, 1188, 1162, 1070, 1025, 1008, 941, 762, 689. HRMS (ESI+) calcd $\text{C}_{21}\text{H}_{21}\text{NaO}_4\text{P}$ 391.1075; found 391.1070 [M+Na].

(R)-Diphenyl cyclohexyl(hydroxy)methylphosphonate (4ej)

Following the general procedure, compound **4ej** was obtained after 92 h of reaction at -38 °C as a white solid in 98% yield (33.9 mg). The ee of the product was determined to be 75% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1 mL/min, $\lambda = 262.4$ nm): $\tau_{\text{major}} = 22.1$ min; $\tau_{\text{minor}} = 26.2$ min. M.p. 100-102 °C. $[\alpha]_{\text{D}}^{26} = -3$ (c 0.96, CHCl_3 , 69% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.34 (m, 4H), 7.15-7.21 (m, 6H), 4.02 (q, $J = 5.7, 12.8$ Hz, 1H), 2.47 (dd, $J = 6.5, 7.2$ Hz, 1H), 2.10-2.13 (m, 1H), 1.95-2.06 (m, 1H), 1.88-1.91 (m, 1H), 1.79-1.81 (m, 2H), 1.66-1.70 (m, 1H), 1.13-1.46 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.3 (d, $J = 10.1$ Hz, 1C), 150.2 (d, $J = 9.8$ Hz, 1C), 129.7 (d, $J = 5.7$ Hz, 4C), 125.2 (m, 2C), 120.6 (d, $J = 4.0$ Hz, 2C), 120.6 (d, $J = 4.0$ Hz, 2C), 72.6 (d, $J = 155.1$ Hz, 1C), 39.8 (d, $J = 2.4$ Hz, 1C), 29.9 (d, $J = 9.5$ Hz, 1C), 27.9 (d, $J = 7.6$ Hz, 1C), 26.1 (1C), 25.9 (d, $J = 17.6$ Hz, 2C). IR (KBr film) (cm^{-1}) ν 3325, 2932, 2852, 1591, 1487, 1448, 1408, 1193, 1161, 1106, 1070, 1003, 972, 935, 802, 774, 690, 661, 475. HRMS (ESI+) calcd $\text{C}_{19}\text{H}_{23}\text{NaO}_4\text{P}$ 369.1232; found 369.1226 [M+Na].

(R)-Diphenyl-1-hydroxy-2,2-dimethylpropylphosphonate (4ek)

Following the general procedure, compound **4ek** was obtained after 94 h of reaction at -38 °C as a white solid in 73% yield (23.4 mg). The ee of the product was determined to be 85% by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, $\lambda = 262.4$ nm): $\tau_{\text{major}} = 28.2$ min; $\tau_{\text{minor}} = 32.6$ min. M.p. 116-120 °C. $[\alpha]_{\text{D}}^{25} = +7$ (c 0.47, acetone, 84% ee). ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.34 (m, 4H), 7.14-7.20 (m, 6H), 3.92 (dd, $J = 6.4, 7.2$ Hz, 1H), 2.59 (dd, $J = 6.8, 7.8$ Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.3 (d, $J = 22.2$ Hz, 1C), 150.2 (d, $J = 21.9$ Hz, 1C), 129.7 (d, $J = 7.6$ Hz, 4C), 125.2 (d, $J = 3.5$ Hz, 1C), 125.1 (d, $J = 3.5$ Hz, 1C), 120.6 (d, $J = 4.0$ Hz, 2C), 120.6 (d, $J = 4.1$ Hz, 2C), 76.3 (d, $J = 152.5$ Hz, 1C), 35.0 (d, $J = 3.6$ Hz, 1C), 26.7 (d, $J = 6.7$ Hz, 3C). IR (KBr film) (cm^{-1}) ν 3357, 2924, 2854, 1590, 1490, 1462, 1377, 1246, 1205, 1189, 1161, 1064, 945, 903, 802, 766, 690. HRMS (ESI+) calcd $\text{C}_{17}\text{H}_{21}\text{NaO}_4\text{P}$ 343.1075; found 343.1070 [M⁺+Na].

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Electronic Supplementary Information (ESI) available: General experimental information, ^1H and ^{13}C NMR spectra and HPLC chromatograms for all final products **4ea-ek**. See DOI: 10.1039/b000000x/

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