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Asymmetric Michael reaction: novel efficient access to chiral β-ketophosphonates

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Abstract—The asymmetric Michael reaction between chiral β-enaminophosphonates derived from (*S*)-1-phenylethylamine and various electrophilic alkenes furnished β,β-disubstituted ketophosphonates in good yields and with excellent enantioselectivity.

1. Introduction

The Michael reaction is known to be one of the simplest and most efficient methods for the construction of quaternary carbon centres. The use of asymmetric variants of this reaction is well documented in the literature, the stereocontrolled synthesis of a quaternary carbon in particular being a challenge for organic chemists. Asymmetric Michael addition onto cyclic or acyclic β-ketoesters has been considered in various ways in the literature and particularly via enaminoester derivatives.[1–7] Until now, there has been no report of such a study on β-ketophosphonates which present great interest not only as precursors of β-amino- and β-hydroxy-phosphonates[8–11] but also as molecules of biological importance.[12–15] Thus, by developing simple and efficient asymmetric synthetic pathways to chiral β-ketophosphonates we would be able to find interesting applications in both organic and medicinal chemistry.

In our laboratory, it has already been proven that Michael-type additions of chiral acyclic enaminoesters derived from (*S*)-1-phenylethylamine to various Michael acceptors furnished, after hydrolysis, Michael adducts in good yields and excellent enantiomeric excesses (ee).[2,3,7] This remarkable remote transfer of chirality can be explained by a six-membered 'aza-ene-synthesis-like' transition state which is secured by intramolecular hydrogen bonding in the enaminoester reactant.[2,3,16] By considering the phosphonate as an ester analogue, we can anticipate the existence of intramolecular hydrogen bonding in the enaminophosphonate similar to that of the enaminoester derivative. Herein, we report an investigation we have made into the reaction between chiral enaminophosphonates and various electrophilic alkenes.

2. Results and discussion

First of all, we synthesized the non-commercial β-ketophosphonate precursors **3a**–**3d** (Scheme 1). For dialkylphosphonates **3a** (R = Et) and **3b** (R = Me), the synthesis was performed in a three step procedure developed by Corbel et al: (a) protection of the ketone group via hydrazone **1**, (b) Arbuzov reaction (intermediates **2a** and **2b**) then (c) deprotection.[17] This led to compounds **3a** and **3b** in good yields, around 60–70% over three steps. For dibenzylphosphonate **3c**, the Arbuzov reaction was realized under vacuum in an attempt to eliminate benzyl chloride formed in the reaction and causing side reactions.[18] This proved to be unsuccessful, causing degradation. An alternative strategy was used with a direct nucleophilic substitution of the chlorine atom of compound **1** by the action of the anion of dibenzylphosphite. When the reaction was carried out at room temperature using Cs_2CO_3 as base,[19] only the β-elimination product was obtained. However, the use

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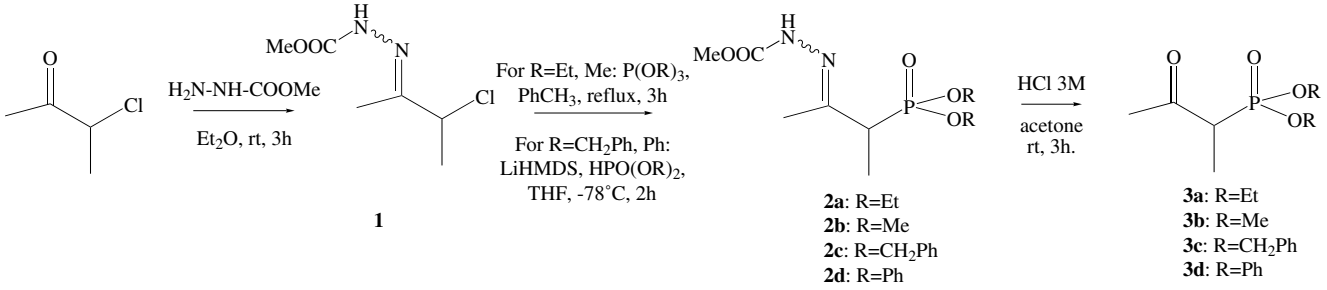


Scheme 1. Synthesis of the ketophosphonate precursors **3a**–**3d**.

at low temperature, −78 °C, of LiHMDS,[20] led, after hydrolysis, to compound **3c** in good yield (63%) over three steps. The same procedure was performed successfully for diphenylphosphonate **3d**, even though in modest 35% yield, over three steps.

These compounds were then condensed with (*S*)-1-phenylethylamine in refluxing toluene or cyclohexane to give the corresponding imino/enaminophosphonates **4a**–**4d** (Scheme 2). Compounds **4a**–**4c** exist in an approximately 35/65 imino/enamino ratio, while compound **4d** exists only in the enamino form. Additions of these crude imino/enaminophosphonates **4a**–**4d** to Michael acceptors, such as phenylvinylsulfone, benzyl and methyl acrylates, acrylonitrile and methylvinylketone (MVK), were performed under neutral conditions in THF. Reaction evolution was followed by ^{31}P NMR and reaction conditions are summarized in Table 1.

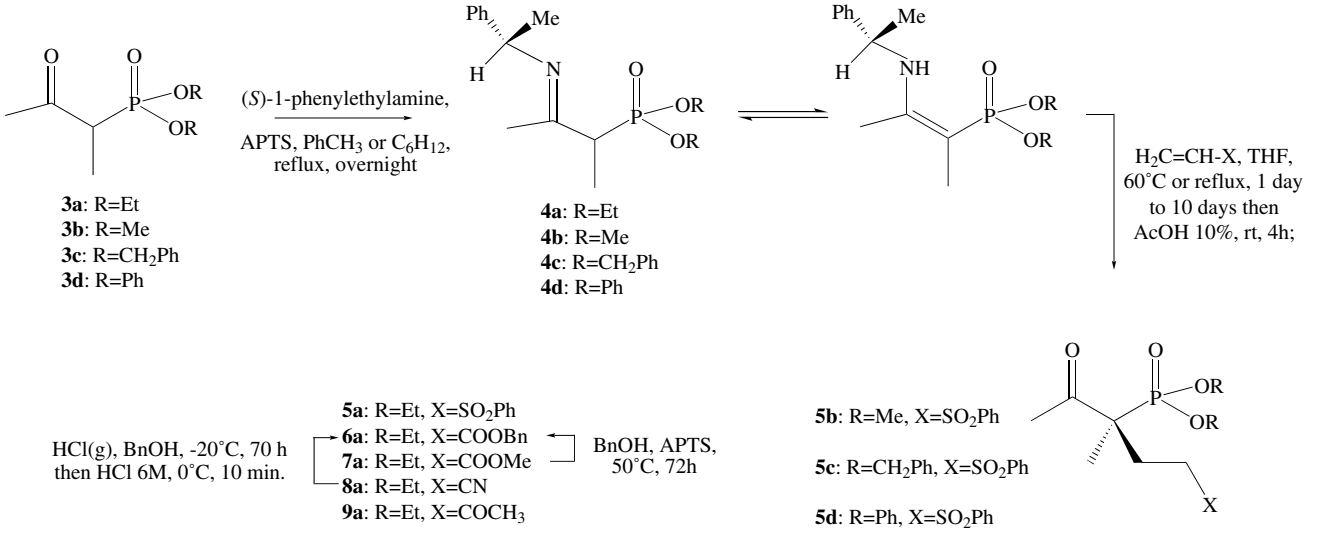
In the case of the diethylphosphonate derivatives, Michael adducts were obtained, after hydrolytic workup (10% AcOH in water, rt, 4 h), in good yields (55–67% over three steps, entries 1–4) except for MVK derivative **9a** (entry 5). Whatever the hydrolytic conditions, it always led to the degradation of the imino precursor. Yields and reactivities are in general comparable to those obtained for enaminoester analogues.[7]

Table 1. Reaction conditions, yield and enantiomeric excess for compounds **5a**–**9a**, **5b**–**5d**

Entry	Compd	Reaction time	*T* (°C)	Yield (%)	ee (%)
1	**5a**	1 d	66	67	94[a]
2	**6a**	3 d	66	55	88[a]
3	**7a**	3 d	66	65	88[b]
4	**8a**	10 d	60	40	85[b]
		1 d ($ZnCl_2$)		62	84[b]
5	**9a**	1 d	20	Degradation	—
6	**5b**	1 d	66	Degradation	—
7	**5c**	1 d	66	39	70[c]
8	**5d**	1 d	66	No reaction	—

[a] Determined by chiral HPLC.
[b] Determined by chiral HPLC via the derivative **6a**.
[c] Determined by ^{31}P NMR on the imino intermediate.

In the case of dimethylphosphonate derivative **5b** (entry 6), the Michael adduct was obtained after hydrolytic workup as the major product, according to the ^{1}H and ^{31}P NMR spectra of the crude product, but was degraded during attempts at purification by column chromatography or distillation.



Scheme 2. Synthesis of the Michael adducts.

The dibenzyl- and diphenyl-phosphonate groups should be more interesting than their diethylphosphonate homologues in the determination of enantiomeric excess by HPLC. In fact, they possessed the chromophore necessary for HPLC characterization.

Unfortunately, the introduction of such groups caused an important decrease in the reactivity of the imino/enaminophosphonates **4c** and **4d**, probably due to disfavoured steric hindrance for the formation of the six-membered transition state. For benzyl imino/enaminophosphonate **4c**, it led to a lower yield of the ketophosphonate **5c**, only 39% (entry 7). For phenyl enaminophosphonate **4d**, we did not observe any reaction under the classical conditions (entry 8).

Enantiomeric excesses (ees) of the Michael adducts **5a**–**8a** were then determined by chiral HPLC using a Daicel Chiralcel OD column. UV detection needed a chromophore group, existing in compounds **5a** and **6a** but not in compounds **7a** and **8a**. Ees of compounds **5a** and **6a** were thus determined directly but for compounds **7a** and **8a** it was necessary to introduce a chromophoric group. A transesterification of the methyl ester derivative **7a** or the Pinner reaction[21] applied to the cyano derivative **8a** in benzylic alcohol led to benzyl ester **6a**. The ees of the compounds **5a**–**8a** were in all cases good to excellent, between 85% and 94% (Table 1, entries 1–4), similar to those obtained for enaminoester derivatives (ee > 90%).[7]

Contrary to our expectations, the ee of the Michael adduct **5c** could not be obtained by chiral HPLC with the Daicel OD column. Whatever the conditions used (varying the chiral column, flow and solvents ratio), the two enantiomers could not be separated. However, analysis of the ^{31}P NMR of the imino intermediate of **5c** before hydrolysis showed the presence of two diastereomers at 42.14 ppm (85%) and 42.48 ppm (15%). This allowed us to evaluate the ee of **5c** as 70%. This low ee could be explained either by considering the steric hindrance caused by the two benzylic groups, which modified the usual approach of the two reactants or by an interfering retro-Michael process taking place during workup, a phenomenon already observed in the case of benzylic enaminoester.[22]

We can conclude that the introduction of dibenzyl- or diphenyl-phosphonate groups caused a dramatic decrease in reactivity and/or in enantioselectivity in comparison with the results obtained for the diethylphosphonate group.

The last goal of our work was determination of the absolute configurations of these adducts. Many attempts have been made to synthesize a solid derivative in order to obtain a single-crystal sample for X-ray analysis, but all attempts have proven unsuccessful. We have therefore used the vibrational circular dichroism (VCD) technique, now widely used to determine the absolute configurations of small-to-medium sized organic molecules.[23–26]

The experimental VCD of **7a** in $CDCl_3$ solution is shown in Figure 1. Conformational analysis (Section 4.8), followed by the density functional theory (DFT) calculation (using GAUSSIAN 03[27]) of the VCD spectra of the ten significantly populated conformations identified leads, for (*S*)-**7a**, to the conformationally averaged VCD spectrum shown in Figure 1. The agreement of the calculated and experimental VCD spectra is moderately good (allowing for the shift in frequency due to the absence of anharmonicity in the calculations, and the less-than-perfect signal-to-noise ratio of

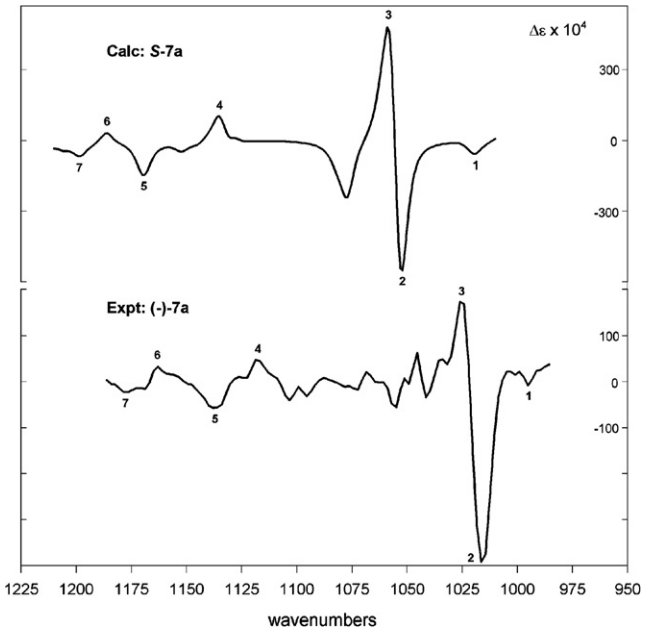
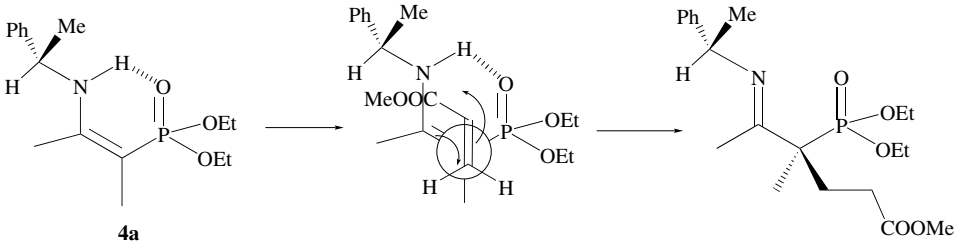


Figure 1. The experimental mid-IR VCD spectrum of (−)-**7a** (normalized to 100% ee), measured in a 0.09 M solution in $CDCl_3$, and the conformationally averaged B3LYP/6-31G* VCD spectrum of (*S*)-**7a**, obtained using Lorentzian band shapes ($\gamma = 4.0\ cm^{-1}$). The numbers indicate the assignment of the experimental VCD spectrum, based on the calculated spectrum.



4a

Scheme 3. Transition state of the reaction involving compound **4a** and methyl acrylate.

the experimental VCD). Compound **7a** has a negative specific rotation ($[\alpha]_D = -10$, normalized to 100% ee). Thus it follows that the absolute configuration of **7a** is (*S*)-(−).

This result is in accordance with the related six-membered 'aza-ene-synthesis-like' transition state postulated consisting of (i) an intramolecular hydrogen bond between the oxygen of the phosphonate group and the NH moiety in compound **4a** and (ii) the *syn*-approach of the methyl acrylate on the less hindered *Si* π-face of enaminophosphonate **4a**, anti to the bulky phenyl group of the chiral amine moiety (Scheme 3).

3. Conclusion

In conclusion, we have demonstrated that the asymmetric Michael reaction on acyclic enaminophosphonate compounds with non-substituted Michael acceptors is practicable with good yields and high enantiomeric excesses, in the same way as for the acyclic enaminoester derivatives. This method gives us the opportunity to access new chiral β-ketophosphonates, as analogues of β-ketoesters. Work is currently in progress to extend this reaction to substituted Michael acceptors.

4. Experimental

4.1. General

Commercial reagents were used without purification unless otherwise mentioned. Prior to use, THF was freshly distilled from sodium-benzophenone, toluene and benzyl alcohol from CaH_2. Acrylonitrile and methyl acrylate were distilled and dried over molecular sieves. All anhydrous reactions were carried out under argon. Analytical thin layer chromatography was performed on Merck 60F-254 precoated silica (0.2 mm) on glass and was developed by UV-light or Kägi-Misher reagent. All flash chromatography separations were performed with Merck Kieselgel 60 (250–500 μm). Melting points were recorded on an electrothermal digital apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat films and were recorded on a Bruker Vector 22 spectrophotometer. ^1H, ^{31}P and ^{13}C NMR spectra were recorded respectively at 200 MHz, 81 MHz and 50 MHz on a Brucker ARX200. $CDCl_3$ was used as internal reference. Specific rotations $[\alpha]_D^{20}$ were measured on a Polartronic E Schmidt+Haensch 2095 polarimeter at the sodium D line (589 nm) and at 20 °C in a 1 dm-cell. Elemental analyses were performed by the Service de Microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyser. Enantiomeric excesses were measured either by chiral HPLC on a Spectrasystem P1000XR with a Spectraseries UV100 spectrophotometer and a chiral column Chiralcel OD, the spectra being treated with the AZUR program, or by analysis of the ^{31}P NMR of the imino intermediate (before hydrolysis). VCD spectra were measured using a Bomem/BioTools ChiralIR instrument. Compounds **1**, **2a** and **2b** and **3a** and **3b** were synthesized according to the procedure described by Corbel.[9]

4.2. General procedure for the synthesis of derivatives 2c and 2d

To a solution of dibenzyl- or diphenylphosphite (12 mmol, 1.2 equiv) in 30 mL of THF was added at −78 °C and under argon a solution of LiHMDS freshly prepared from a solution of BuLi 1.6 M in cyclohexane (8.3 mL, 13 mmol, 1.3 equiv) and HMDS (2.6 mL, 12 mmol, 1.2 equiv) in 5 mL of THF at −78 °C. After 30 min, HMPA (5 mL) was added and the mixture stirred for further 30 min. A solution of compound **1** (1.8 g, 10 mmol, 1 equiv) in 25 mL of THF was added dropwise and the mixture stirred at −78 °C for 2 h, then at −15 °C for 2 h. The mixture was then quenched by the addition of aqueous NH_4Cl, diluted with water then extracted with EtOAc. The organic layers were then mixed up, washed with NH_4Cl, water, then brine, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by column chromatography (DCM 100 to DCM/MeOH 95/5) to yield the desired compound.

4.2.1. Dibenzyl [3-(methoxycarbonyl-hydrazono)-but-2-yl]-phosphonate 2c. Colourless oil (2.96 g, 73% yield); R_f: 0.65 (DCM/MeOH 95:5); ^1H NMR ($CDCl_3$): δ 1.28 (dd, $^3J = 7.2$ Hz, $^3J_P = 18.4$ Hz, 3H, CH_3CH), 1.79 (d, $^4J_P = 2.6$ Hz, 3H, $CH_3C{=}N$), 3.07 (qd, $^3J = 7.2$ Hz, $^2J_P = 22.6$ Hz, 1H, CH_3CH), 3.63 (s, 3H, $COOCH_3$), 4.80–5.00 (m, 4H, $PO(OCH_2Ph)_2$), 7.00–7.20 (m, 10H, H_{ar}), 8.58 (br s, 1H, NH); ^{31}P NMR ($CDCl_3$): δ 41.00; ^{13}C NMR ($CDCl_3$): δ 11.9 (d, $^2J_P = 5.7$ Hz, CH_3CH), 13.4 ($CH_3C{=}N$), 41.2 (d, $^1J_P = 135.8$ Hz, CH_3CH), 52.1 ($COOCH_3$), 67.1 (d, $^2J_P = 6.4$ Hz, $PO(OCH_2Ph)_2$), 127.3 (CH_{ar}), 127.4 (CH_{ar}), 128.0 (CH_{ar}), 135.7 (Cq_{ar}), 149.3 (d, $^2J_P = 6.0$ Hz, C=N), 154.3 (CO); IR (cm^{-1}): 3239, 2944, 1728, 1591, 1527, 1488, 1456, 1361, 1264, 1209, 1184, 1161, 1070, 1025.

4.2.2. Diphenyl [3-(methoxycarbonyl-hydrazono)-but-2-yl]-phosphonate 2d. Colourless oil (1.86 g, 49% yield); R_f: 0.30 (DCM/MeOH 95:5); ^1H NMR ($CDCl_3$): δ 1.60 (dd, $^3J = 7.4$ Hz, $^3J_P = 19.4$ Hz, 3H, CH_3CH), 1.96 (d, $^4J_P = 3.0$ Hz, 3H, $CH_3C{=}N$), 3.49 (qd, $^3J = 7.2$ Hz, $^2J_P = 23.2$ Hz, 1H, CH_3CH), 3.85 (s, 3H, $COOCH_3$), 7.00–7.20 (m, 10H, H_{ar}), 7.90 (br s, 1H, NH); ^{31}P NMR ($CDCl_3$): δ 32.90; ^{13}C NMR ($CDCl_3$): δ 12.2 (d, $^2J_P = 5.9$ Hz, CH_3CH), 13.6 ($CH_3C{=}N$), 41.8 (d, $^1J_P = 136.7$ Hz, CH_3CH), 52.7 ($COOCH_3$), 120.5 (CH_{ar}), 125.0 (CH_{ar}), 129.39 (CH_{ar}), 148.4 (d, $^2J_P = 6.4$ Hz, Cq_{ar}), 150.0 (d, $^2J_P = 9.3$ Hz, C=N), 154.5 (CO); IR (cm^{-1}): 3242, 2244, 1727, 1591, 1527, 1489, 1456, 1371, 1264, 1210, 1184, 1161, 1070, 1025.

4.3. General procedure for the hydrolysis into derivatives 3c–3d

A solution of compound **2c**–**2d** 1 M in an acetone/HCl 3 M: 1/1 mixture was stirred at room temperature for 3 h, then diluted with water. Acetone was removed and the aqueous layer then extracted with dichloromethane. The organic layers were then mixed up, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by

column chromatography (DCM 100 to DCM/MeOH 95:5) to yield the desired compound.

4.3.1. Dibenzyl (3-oxo-but-2-yl)-phosphonate 3c. Colourless oil (90% yield); R_f: 0.75 (DCM/MeOH 95:5); ^{1}H NMR ($CDCl_3$): δ 1.36 (dd, $^3J = 7.2$ Hz, $^3J_P = 18.4$ Hz, 3H, CH_3CH), 2.28 (s, 3H, $COCH_3$), 3.21 (qd, $^3J = 7.2$ Hz, $^2J_P = 25.6$ Hz, 1H, CH_3CH), 4.95–5.10 (m, 4H, $PO(OCH_2Ph)_2$), 7.10–7.30 (m, 10H, H_{ar}); ^{31}P NMR ($CDCl_3$): δ 37.10; ^{13}C NMR ($CDCl_3$): δ 10.4 (d, $^2J_P = 6.3$ Hz, CH_3CH), 29.9 (CH_3CO), 47.0 (d, $^1J_P = 126.5$ Hz, CH_3CH), 67.4 ($PO(OCH_2Ph)_2$), 127.5 (CH_{ar}), 128.7 (CH_{ar}), 128.8 (CH_{ar}), 135.5 (Cq_{ar}), 203.0 (d, $^2J_P = 3.8$ Hz, CO); IR (cm^{-1}): 2944, 2894, 1713, 1452, 1377, 1358, 1304, 1244, 1213, 1149, 1082, 989.

4.3.2. Diphenyl (3-oxo-but-2-yl)-phosphonate 3d. Colourless oil (73% yield); R_f: 0.65 (DCM/MeOH 95:5); ^{1}H NMR ($CDCl_3$): δ 1.58 (dd, $^3J = 7.0$ Hz, $^3J_P = 19.0$ Hz, 3H, CH_3CH), 2.45 (s, 3H, $COCH_3$), 3.54 (qd, $^3J = 7.2$ Hz, $^2J_P = 25.8$ Hz, 1H, CH_3CH), 7.00–7.20 (m, 10H, H_{ar}); ^{31}P NMR ($CDCl_3$): δ 29.10; ^{13}C NMR ($CDCl_3$): δ 10.6 (d, $^2J_P = 6.7$ Hz, CH_3CH), 30.2 (CH_3CO), 47.0 (d, $^1J_P = 127.8$ Hz, CH_3CH), 120.1 (d, $^3J_P = 3.7$ Hz, CH_{ar}), 125.1 (CH_{ar}), 129.4 (CH_{ar}), 149.7 (d, $^2J_P = 9.2$ Hz, Cq_{ar}), 202.2 (d, $^2J_P = 3.9$ Hz, CO); IR (cm^{-1}): 3239, 2944, 1728, 1591, 1527, 1488, 1456, 1361, 1264, 1209, 1184, 1161, 1070, 1025.

4.4. General procedure for the synthesis of derivatives 4a–4d

To a solution of compound **3a**–**3d** (1 equiv) in freshly distilled toluene or cyclohexane (1 M) were added under an inert atmosphere, catalytic amount of APTS and (*S*)-1-phenylethylamine (1.1 equiv). After stirring at reflux overnight using a Dean-Stark apparatus, the mixture was concentrated to yield the desired compound which was used without any purification.

4.4.1. Diethyl (*S*)-[3-(1-phenyl-ethylimino)-but-2-yl]-phosphonate 4a. Yellow oil (quantitative yield); ^{1}H NMR ($CDCl_3$): δ 1.25–1.75 (m, 12H, $P(OCH_2CH_3)_2CH_3CH$ and CH_3), 1.80 (s, 3H, $CH_3C{=}N$ enamine), 2.05 (d, $^4J_p = 2.0$ Hz, 3H, $CH_3C{=}N$ imine), 2.90–3.20 (m, 1H, CH_3CH imine), 3.90–4.30 (m, 4H, $P(OCH_2CH_3)_2$), 4.57 (qd, $^2J = 6.9$ Hz and $^2J_{NH} = 8.0$ Hz, 1H, CH_2 enamine), 4.47 (q, $^2J = 6.6$ Hz, 1H, CH imine), 7.35 (m, 10H, H_{ar}), 8.17 (d, $J = 8.0$ Hz, 1H, NH enamine); ^{31}P NMR ($CDCl_3$): δ 40.75 + 40.89 (imine), 41.67 (enamine).

4.4.2. Dimethyl (*S*)-[3-(1-phenyl-ethylimino)-but-2-yl]-phosphonate 4b. Yellow oil (quantitative yield); ^{1}H NMR ($CDCl_3$): δ 1.30–1.60 (m, 12H, CH_3CH and CH_3), 1.73 (s, 3H, $CH_3C{=}N$ enamine), 1.96 (d, $^4J_p = 1.8$ Hz, 3H, $CH_3C{=}N$ imine), 2.90–3.20 (m, 1H, CH_3CH imine), 3.55–3.80 (m, 6H, $P(OCH_3)_2$), 4.64 (qd, $^2J = 6.8$ Hz and $^2J_{NH} = 7.2$ Hz, 1H, CH enamine), 4.47 (q, $^2J = 7.0$ Hz, 1H, CH imine), 7.00–7.50 (m, 10H, H_{ar}), 8.17 (d, $J = 7.2$ Hz, 1H, NH enamine); ^{31}P NMR ($CDCl_3$): δ 43.31 + 43.48 (imine), 44.74 (enamine).

4.4.3. Dibenzyl (*S*)-[3-(1-phenyl-ethylimino)-but-2-yl]-phosphonate 4c. Yellow oil (quantitative yield); ^{1}H NMR ($CDCl_3$): δ 1.40–1.80 (m, 12H, CH_3CH and CH_{32} and $CH_3C{=}N$), 2.90–3.20 (m, 1H, CH_3CH imine), 3.50–5.20 (m, 5H, $P(OCH_2Ph)_2$ and CH_2), 7.00–7.50 (m, 10H, H_{ar}), 8.35 (d, $J = 7.2$ Hz, NH enamine); ^{31}P NMR ($CDCl_3$): δ 41.77 + 41.86 (imine), 42.49 (enamine).

4.4.4. Diphenyl (*S*)-[3-(1-phenyl-ethylimino)-but-2-yl]-phosphonate 4d. Yellow oil (quantitative yield); ^{1}H NMR ($CDCl_3$): δ 1.30–1.50 (m, 6H, CH_3CH and CH_3), 1.62 (s, 3H, $CH_3C{=}N$), 4.44 (qd, $^2J = 8.0$ Hz and $^2J_{NH} = 7.2$ Hz, 1H, CH_2), 6.90–7.40 (m, 10H, H_{ar}), 8.13 (d, $J = 7.8$ Hz, 1H, NH enamine); ^{31}P NMR ($CDCl_3$): δ 35.56.

4.5. General procedure for the Michael reaction between derivatives 4a–4d and electrophilic alkenes

To a solution of compound **4a**–**4d** (1 equiv) in freshly distilled tetrahydrofuran (1 M) were added under an inert atmosphere, catalytic amounts of hydroquinone and the electrophilic alkene (1.5–8 equiv) dropwise. After stirring the mixture at reflux for 1–10 days (evolution reaction was monitored by ^{31}P NMR) and cooling, AcOH 10% was added. After further stirring at room temperature for 4 h at room temperature, tetrahydrofuran was evaporated and the aqueous layer was extracted with dichloromethane. The organic layer was then washed with HCl 1 M and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/EtOAc 3:7) to yield the desired compound.

4.5.1. Diethyl (*S*)-[2-(2-benzenesulfonyl-ethyl)-3-oxo-but-2-yl]-phosphonate 5a. Colourless oil (67% yield); ee = 94%; R_f: 0.15 (cyclohexane/EtOAc 5:5); ^{1}H NMR ($CDCl_3$): δ 1.25 + 1.26 (t, $^3J = 6.9$ Hz, 2×3H, $PO(OCH_2CH_3)_2$), 1.37 (d, $^3J_P = 17.1$ Hz, 3H, CH_3), 2.10–2.30 (m, 4H, CH_2), 2.24 (s, 3H, $COCH_3$), 2.95–3.10 (m, 2H, CH_2SO_2), 4.07 + 4.09 (2 qd, $^3J = 7.0$ Hz, $^3J_P = 9.2$ Hz, 2×2H, $PO(OCH_2CH_3)_2$), 7.50–7.70 (m, 3H, H_{ar}), 7.75–7.95 (m, 2H, H_{ar}); ^{31}P NMR ($CDCl_3$): δ 37.34; ^{13}C NMR ($CDCl_3$): δ 15.8 + 15.9 (2d, $^3J_P = 5.7$ Hz, $PO(OCH_2CH_3)_2$), 16.9 (d, $^2J_P = 5.3$ Hz, CH_3), 26.0 (d, $^2J_P = 3.2$ Hz, CH_2), 27.2 (CH_3CO), 51.4 (d, $^3J_P = 9.4$ Hz, CH_2SO_2), 52.7 (d, $^1J_P = 130$ Hz, C_q), 62.8 + 62.9 (2d, $^2J_P = 7.4$ Hz, $PO(OCH_2CH_3)_2$), 127.6 (CH_{ar}), 128.9 (CH_{ar}), 133.4 (CH_{ar}), 138.3 (C_{qar}), 204.4 (CO); IR (cm^{-1}): 2984, 1707, 1447, 1244, 1146, 1015; $[\alpha]_D^{20} = -26$ (*c* 2.00, CH_2Cl_2). Anal. Calcd for $C_{16}H_{25}O_6PS$: C, 51.05; H, 6.69. Found: C, 51.28; H, 6.89; HPLC (hexane/*i*PrOH 94/6, 1.5 mL/min, $\lambda = 217$ nm): $t_R = 21.6$ min (minor enantiomer) and 23.3 min (major enantiomer).

4.5.2. Diethyl (*S*)-[2-(2-benzyloxycarbonyl-ethyl)-3-oxo-but-2-yl]-phosphonate 6a. Colourless oil (55% yield); ee = 88%; R_f: 0.30 (cyclohexane/EtOAc 3:7); ^{1}H NMR ($CDCl_3$): δ 1.28 + 1.29 (t, $^3J = 7.1$ Hz, 2×3H, $PO(OCH_2CH_3)_2$), 1.38 (d, $^3J_P = 16.8$ Hz, 3H, CH_3), 2.00–2.50 (m, 4H, CH_2CH_2COO), 2.30 (s, 3H, $COCH_3$), 4.10 + 4.11 (2 qd, $^3J = 7.1$ Hz, $^3J_P = 9.0$ Hz, 2×2H, $PO(OCH_2CH_3)_2$), 5.09 (s, 2H, OCH_2Ph), 7.32 (s, 5H, Ph); ^{31}P NMR ($CDCl_3$): δ 38.58; ^{13}C NMR ($CDCl_3$): δ

15.9 (d, $^3J_P = 5.6$ Hz, PO(OCH$_2$*C*H$_3$)$_2$), 16.1 (d, $^2J_P = 5.1$ Hz, CH$_3$), 27.4 (COCH$_3$), 27.8 (d, $^2J_P = 3.5$ Hz, CH$_2$), 28.9 (d, $^3J_P = 11.5$ Hz, *C*H$_2$COO), 53.3 (d, $^1J_P = 139.2$ Hz, C$_q$), 62.3 + 62.4 (2d, $^2J_P = 6.0$ Hz, PO(O*C*H$_2$CH$_3$)$_2$), 65.9 (O*C*H$_2$Ph), 127.7 (CH$_{ar}$), 128.0 (CH$_{ar}$), 135.4 (Cq$_{ar}$), 172.0 (*C*OOBn), 205.0 (CO); IR (cm^{-1}): 2983, 2932, 1734, 1705, 1498, 1389, 1358, 1245, 1163, 1046, 1016; $[\alpha]_D^{20} = +11$ (*c* 2.00, CH$_2$Cl$_2$). Anal. Calcd for C$_{18}$H$_{28}$O$_6$P: C, 58.37; H, 7.35. Found: C, 58.12; H, 7.62; HPLC (hexane/*i*PrOH 96/4, 1 mL/min, $\lambda = 208$ nm): $t_R = 13.2$ min (minor enantiomer) and 16.5 min (major enantiomer).

4.5.3. Diethyl (*S*)-[2-(2-methoxycarbonyl-ethyl)-3-oxo-but-2-yl]-phosphonate 7a. Colourless oil (65% yield); ee = 88%; R_f: 0.20 (hexane/EtOAc 3:7); ^{1}H NMR (CDCl$_3$): δ 1.25 + 1.26 (t, $^3J = 7.1$ Hz, 2 × 3H, PO(OCH$_2$*C*H$_3$)$_2$), 1.33 (d, $^3J_P = 16.8$ Hz, 3H, CH$_3$), 1.90–2.40 (m, 4H, *C*H$_2$*C*H$_2$-COO), 2.26 (s, 3H, CO*C*H$_3$), 3.59 (s, 3H, COOCH$_3$), 4.06 + 4.07 (2 qd, $^3J = 7.1$ Hz, $^3J_P = 9.0$ Hz, 2 × 2H, PO(O*C*H$_2$CH$_3$)$_2$); ^{31}P NMR (CDCl$_3$): δ 38.57; ^{13}C NMR (CDCl$_3$): δ 15.5 (d, $^3J_P = 5.6$ Hz, PO(OCH$_2$*C*H$_3$)$_2$), 15.7 (d, $^2J_P = 5.1$ Hz, CH$_3$), 26.9 (COCH$_3$), 27.4 (d, $^2J_P = 3.9$ Hz, CH$_2$), 28.3 (d, $^2J_P = 11.6$ Hz, *C*H$_2$COO), 50.7 (COO*C*H$_3$), 53.0 (d, $^1J_P = 129$ Hz, C$_q$), 61.9 + 62.0 (2d, $^2J_P = 7.3$ Hz, PO(O*C*H$_2$CH$_3$)$_2$), 172.1 (*C*OOCH$_3$), 204.4 (CO); IR (cm^{-1}): 2984, 1737, 1705, 1438, 1245, 1046, 1016; $[\alpha]_D^{20} = -10$ (*c* 1.88, CH$_2$Cl$_2$). Anal. Calcd for C$_{12}$H$_{23}$O$_6$P: C, 48.98; H, 7.88. Found: C, 48.68; H, 8.04.

4.5.4. Diethyl (*S*)-[2-(2-cyano-ethyl)-3-oxo-but-2-yl]-phosphonate 8a. Yellow oil (66% yield); R_f: 0.25 (hexane/EtOAc 3:7); ee = 85%; ^{1}H NMR (CDCl$_3$): δ 1.34 + 1.35 (t, $^3J = 7.1$ Hz, 2 × 3H, PO(OCH$_2$*C*H$_3$)$_2$), 1.50 (d, $^3J_P = 17.2$ Hz, 3H, CH$_3$), 2.00–2.50 (m, 4H, CH$_2$), 2.35 (s, 3H, CO*C*H$_3$), 4.14 + 4.16 (2 qd, $^3J = 7.1$ Hz, $^3J_P = 11.6$ Hz, 2 × 2H, PO(O*C*H$_2$CH$_3$)$_2$); ^{31}P NMR (CDCl$_3$): δ 37.33; ^{13}C NMR (CDCl$_3$): δ 12.2 (d, $^2J_P = 10.9$ Hz, *C*H$_3$C$_q$), 15.8 (d, $^3J_P = 5.4$ Hz, PO(OCH$_2$*C*H$_3$)$_2$), 16.4 (d, $^2J_P = 5.4$ Hz, *C*H$_2$C$_q$), 27.2 (*C*H$_3$CO), 28.6 (d, $^3J_P = 2.9$ Hz, *C*H$_2$CN), 53.0 (d, $^1J_P = 129.1$ Hz, C$_q$), 62.5 + 62.7 (2d, $^2J_P = 7.7$ Hz, PO(O*C*H$_2$CH$_3$)$_2$), 118.8 (CN), 204.3 (CO); IR (cm^{-1}): 2984, 2247, 1706, 1445, 1245, 1163, 1043, 1015; $[\alpha]_D^{20} = -45$ (*c* 1.5, CH$_2$Cl$_2$). Anal. Calcd for C$_{11}$H$_{20}$NO$_4$P: C, 50.57; H, 7.72; N, 5.36. Found: C, 50.45; H, 7.83; N, 5.29.

4.5.5. Dibenzyl (*S*)-[2-(2-Benzenesulfonyl-ethyl)-3-oxo-but-2-yl]-phosphonate 5c. Colourless oil (39% yield); R_f: 0.20 (cyclohexane/EtOAc 5:5); ee = 70%; ^{1}H NMR (CDCl$_3$): δ 1.55 (d, $^3J_P = 17.2$ Hz, 3H, CH$_3$), 2.20–2.60 (m, 2H, CH$_2$C$_q$), 2.39 (s, 3H, CO*C*H$_3$), 3.10–3.60 (m, 2H, CH$_2$SO$_2$), 5.00–5.30 (m, 4H, PO(O*C*H$_2$Ph)$_2$), 7.40–8.10 (m, 15H, H$_{ar}$); ^{31}P NMR (CDCl$_3$): δ 38.63; ^{13}C NMR (CDCl$_3$): δ 17.2 (d, $^2J_P = 5.0$ Hz, *C*H$_3$C$_q$), 26.3 (d, $^2J_P = 2.9$ Hz, CH$_2$), 27.4 (*C*H$_3$CO), 51.5 (d, $^3J_P = 9.2$ Hz, *C*H$_2$SO$_2$), 53.0 (d, $^1J_P = 135.1$ Hz, C$_q$), 68.2 (d, $^2J_P = 7.2$ Hz, PO(O*C*H$_2$Ph)$_2$), 127.8 (CH$_{ar}$), 128.4 (CH$_{ar}$), 129.0 (CH$_{ar}$), 138.5 (C$_{qar}$), 204.9 (CO); IR (cm^{-1}): 2976, 2362, 1745, 1591, 1486, 1364, 1298, 1273, 1247, 1184, 1156, 1127, 1070, 1017, 999; $[\alpha]_D^{20} = +8$ (*c* 1.00, CH$_2$Cl$_2$). Anal. Calcd for C$_{26}$H$_{29}$O$_6$PS: C, 62.39; H, 5.84. Found: C, 62.56; H, 5.99.

4.6. Transesterification of compound 7a into compound 6a

A solution of **7a** (400 mg, 1.36 mmol, 1 equiv) and a catalytic amount of APTS in 1 mL of freshly distilled benzyl alcohol was stirred at 50 °C for 72 h. The mixture was concentrated and the residue purified by column chromatography (cyclohexane/EtOAc 5:5–3:7) to yield compound **6a** (340 mg, 68% yield).

4.7. Pinner reaction of compound 8a into compound 6a

Anhydrous HCl(g) was bubbled into benzyl alcohol maintained in an ice bath over a period of 10 min to saturation. Compound **8a** (180 mg, 0.69 mmol, 1 equiv) was diluted into 1 mL of this solution under an inert atmosphere and the flask was capped with a septum and kept at −20 °C for 70 h. The mixture was then diluted at 0 °C with 0.5 mL of HCl 6 M. After stirring for 10 min at 0 °C, the mixture was diluted with 2 mL of water, extracted with 3 × 5 mL of DCM. The organic layers were combined, washed with 10 mL of brine, dried over Na$_2$SO$_4$, filtered then concentrated and the residue purified by column chromatography (cyclohexane/EtOAc 5:5–3:7) to yield compound **6a** (60 mg, 24% yield).

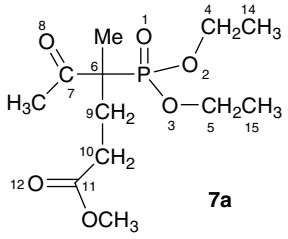
Table 2. B3LYP/6-31G* relative energies,[a] free energies,[a] population percentages,[b] and key dihedral angles[c] of the conformations of **7a**

	Δ*E*	Δ*G*	*P* (%)	D1	D2	D3	D4	D5	D6	D7	D8	D9
a	0.92	0.00	35.09	30.00	55.61	−53.59	−93.34	−179.97	179.94	−4.32	−149.12	−172.69
b	2.00	0.01	34.43	14.31	50.92	64.83	117.57	178.04	177.14	−14.13	−136.65	−173.20
c	1.35	0.83	8.65	29.03	57.69	−52.95	−93.05	−179.99	179.27	−3.59	−153.17	−87.35
d	1.97	1.17	4.82	30.58	54.89	−54.04	−91.80	−178.23	−179.71	121.83	−151.03	−174.04
e	1.23	1.27	4.08	30.12	53.59	−55.03	−95.40	−177.05	83.62	34.97	−151.86	−174.23
f	0.00	1.32	3.80	29.95	54.14	−51.05	−87.03	−169.22	−58.42	87.74	−157.36	−171.51
g	0.43	1.41	3.27	29.17	53.33	−53.37	−87.85	−168.69	−58.56	87.69	−149.90	−88.93
h	1.87	1.59	2.40	29.61	53.93	−55.76	−91.63	178.44	74.37	−126.39	−147.07	−173.57
i	1.71	1.75	1.84	29.48	56.65	−53.76	−93.96	−177.63	83.49	34.57	−153.10	−87.70
j	1.95	1.82	1.62	−54.39	−22.53	−68.24	−112.67	−169.14	85.62	20.41	172.24	−142.46

[a] In kcal/mol.
[b] Based on Δ*G*.
[c] D1: O1PO2C4; D2: O1PO3C5; D3: O1PC6C7; D4: PC6C7O8; D5: PC6C9C10; D6: C6C9C10C11; D7: C9C10C11O12; D8: PO2C4C14; D9: PO3C5C15.

4.8. Conformational analysis of 7a

The conformations of **7a** with B3LYP/6-31G* DFT free energies within a range of 2.0 kcal/mol are given in Table 2. Room-temperature equilibrium populations, obtained from the relative free energies using Boltzmann statistics, and key dihedral angles, which define the conformational structures, are also given in Table 2. All DFT calculations were carried out using GAUSSIAN 03.[27]



7a

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