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New phosphine oxide aziridinyl phosphonates as chiral Lewis bases for the Abramov-type phosphonylation of aldehydes

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ABSTRACT

A series of Lewis bases were screened for Abramov-type phosphine additions to aldehydes. A novel phosphine oxide aziridinyl phosphonate **POAP-A** was found to be better than the others in forming the product in 96% yield and with 42% ee. The absolute configuration of the newly synthesized **POAP** Lewis bases was determined by single-crystal X-ray analysis.

1. Introduction

Optically active α-hydroxy phosphonates are biologically important compounds.[1] The phosphonylation of aldehydes with dialkyl (Pudovic-type) or trialkyl phosphites (Abramov-type) is a useful method for the synthesis of these compounds.[2] Although the asymmetric addition of dialkyl phosphites to aldehydes has been successfully studied by different groups,[3] the first asymmetric addition of trialkyl phosphites to aldehydes was reported by Nakajima et al. in 2008 with the highest ee of 49%.[4] In a recent study, the same group reported a new catalyst system that provided α-hydroxy phosphonates with modest selectivity.[5] These results show that new and more effective catalysts need to be developed for highly enantioselective trialkyl phosphite additions to aldehydes. In this respect, we have recently synthesized new phosphine oxide aziridinyl phosphonates **POAP** and investigated their organocatalytic activity as Lewis bases for $SiCl_4$ mediated Abramov-type enantioselective trialkyl phosphite additions to aldehydes. Herein we report the results of our studies.

2. Results and discussion

The synthesis of phosphine oxide aziridinyl phosphonates **POAP** was achieved using a Gabriel–Cromwell reaction starting from a vinyl phosphonate. Bromination of this compound provided **1**, which was reacted with Et_3N to yield compound **2** by HBr elimination. The reaction of this compound with (*R*)-2-amino-1-butanol provided aziridinyl phosphonates **4a** and **4b** in a total yield of 90%. These compounds were also synthesized by starting from easily available acetyl phosphonate as shown in Scheme 1.[6] In the next step, **4a** and **4b** were tosylated individually to provide **5a** and **5b** in 90% and 85% yields, respectively. Finally, phosphorylation by displacement with $KPPh_2$ and then treatment with hydrogen peroxide provided **POAP-A** and **POAP-B**. The absolute stereochemistry of **POAP-B** was determined by single crystal X-ray analysis (Fig. 1).[7]

After synthesizing the chiral Lewis bases, their performance was tested for the Abramov-type enantioselective trialkyl phosphite additions to aldehydes. By adopting a literature procedure,[4] triethyl phosphite was reacted with anisaldehyde in the presence of chiral Lewis bases (**LB**) and $SiCl_4$. The results of the optimization studies are summarized in Table 1.

Lewis base screening experiments performed using the previously synthesized **4a**, **4b**, **AP**,[6] **POFAM**,[8] and the newly synthesized **POAP** compounds showed that **POAP-A** gave the best results (Table 1, entries 2–10). The reaction was then repeated with this **LB** at −90 °C hoping to increase the ee, but the result did not change (entry 11). Next, the effect of additives was investigated. Screening of HMPA, TMEDA, Bu_4NI, and Et3N–*i*Pr2NEt mixtures did not give the expected results; the ee remained low (entries 12–15). Therefore, $^{i}Pr_2NEt$ was used as the additive for the rest of the optimization studies. While studying the additive concentration, 0.2 equiv were found to be the optimum amount (entries 16–18). In previous literature studies, the slow addition (over 2 h) of $SiCl_4$ was reported to be important.[4] In our studies, adding $SiCl_4$ in either 2 h or 10 min showed no effect on the ee and a very minor effect on the yield (entries 10 and 19). Lowering, or increasing, the amount of both $(EtO)_3P$ and $SiCl_4$ had no significant effect on ee (entries 22–24) either. Finally with the optimum additive amount in hand, the reactions were repeated at −98 °C using three different conditions (entries 25–27). In all the cases, the ee was approximately the same. In addition to DCM, the reaction was also carried out in toluene, THF, and acetonitrile. In these solvents, the product was formed in 98%, 77%, and 71% yields with enantioselectivities of 13%, 14% and 19%, respectively. Therefore, DCM was determined

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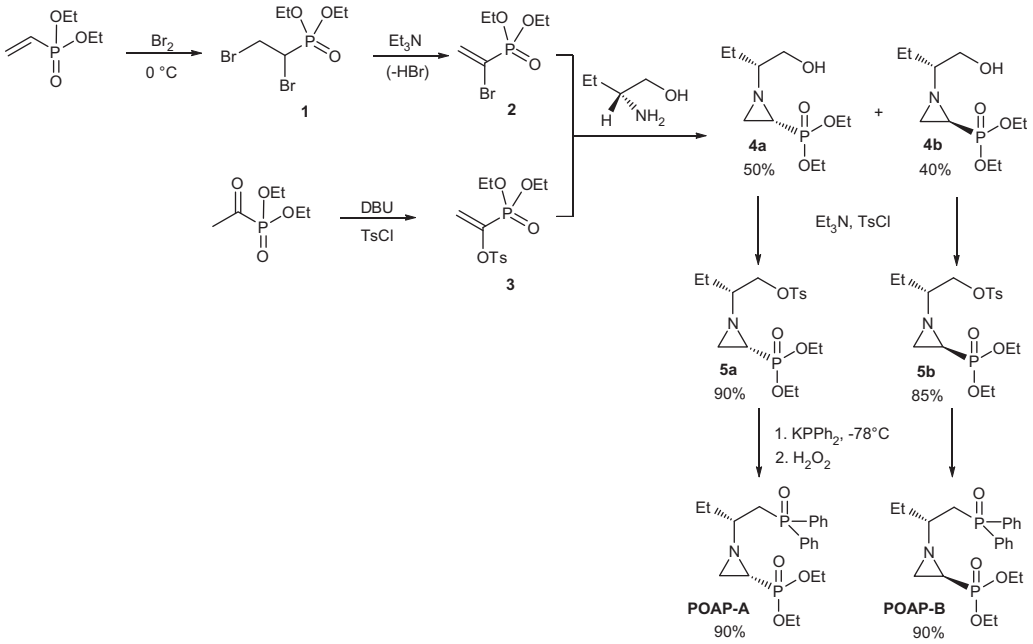


Scheme 1. Synthesis of **POAP** chiral Lewis bases.

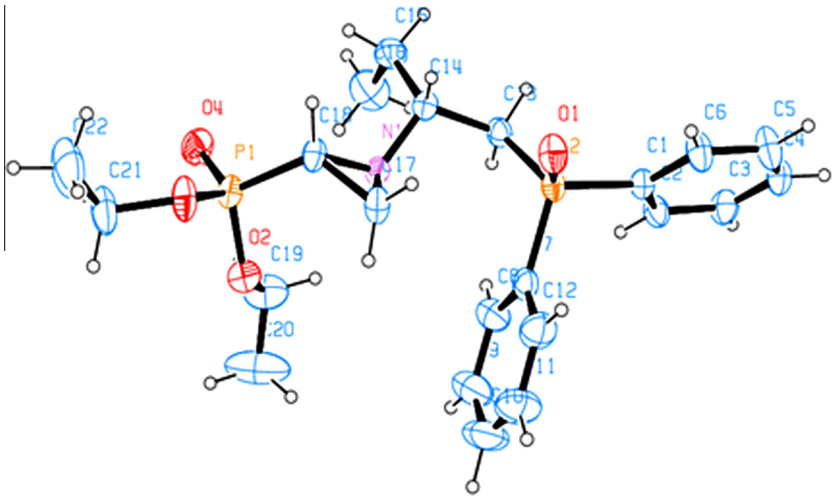


Figure 1. X-ray crystal structure of **POAP-B**.

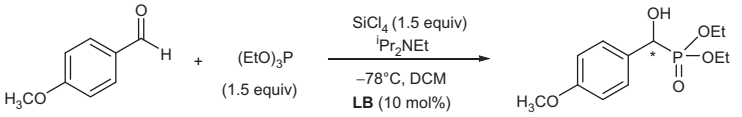
to be the solvent of choice for the reaction. Although the optimal catalyst **POAP-A** did not provide exceptionally high ee values under different reaction conditions, the aldehyde screening was carried out using procedure A in order to determine whether the catalyst was substrate dependent. The results of these studies are summarized in Table 2.

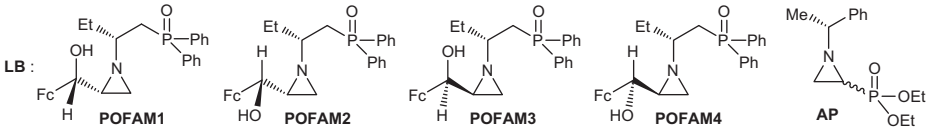
From the aldehyde screening experiments, we could see that the products were formed in good to excellent yields except in the case of *p*-tolualdehyde (Table 2, entry 7). In terms of enantioselectivity, the results of anisaldehyde, benzaldehyde, and 1-naphthaldehyde were very similar, with the ee being 38–44% (entries 1, 2, and 8). For crotonaldehyde, *m*-nitrobenzaldehyde, *p*-tolualdehyde, 2-naphthaldehyde, and ferrocenecarboxaldehyde, the enantioselectivity was approximately 30% (entries 3, 5, 7, 9, and 10). The remaining two aldehydes, *m*-anisaldehyde and *m*-bromobenzaldehyde, gave the lowest ees of 17% and 13%, respectively (entries 4 and 6).

3. Conclusion

A series of different chiral Lewis bases **4a**, **4b**, **AP**, **POFAM** series, and **POAP** were screened for enantioselective Abramov-type triethyl phosphite additions to aldehydes. Among them newly synthesized **POAP-A**, with phosphate and phosphine oxide groups, was found to be better than the others. Although different reaction conditions ($SiCl_4$ addition, temperature, concentration, solvents, and so on) were tried, the ee could not be increased above 44%. The slow addition of $SiCl_4$, previously reported to be important for this reaction, was found not to be significant for our catalyst. In terms of enantioselectivity, our results resemble the literature results where the highest ee was reported to be approximately 50% for the same reaction. The low enantioselectivity of the reaction can be attributed to the background reaction, which takes place without the chiral Lewis base.

Table 1
Triethyl phosphite addition to anisaldehyde





Entry	LB	Method	Additive (equiv)	Yield[a] (%)	ee[b] (%)
1	—	A	$^{i}Pr_2NEt$ (1.5)	72	—
2	**POFAM1**	A	$^{i}Pr_2NEt$ (1.5)	84	10
3	**POFAM2**	A	$^{i}Pr_2NEt$ (1.5)	85	5
4	**POFAM3**	A	$^{i}Pr_2NEt$ (1.5)	55	7
5	**POFAM4**	A	$^{i}Pr_2NEt$ (1.5)	74	11
6	**AP**	A	$^{i}Pr_2NEt$ (1.5)	73	2
7	**4a**	A	$^{i}Pr_2NEt$ (1.5)	70	4
8	**4b**	A	$^{i}Pr_2NEt$ (1.5)	80	5
9	**POAP-B**	A	$^{i}Pr_2NEt$ (1.5)	70	2
10	**POAP-A**	A	$^{i}Pr_2NEt$ (1.5)	91	34
11[c]	**POAP-A**	A	$^{i}Pr_2NEt$ (1.5)	80	35
12	**POAP-A**	A	HMPA (1.5)	56	*rac*
13	**POAP-A**	A	TMEDA (1.0)	51	11
14	**POAP-A**	A	Bu_4NI (1.5)	93	11
15	**POAP-A**	A	Et_3N (1.5) $^{i}Pr_2NEt$ (0.75)	47	7
16	**POAP-A**	A	$^{i}Pr_2NEt$ (1.0)	86	35
17	**POAP-A**	A	$^{i}Pr_2NEt$ (0.5)	91	37
18	**POAP-A**	A	$^{i}Pr_2NEt$ (0.2)	92	42
19	**POAP-A**	B	$^{i}Pr_2NEt$ (1.5)	95	34
20	**POAP-A**	B	$^{i}Pr_2NEt$ (0.1)	62	36
21	**POAP-A**	B	$^{i}Pr_2NEt$ (0.35)	91	39
22[d]	**POAP-A**	B	$^{i}Pr_2NEt$ (0.2)	76	34
23[e]	**POAP-A**	B	$^{i}Pr_2NEt$ (0.35)	51	31
24[f]	**POAP-A**	B	$^{i}Pr_2NEt$ (0.35)	50	32
25[c]	**POAP-A**	A	$^{i}Pr_2NEt$ (0.2)	41	43
26[c]	**POAP-A**	B	$^{i}Pr_2NEt$ (0.2)	56	41
27[c]	**POAP-A**	C	$^{i}Pr_2NEt$ (0.2)	76	40
28	—	A	$^{i}Pr_2NEt$ (0.2)	52	—

A—$SiCl_4$ was added over 2 h to a solution of **LB**, $P(OEt)_3$, and additive in DCM; stirring was continued for another hour and hydrolyzed.
B—$SiCl_4$ was added over 10 min to a solution of **LB**, $P(OEt)_3$, and additive in DCM; the reaction mixture was stirred for 2 h.
C—$SiCl_4$ was added directly at once to a solution of **LB**, $P(OEt)_3$, and additive in DCM; the reaction mixture was stirred for 2 h.
[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Reaction was carried out at −98 °C.
[d] $P(OEt)_3$ and $SiCl_4$ were used in 1.05 equiv.
[e] $P(OEt)_3$ was used in 2.0 equiv.
[f] $SiCl_4$ was used in 2.0 equiv.

4. Experimental

4.1. General

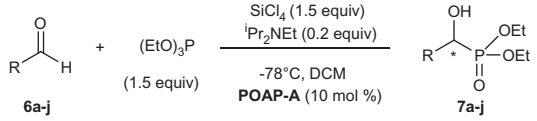
All asymmetric reactions were performed under an inert atmosphere in dry glassware. DCM was dried and distilled from calcium hydride prior to use. $P(OEt)_3$ was distilled from sodium. Diisopropylethylamine was distilled from calcium hydride.

The products were purified by flash column chromatography on Silica Gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were performed on 250 μm Silica Gel 60 F254 plates. Enantiomeric excess (ee) was determined by chiral HPLC. Melting points were taken in open-end capillary tubes and are uncorrected. IR spectra are reported in reciprocal centimeters (cm^{-1}). ^{1}H, ^{13}C, and ^{31}P NMR spectra were reported on a Brucker spectrospin Avance DPX-400 Ultra shield instrument at 400, 100, and 162 MHz, respectively relative to TMS for ^{1}H and ^{13}C NMR and H_3PO_4 for ^{31}P NMR. A Rudolph Research Analytical Autopol III Polarimeter was used to measure optical rotations.

4.1.1. (*R*)-2-((*R*)-2-(Diethoxyphosphoryl)aziridin-1-yl)butyl 4-methylbenzenesulfonate 5a

Diethyl ((*R*)-1-((*R*)-1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate **4a** (502 mg, 2.00 mmol) was dissolved in DCM (4 mL) at room temperature. Then Et_3N (0.42 mL, 3.00 mmol) was added. To this stirred solution was added *p*-toluenesulfonyl chloride (570 mg, 3 mmol). Next, the reaction mixture was stirred at room temperature overnight at which point TLC showed no starting material. To the reaction flask, water (15 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (15 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude pale yellow viscous liquid was purified by flash column chromatography on silica gel using EtOAc as the eluent. After purification, 2-(2-(diethoxy-

Table 2
Aldehyde screening studies



Entry	R	Substrate	Yield[a] (%)	ee[b] (%)
1	*p*-$MeOC_6H_4$	**6a**	92	42
2	Ph	**6b**	98	38
3	(*E*)-PhCH=CH	**6c**	99	29
4	*m*-$MeOC_6H_4$	**6d**	95	17
5	*m*-$NO_2C_6H_4$	**6e**	97	32
6	*m*-BrC_6H_4	**6f**	87	13
7	*p*-MeC_6H_4	**6g**	62	30
8	1-Naphthyl	**6h**	89	44
9	2-Naphthyl	**6i**	90	30
10	Ferrocenyl	**6j**	90	28

[a] Isolated yields.
[b] Determined by chiral HPLC.

phosphoryl)aziridin-1-yl)butyl 4-methylbenzenesulfonate **5a** was obtained as a light yellow oil in 90% yield (730 mg, 1.80 mmol). R_f = 0.41, EtOAc; $[\alpha]_D^{25} = -12.5$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 7.80 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.10 (m, 4H), 4.07 (m, 2H), 2.46 (s, 3H), 2.15 (dd, *J* = 5.4 and 1.8 Hz, 1H), 2.03 (d, *J* = 4.4 Hz, 1H), 1.67 (ddd, *J* = 18.4, 6.8, and 4 Hz, 1H), 1.61 (t, *J* = 2.4 Hz, 1H) 1.58 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR δ 144.4 (C_q, ArC-S), 133.2 (C_q, ArC-CH_3), 129.7 (CH, 2C, Ph), 127.9 (CH, 2C, Ph), 71.2 (CH_2-OTs), 68.4 (CH, d, J_{C-P} = 6.3 Hz), 61.5 (OCH_2CH_3, d, J_{C-P} = 6.3 Hz), 60.7 (OCH_2CH_3, d, J_{C-P} = 6.3 Hz), 30.7 (CH, aziridine, d, J_{C-P} = 218.5 Hz), 29.3 (CH_2CH_3, d, J_{C-P} = 5.2 Hz), 24.9 (CH_2 aziridine), 21.6 (CH_3, Ts), 15.1 (OCH_2CH_3,d, J_{C-P} = 5.3 Hz), 15.0 (OCH_2CH_3, d, J_{C-P} = 5.3 Hz), 9.89 (CH_3); ^{31}P NMR δ 22.31; IR (neat, cm^{-1}) 2978, 1358, 1247, 1175, 1022, 962, 812, 787, 664.

4.1.2. (*R*)-2-((*S*)-2-(Diethoxyphosphoryl)aziridin-1-yl)butyl 4-methylbenzenesulfonate 5b

Starting from ((*R*)-1-((*S*)-1-hydroxybutan-2-yl)aziridin-2-yl)phosphonate **4b** (302 mg, 1.20 mmol) and following the same procedure reported for **5a**, **5b** was obtained as a light yellow oil in 85% yield (414 mg, 1.02 mmol). R_f = 0.57, EtOAc; $[\alpha]_D^{25} = +44$ (*c* 2.4, CH_2Cl_2); ^{1}H NMR δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.08 (m, 4H), 4.05 (m, 2H), 2.46 (s, 3H), 2.06 (dd, *J* = 8.8 and 4.0 Hz, 1H), 1.75 (t, *J* = 7.2 Hz, 1H), 1.62 (d, *J* = 2.4 Hz, 1H), 1.58 (m, 2H), 1.49 (ddd, *J* = 19.0, 6.8, and 4 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 144.7 (C_q, ArC-S), 133.2 (C_q, ArC-CH_3), 129.8 (CH, 2C, Ph), 127.8 (CH, 2C, Ph), 71.8 (CH_2-OTs), 69.7 (CH, d, J_{C-P} = 7.5 Hz), 62.4 (OCH_2CH_3, d, J_{C-P} = 6.5 Hz), 31.6 (CH_2CH_3, d, J_{C-P} = 5.5 Hz), 30.0 (CH-aziridine, d, J_{C-P} = 219.3 Hz), 24.7 (CH_2-aziridine), 21.6 (CH_3, Ts), 16.5 (OCH_2CH_3, d, J_{C-P} = 6.0 Hz), 16.4 (OCH_2CH_3, d, J_{C-P} = 6.0 Hz), 9.67 (CH_3); ^{31}P NMR δ 22.70; IR (neat, cm^{-1}) 2980, 1357, 1245, 1175, 1022, 959, 812, 787, 665.

4.1.3. Diethyl ((*R*)-1-((*R*)-1-(diphenylphosphoryl)butan-2-yl) aziridin-2-yl)phosphonate POAP-A

Tosylate **5a** (1.50 g, 3.70 mmol) was dissolved in dry THF (9 mL). Then, potassium diphenylphosphide (8.88 mL, from 0.5 M THF solution) was added to the reaction flask slowly over 45 min at −78 °C. After 4 h stirring at this temperature, TLC showed no starting material. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (25 mL). The two layers were separated and the aqueous layer was extracted with DCM (25 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as a colorless oil. Then it was dissolved in acetone (120 mL) and stirred with H_2O_2 (30% aq, 1.74 mL, 18.5 mmol) at rt. After 1 h, TLC showed no starting material. The reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (4 mL). The extraction was performed by adding DCM (25 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated to give a light yellow oil. The crude product was purified by flash column chromatography using silica gel (hexane/acetone 2:1 + 2% Et_3N). Diethyl 1-(1-diphenylphosphoryl) butan-2-yl) aziridin-2-ylphosphonate **POAP-A** was isolated in 90% yield (1.45 g, 3.33 mmol) as a light yellow oil. R_f = 0.26, hexane/acetone 2:1 + 2% Et_3N; $[\alpha]_D^{25} = -8.2$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR δ 7.80–7.70 (m, 4H), 7.55–7.40 (m, 6H), 4.20–4.05 (m, 4H), 2.75–2.55 (m, 2H), 2.25–2.15 (m, 1H), 1.75–1.60 (m, 4H), 1.40–1.35 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 134.0 (Cq, ArC-P), 133.8 (Cq, ArC-P), 131.7 (CH, 2C, Ph), 130.9 (CH, Ph), 130.8 (CH, Ph), 130.7 (CH, Ph), 130.6 (CH, Ph), 128.7 (CH, Ph), 128.6 (CH, Ph), 128.6 (CH, Ph), 128.5 (CH, Ph), 65.7 (CH, d, J_{C-P} = 7.1 Hz), 62.5 (OCH_2CH_3, d, J_{C-P} = 6.7 Hz), 62.4 (OCH_2CH_3, d, J_{C-P} = 6.1 Hz), 35.2 (CH_2-aziridine), 33.8 (CH_2, d, J_{C-P} = 6.5 Hz), 29.8 (CH-aziridine, d, J_{C-P} = 216.3 Hz), 28.9 (CH_2CH_3), 16.8 (OCH_2CH_3, d, J_{C-P} = 5.3 Hz), 16.2 (OCH_2CH_3, d, J_{C-P} = 5.3 Hz), 9.70 (CH_3); ^{31}P NMR δ 23.2 ($P(O)(OEt)_2$), 28.5 ($P(O)Ph_2$); IR (neat, cm^{-1}) 2987, 2921, 2875, 1452, 1260, 1171, 1020, 739, 713. HRMS-EI (*m*/*z*): calcd for $C_{22}H_{32}NO_4P_2$ $[M+H]^+$: 436.1807; found: 436.1811.

4.1.4. Diethyl ((*S*)-1-((*R*)-1-(diphenylphosphoryl)butan-2-yl) aziridin-2-yl)phosphonate POAP-B

Starting from tosylate **5b** (1.21 g, 3.00 mmol) and following the same procedure reported for **POAP-A**, diethyl 1-(1-diphenylphosphoryl)butan-2-yl)aziridin-2-yl phosphonate **POAP-B** was obtained in 85% yield (1.11 g, 2.55 mmol) as a white solid. R_f = 0.20, hexane/acetone 2:1 + 2% Et_3N; mp: 108−109 °C; $[\alpha]_D^{25} = +6.0$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.82 (ddd, *J* = 11.5, 8.0, and 1.6 Hz, 2H), 7.70 (ddd, *J* = 11.5, 8.0, and 1.6 Hz, 2H), 7.55–7.40 (m, 6H), 4.20–4.00 (m, 4H), 2.65–2.40 (m, 2H), 1.95–1.80 (m, 1H), 1.70–1.45 (m, 5H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 131.7 (Cq, ArC-P, 2C), 130.8 (CH, 2C, Ph), 130.4 (CH, Ph, 2C), 128.7 (CH, Ph, 3C), 128.6 (CH, Ph, 3C), 65.5 (CH, d, J_{C-P} = 7.5 Hz), 62.4 (CH, d, J_{C-P} = 6.3 Hz), 62.3 (OCH_2CH_3, d, J_{C-P} = 6.3 Hz), 32.5 (CH-aziridine, d, J_{C-P} = 218.2 Hz), 31.9 (CH_2, CH_2-P, d, J_{C-P} = 5.1 Hz), 28.5 (CH_2-aziridine, J_{C-P} = 6.9 Hz), 25.2 (CH_2CH_3), 16.4 (O CH_2CH_3, d, J_{C-P} = 9.7 Hz), 9.13 (CH_3); ^{31}P NMR δ 22.90 ($PO(OEt)_2$), 28.34 ($P(O)Ph_2$); IR (neat, cm^{-1}) 2978, 2911, 2863, 1454, 1270, 1161, 1023, 749, 723. HRMS−EI (*m*/*z*): calcd for $C_{22}H_{32}NO_4P_2$ $[M+H]^+$: 436.1807; found: 436.1810.

4.2. General procedure for the asymmetric triethyl phosphite addition to aldehydes

Aldehyde (0.50 mmol), ^{i}Pr$_2$NEt (19 μL, 0.10 mmol), and chiral Lewis base (10 mol %) were mixed in dry DCM (1 mL) at −78 °C in a flame dried Schlenk tube under a nitrogen atmosphere. To this solution was added $P(OEt)_3$ (130 μL, 0.75 mmol). Next, $SiCl_4$ (86 μL, 0.75 mmol) solution in DCM (2 mL, prepared in a different flask under dry conditions) was added to the reaction flask over 2 h (method A). After stirring for another hour, TLC analysis (hexane/acetone 2:1) showed no starting material. The reaction mixture was hydrolyzed by adding water (2 mL) and saturated $NaHCO_3$ (5 mL). Next, EtOAc (5 mL) was added and the reaction flask was stirred for approximately 1 h, after which the mixture was filtered through a short Celite pad. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with brine and dried over $MgSO_4$. The concentrated crude prod-

uct was purified by flash column chromatography using silica gel (hexane/acetone 2:1). The enantioselectivity was determined by HPLC using a chiralcel AS-H column.

4.2.1. Diethyl 1-hydroxy-1-(4-methoxyphenyl)methyl phosphonate 7a

R_f = 0.31 hexane/acetone 1:1; $[\alpha]_D^{25} = -12.0$ (*c* 1.0, $CHCl_3$) for 28% ee (S). Lit.[4] $[\alpha]_D^{18} = +14.1$ (*c* 1.01, $CHCl_3$) for 40% ee (*R*); ^{1}H NMR δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 3.80 (s, 3H), 3.93–4.09 (m, 4H), 4.15 (m, 1H), 4.91 (dd, *J* = 9.8 and 5.4 Hz, 1H,), 6.86 (d, *J* = 8.8 Hz, 2H), 7.39 (dd, 8.6 and 2.2 Hz, 2H); ^{31}P NMR: δ 21.83; IR (neat, cm^{-1}) 3244, 2963, 1510, 1223, 1196, 1169, 1057, 961, 795; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 21.0 min (*R*, minor), 34.0 min (*S*, major).

4.2.2. Diethyl 1-hydroxy-1-phenylmethylphosphonate 7b

R_f = 0.40, hexane/acetone 1:1; $[\alpha]_D^{25} = -10.1$ (*c* 1.0, $CHCl_3$) for 28% ee (S). Lit.[4] $[\alpha]_D^{27} = +14.8$ (*c* 1.01, $CHCl_3$) for 41% ee (*R*); ^{1}H NMR δ 1.22 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 4.14 (br, s, 1H), 4.04 (m, 4H), 4.98 (dd, *J* = 10.6 and 5.0 Hz, 1H), 7.32 (m, 3H), 7.46 (m, 2H); ^{31}P NMR: δ 21.55; IR (neat, cm^{-1}) 3250, 2991, 2097, 1448, 1224, 1045, 1019, 959, 700; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 17.0 min (*R*, minor), 22.0 min (*S*, major).

4.2.3. Diethyl 1-hydroxy-3-phenylprop-2-enyl-phosphonate 7c

R_f = 0.34, hexane/acetone 1:1; $[\alpha]_D^{25} = -6.0$ (*c* 1.0, $CHCl_3$) for 28% ee (*S*). Lit.[4] $[\alpha]_D^{18} = +7.7$ (*c* 0.92, $CHCl_3$) for 49% ee (*R*); mp: 99.0–99.5 °C; ^{1}H NMR δ 1.35 (t, *J* = 7.2 Hz, 6H), 3.15 (m, 1H), 4.18–4.26 (m, 4H), 4.63–4.69 (m, 1H), 6.29 (dt, *J* = 15.6 and 5.6 Hz, 1H), 6.76 (ddd, *J* = 16.0, 5.0, and 1.4 Hz, 1H), 7.24 (m, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H); ^{31}P NMR δ 21.52; IR (neat, cm^{-1}) 3244, 2982, 1446, 1223, 1014, 960, 756, 729; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 9:1, flow 1.0 mL min^{-1}, t_R = 17.6 min (*R*, minor), 44.4 min (*S*, major).

4.2.4. Diethyl 1-hydroxy-(3-methoxyphenyl)methyl phosphonate 7d

R_f = 0.36 hexane/acetone 2:1; $[\alpha]_D^{25} = -3.6$ (*c* 1.0, $CHCl_3$) for 17% ee. Lit.[3g] $[\alpha]_D^{20} = +13.0$ (*c* 0.25, $CHCl_3$) for 71% ee; ^{1}H NMR δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 3.86 (b, 1H), 3.81 (s, 3H), 4.00–4.14 (m, 4H), 5.0 (dd, *J* = 10.8 and 1.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H) 7.07 (m, 2H), 7.27 (t, *J* = 7.9 Hz, 1H); ^{31}P NMR ($CDCl_3$): δ 21.52; IR (neat, cm^{-1}) 3266, 2982, 1601, 1229, 1018, 963, 790, 749, 693; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 13.61 min (minor), 24.78 min (major).

4.2.5. Diethyl 1-hydroxy-(3-nitrophenyl)methylphosphonate 7e

R_f = 0.25 hexane/acetone 2:1; $[\alpha]_D^{25} = -4.0$ (*c* 1.0, $CHCl_3$) for 32% ee. Lit.[3e] $[\alpha]_D^{22} = -30$ (*c* 0.13, $CHCl_3$) for 52% ee ^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 4.12 (m, 4H), 4.35 (b, 1H), 5.15 (d, *J* = 11.2 Hz 1H), 7.54 (t, *J* = 8 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.20 (CH_3), 65.58 (OCH_2CH_3), 86.78 (CHOH), 121.85 (Ph, 1C), 122.92 (Ph, 1C), 128.99 (Ph, 1C), 132.86 (Ph, 1C), 174.42 (Cq, Ph), 176.43 (Cq, Ph); ^{31}P NMR ($CDCl_3$): δ 21.52; IR (neat, cm^{-1}) 3233, 2982, 1535, 1347, 1206, 1038, 1014, 951, 801, 686; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 47.91 min (minor), 49.49 min (major).

4.2.6. Diethyl 1-hydroxy-(3-bromophenyl)methylphosphonate 7f[9]

R_f = 0.48 hexane/acetone 2:1; $[\alpha]_D^{25} = -1.5$ (*c* 1.0, $CHCl_3$) for 13% ee. ^{1}H NMR δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 3.05 (m, 1H), 4.01 (m, 4H), 4.97 (dd, *J* = 10.4 & 4.8 Hz 1H), 7.17 (b, 1H), 7.19(b, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 16.38 (CH_3), 63.0 (OCH_2CH_3), 85.22 (CHOH), 122.92 (Ph, 1C), 126.99 (Ph, 1C), 129.20 (Ph, 1C), 133.20 (Ph, 1C), 157.98 (Ph, Cq), 167.21(Ph, Cq), ^{31}P NMR δ 21.52; IR (neat, cm^{-1}) 3240, 2984, 1224, 1184, 1010, 964, 796, 687; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 8.46 min (minor), 10.34 min (major).

4.2.7. Diethyl 1-hydroxy-(4-methylphenyl)methylphosphonate 7g

R_f = 0.35 hexane/acetone 2:1; $[\alpha]_D^{25} = -10.5$ (*c* 1.0, $CHCl_3$) for 30% ee. Lit.[3g] $[\alpha]_D^{20} = +27.7$ (*c* 0.22, $CHCl_3$) for 80% ee; ^{1}H NMR δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 3.02 (d, *J* = 10.4 Hz, 1H), 3.98–4.12 (m, 4H), 4.97 (dd, *J* = 10.4 and 4.4 Hz 1H), 7.17 (d, *J* = 8 Hz 2H), 7.37 (dd, *J* = 8.2 and 2.4 Hz, 2H); ^{31}P NMR δ 21.52; IR (neat, cm^{-1}) 3241, 2985, 1415, 1225, 1048, 963, 882, 797, 688; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 8.02 min (minor), 11.03 min (major).

4.2.8. Diethyl 1-hydroxy-1-(naphthyl)methylphosphonate 7h

R_f = 0.20 hexane/acetone 2:1; $[\alpha]_D^{25} = -19.0$ (*c* 1.0, $CHCl_3$) for 44% ee. Lit.[4] $[\alpha]_D^{19} = +11.5$ (*c* 1.01, $CHCl_3$) for 9% ee. ^{1}H NMR δ 1.05 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 3.16 (dd, 10.8 and 5.2 Hz 1H), 3.98–4.06 (m, 4H), 5.86 (dd, *J* = 11.6 and 4.4 Hz, 1H), 7.48–7.56 (m, 3H), 7.82–7.90 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 1H); ^{31}P NMR δ 21.52; IR (neat, cm^{-1}) 3217, 2978, 1392, 1199, 1024, 955, 770, 752, 634; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 10.19 min (minor), 33.51 min (major).

4.2.9. Diethyl 1-hydroxy-2-(naphthyl)methylphosphonate 7i

R_f = 0.25 hexane/acetone 2:1; $[\alpha]_D^{25} = -11.0$ (*c* 1.0, $CHCl_3$) for 30% ee. Lit.[4] $[\alpha]_D^{22} = +11.9$ (*c* 1.0, $CHCl_3$) for 33% ee; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 3.36 (b, 1H), 3.99–4.07 (m, 4H), 5.20 (dd, *J* = 10.8 and 2.8 Hz 1H), 7.45–7.53 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.81–7.84 (m, 3H), 7.96 (s, 1H); ^{31}P NMR δ 21.52; IR (neat, cm^{-1}) 3268, 2981, 1359, 1231, 1055, 1012, 946, 750, 641; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 11.34 min. (minor), 15.35 min (major).

4.2.10. Diethyl 1-hydroxy(ferrocenyl)methylphosphonate 7j[10]

R_f = 0.42, hexane/acetone 2:1, yellow oily product; $[\alpha]_D^{25} = +3.5$ (*c* 1.0, $CHCl_3$) for 28% ee; ^{1}H NMR: δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 3.44 (br, 1H), 3.95 (m, 4H), 4.10 (s, Fc, 2H), 4.15 (s, Fc, 5H), 4.21 (s, Fc, 1H), 4.35 (s, Fc, 1H), 4.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.08 (CH_3), 63.52 (CHOH), 63.72 (OCH_2CH_3), 65.34 (Fc, CH), 65.52 (Fc, CH), 65.71 (Fc, CH), 65.76 (Fc, CH), 66.35 (Fc, 5C), 83.42 (Fc, Cq) ^{31}P NMR ($CDCl_3$): δ 21.04; IR (neat, cm^{-1}) 3288, 2981, 1221, 1002, 960, 809; HPLC: Chiralpak AS-H column, UV detection at 254 nm, eluent: hexane/2-propanol 4:1, flow 1.0 mL min^{-1}, t_R = 24.0 min (major), 65.0 min (minor).

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