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Enantioselective Organocatalytic Synthesis of α-Cyclopropylphosphonates through a Domino Michael Addition/Intramolecular Alkylation Reaction

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An organocatalytic domino reaction consisting of Michael addition/intramolecular alkylation between α,β-unsaturated aldehydes and bromophosphonoacetates was developed. Highly functionalised cyclopropylphosphonates containing three chiral centres, one of them quaternary, were obtained with good diastereoselectivities of up to 83:17 and very high enantioselectivities of up to 99%.

Introduction

The cyclopropane ring is found in more than 4000 natural compounds with a diverse range of biological activity,[1] as for example in chrysanthemic acid, which is present in the flowers of *Chrysanthemum cinerariaefolium*, where it performs a defensive role in the plant. It is also present in about 100 pharmaceutical products,[2] in many agrochemicals,[3] and it is a useful synthetic intermediate.[4] This structure is used in medicinal chemistry to increase conformational rigidity, which may increase the activity of a drug or reduce its side effects,[5] and for lead optimisation, to explore lipophilic binding pockets, hydrophobic interactions and bioactive conformations.[6]

We have been interested in the chemistry of phosphonates for some time and have developed some novel methods to synthesise chiral phosphonates based on enantioselective catalysis by metals complexed to chiral ligands or by chiral organocatalysts.[7] We have now extended our studies and developed enantioselective methodologies for the synthesis of chiral α-cyclopropylphosphonates (α-CPPs). These compounds (e.g., **A**–**F**, Figure 1) have diverse biological activities.[8] In phosphonates, the configuration of the chiral centre is often crucial for biological activity, because they have to interact with chiral biomolecules. Optically pure α-CPPs have been synthesised until now mainly by racemic methods followed by resolution, with chiral auxiliaries, or from chiral reagents.[9] Catalytic enantioselective methods are more efficient, since a small amount of a chiral catalyst produces large amounts of chiral substance in shorter synthetic routes, but examples are scarce.[9] The catalytic enantioselective synthesis of chiral cyclopropylphosphonates was reported for the first time in 2003 by Simonneaux and coworkers,[10] but since then there have been very few examples.[11] The methods reported were based on the use of transition-metal-induced carbene transfer in the presence of chiral ligands from *N*-diazomethylphosphonates to styrenes and from aryldiazomethylphosphonates to styrenes, and the products were obtained with very high enantiomeric excess in many cases.[10,11] Since electron-donating substituents are required to stabilise the resulting metal-carbenoids, Fischer type carbenes with electrophilic character are required, and the olefinic reaction partner also needs electron-donating substituents;[9b] the α-CPPs thus produced had the phosphoryl group and benzene or other aromatic substituents as the only substituents, and were therefore poor chiral intermediates. In 2013, the first example of the use of a diac-

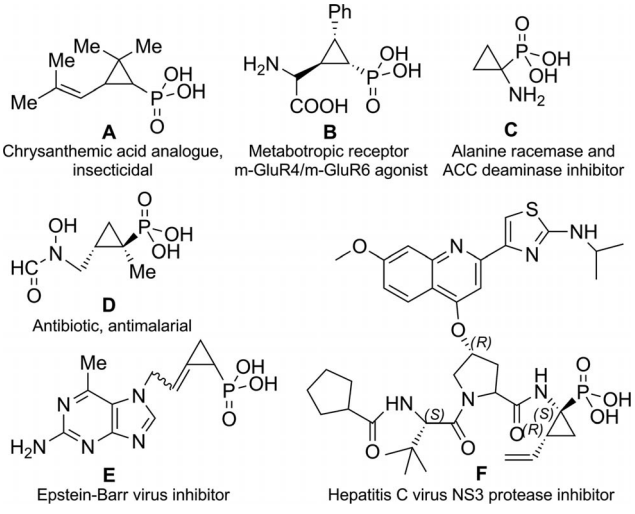

Figure 1. Potent biologically active α-cyclopropylphosphonates.

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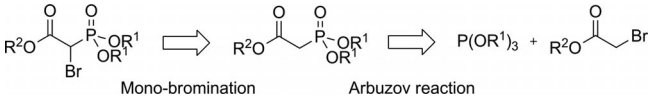
ceptor diazo compound (an α-cyano diazophosphonate reagent) was developed by Charette and co-workers,[12] thus broadening the synthetic utility of the catalytic enantioselective cyclopropylphosphonylation.

Organocatalysis could provide an attractive alternative. Organocatalysts are environmentally friendly, stable, function under mild conditions, and they can usually be handled in air. More importantly, they have much greater functional group tolerance, which could imply that additional functional groups could be initially incorporated in the cyclopropane ring for further synthetic elaboration into biologically active targets. Enantioselective organocatalytic cyclopropane synthesis has attracted the attention of the chemical community in the last few years. A first example was developed by Vignola and List,[13] through intramolecular α-alkylation mediated by proline and proline derivatives and, since then, a few methods have been developed. Although a large variety of synthetic strategies have been used, as well as catalysts with different modes of activation, most of the methods developed involve Michael initiated ring closure (MIRC) methodology, consisting of a domino process of Michael addition/intramolecular alkylation with electron-poor olefins.[14] Cyclopropanes with a variety of substituents and one to three chiral centres, have been synthesised from enones,[15] α,β-unsaturated esters,[15a,1] enals,[16,17] nitroalkenes,[18] α,β-unsaturated-α-cyanoimides,[19] β-substituted methylidenemalononitriles,[20] vinylselenones,[21] allylic alcohols,[22] alkylidene oxindoles,[23] 2-arylidene-1,3-indandiones,[24] and 4-nitro-5-styrylisoxazoles,[25] often with very high diastereomeric ratios (*dr*) and enantiomeric excess (*ee*). However, during this period there was only one report of an organocatalysed synthesis of cyclopropylphosphonates, in which proline and some of its derivatives were used to catalyse the cyclopropanation reaction between α-methylacrolein and α-diazobenzylphosphonates.[26] However, although the products were obtained in moderate to good yields, the diastereoselectivity was only moderate and racemic mixtures were obtained.

Having in mind the synthetic versatility of the formyl group, we decided to attempt the synthesis of α-CPPs based on a methodology previously developed for reactions of α,β-unsaturated aldehydes.[17a] The first organocatalytic cyclopropanation of enals was reported by Cordova and co-workers[17a] in 2007 and, shortly after, by Wang and co-workers.[17b] Iminium-enamine catalysis mediated by chiral pyrrolidines was used effectively to promote the reaction between bromomalonates and enals (the Bingel–Hirch reaction), and also that of 2-bromo 3-keto esters.[17a,17c] Cyclopropanes with two chiral centres were obtained with high *ee* and *dr* values through the application of this domino protocol. Later, Cordova and co-workers applied this methodology to the nitrocyclopropanation of enals.[17d] This reaction has since been studied in more detail by Moyano and Rios with 2-bromo keto esters,[17e] and by Vicario and co-workers, who showed that water could also be used as solvent.[17f] Campagne and co-workers applied the reaction to β-unsubstituted-α,β-unsaturated aldehydes,[17g] Ye and co-workers showed that chloroacetophenone could be used as the Michael donor,[17h] and Kanger and co-workers used it to synthesise spirocyclopropylindoles from 2-chlorooxindoles and enals.[17i] We chose to use α-bromophosphonoacetates as Michael donors, with the aim of obtaining highly substituted cyclopropylphosphonates with three chiral centres, one of which was quaternary. Since a "one-pot" domino process is involved, eight stereoisomers may be produced from achiral starting materials, which is clearly a delicate stereochemical problem to control. One-pot processes have, however, the advantage that several steps may be carried out in a single synthetic operation, thus avoiding multiple extraction and purification procedures and minimising time and costs.

Results and Discussion

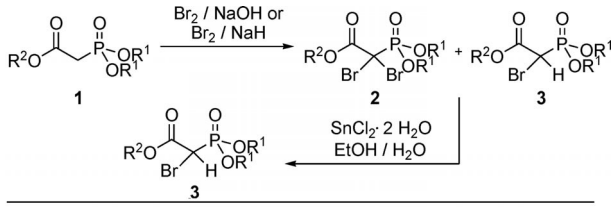
The α-bromophosphonoacetates required as substrates for the envisaged domino reactions were not commercially available. An obvious route to obtain these compounds is through direct bromination of the corresponding phosphonoacetates, which could themselves be easily obtained through an Arbuzov reaction between a trialkylphosphite and an α-bromo ester (Scheme 1).



Scheme 1. Possible route to the α-bromophosphonoacetates.

However, since α-bromophosphonoacetates are more reactive towards bromination than the parent compound, monobromination is difficult to achieve,[27,28] and this has been demonstrated to be so under a large variety of reaction conditions by Olpp and Brückner for ethyl bromo(diphenylphosphono)acetate.[27] Mixtures of unreacted phosphonoacetate can be obtained together with the mono and the (frequently predominating) dibrominated products, which presents a difficult purification challenge. Not only do the mono- and dibrominated phosphonoacetates have very high boiling points, they are also very difficult to separate by column chromatography, due to their very similar R_f values under a large variety of conditions, as also observed during the course of this work. Hence, procedures similar to the two-step process developed by McKenna and Khawli for the synthesis of triethyl bromophosphonoacetate were used.[29] In this case, α,α-dibrominated phosphonoacetates are produced first with freshly prepared sodium hypobromite, and then reduced with monohydrated $SnCl_2$ to the desired monobrominated derivatives. This approach was also used by Tago and Kogen to obtain bis(2,2,2-trifuoroethoxy)bromophosphonoacetate, which was needed as a Wittig–Horner reagent.[28] The phosphonoacetates needed for this work were obtained through the application of Arbuzov reactions, and modified McKenna and Khawli procedures were then used for the synthesis of the α-bromophosphonoacetates. The results are shown in Table 1.

Table 1. Synthesis of 3-bromo(dialkylphosphono)acetates **3**.



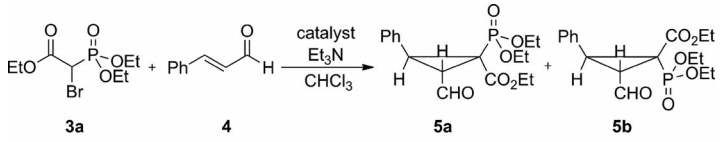
Entry	1	R^1	R^2	3	δ_P [ppm]	Yield [%][a]
1	**a**	Et	Et	**3a**	12.6	52
2	**b**	*i*Pr	Et	**3b**	10.5	26
3	**c**	Me	Me	**3c**	14.9	33
4	**d**	Me	*t*Bu	**3d**	15.7	27
5	**e**	Me	Et	**3e**	15.1	79

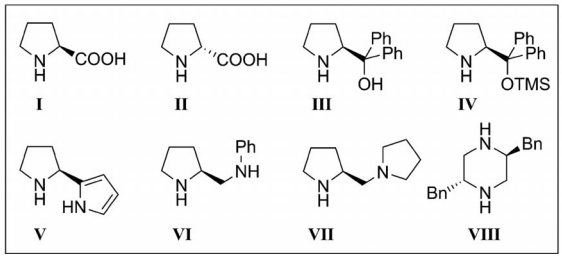
[a] Overall yield over the two reaction steps.

α-Bromophosphonoacetates **3** were obtained in moderate to good overall yields (not optimised) for the two-step sequence from phosphonoacetates **1**. The identity of the products was established by NMR and IR spectroscopy, and by elemental analysis. Monosubstitution at the carbon atom alpha to the phosphorus was confirmed by the chemical shift values and signal integration in the ^{1}H NMR spectrum and by DEPT-135 experiments, which showed positive signals for α-CHP carbon atoms, thus confirming monosubstitution. The bromination reactions were not very reproducible and, in some cases, the crude product obtained initially was rebrominated. After monoreduction with tin chloride, the products were purified by column chromatography and were then ready to use in the next step.

We then investigated the possibility of using iminium-enamine catalysis to promote the formation of the desired cyclopropanes. To this end, a series of chiral amines was selected and the reaction was attempted with ethyl bromo(diethoxyphosphoryl)acetate (**3a**) (Table 2). As initial conditions, we tested chloroform as solvent and triethylamine as a stoichiometric base, which were the conditions found to be the best in the method initially developed by Córdova and co-workers for reactions of diethyl bromomalonate.[17a] In addition to the chiral amine, a stoichiometric amount of base is usually needed in these reactions, presumably to trap the hydrobromic acid that is formed.

Table 2. Catalyst screening.[a]





Entry	Cat.	*t* [h]	Conv. [%][b]	Yield [%][c]	*dr* (**5a/5b**)[d]	*ee* (**5a**) [%][e]	*ee* (**5b**) [%][e]
1	**I**	23	97	70	78:22	16	11
2	**II**	23	96	74	76:24	(–)-14	6
3	**III**	22	78	49	74:26	26	24
4	**IV**	2.5	100	60	70:30	98	>99
5	**V**	22	98	72	75:25	24	22
6	**VI**	48	67	49	70:30	(–)-24	50
7	**VII**	3.5	100	74	77:23	41	35
8	**VIII**	3.5	92	72	75:25	(–)-22	10

[a] Reaction conditions: phosphonate **3a** (0.10 mmol), cinnamaldehyde (3.6 equiv.), Et_3N (1.1 equiv.), catalyst (0.2 equiv.), $CHCl_3$ (0.30 mL), room temp. [b] Conversion: percentage of **3a** that reacted. [c] Yield relative to the amount reacted. Calculated from the ^{31}P NMR spectra, from the ratio of the signals using tetraethyl methylenediphosphonate as internal standard. [d] From the signal ratios in ^{31}P NMR spectra. [e] Calculated from ^{31}P NMR and ^{1}H NMR spectra from the ratio of the signals of the diastereoisomeric imines formed through reaction with L-Val-OMe.[30]

Preliminary experiments showed the formation of two diastereoisomeric cyclopropanes, and three or four minor side products. Other reactions, i.e., simple Michael addition, epoxide formation, or rearrangement, may compete with cyclopropane formation, if the reaction conditions are not optimum, as previously observed.[17b,17c] When the proportion of cinnamaldehyde was increased, the formation of other products was suppressed, and a ratio of cinnamaldehyde to phosphonate of 3.6:1 was found to be optimal. Hence, the remaining experiments were conducted with this ratio of aldehyde to phosphonate.

Cyclopropanes were obtained with all the amines tried, **I**–**VIII** (Table 2). The reactions were found to be slow in all cases, taking more than a day, except with pyrrolidine derivative **IV** (entry 4), and with diamines **VII** and **VIII** (entries 7 and 8), which gave full conversion to products in 2.5–3.5 h. Two diastereomeric cyclopropanes were obtained, as discussed below, in moderate to good yields and with similar moderate diastereoselectivities, which varied from 70:30 to 78:22. On the other hand, the enantioselectivity varied immensely, with the products being almost racemic with D-proline to practically optically pure with pyrrolidine **IV**.

Table 3. Solvent screening.[a]

Entry	Solvent	*t* [h]	Conv. [%][b]	Yield [%][c]	*dr*[d] (**5a/5b**)	*ee* (**5a**) [%][e]	*ee* (**5b**) [%][e]
1	$CHCl_3$	2.5	100	60	70:30	98	>99
2	MeCN	2.5	100	53	66:33	>99	>99
3	CH_2Cl_2	2.5	100	51	65:35	>99	>99
4	THF	2.5	100	59	60:40	97	>99
5	toluene	2.0	100	53	54:46	>99	>99
6	MeOH	2.0	100	74	80:20	96	>99
7	EtOH	1.5	100	51	76:24	>99	>99
8	EtOH	2.0	100	75	74:26	n.d.[f]	n.d.[f]

[a] Reaction conditions: phosphonate **3a** (0.10 mmol), cinnamaldehyde (3.6 equiv.), Et_3N (1.1 equiv.), catalyst **IV** (0.2 equiv.), solvent (0.30 mL), room temp. [b] Conversion: percentage of **3a** that reacted. [c] Yield relative to the amount reacted. Calculated from the ^{31}P NMR spectra, from the ratio of the signals using tetraethyl methylenediphosphonate as internal standard. [d] From the signal ratios in the ^{31}P NMR spectra. [e] Calculated from ^{31}P NMR and ^{1}H NMR spectra from the ratio of the signals of the diastereoisomeric imines formed through reaction with L-Val-OMe.[30] [f] n.d.: not determined.

Hoping to further optimise the chemoselectivity, the yields and the diastereoselectivity, the reaction was then tried in different solvents (Table 3), with pyrrolidine **IV** as catalyst. The highest yields and diastereoselectivity were obtained in methanol and ethanol (Table 3, entries 6 and 7). In methanol, the product was obtained in 74% yield, and a diastereoselectivity of 80:20. The *ee* of the major diastereoisomer was slightly lower, changing from 99% in $CHCl_3$ to 96%; however, because the diastereoselectivity increased from 70:30, these were selected as the best conditions for the remaining work. In addition, in this solvent, only one side product was obtained (δ_P = 18.93 ppm), making up ca. 10% of the crude product. This substance was not identified. The remaining difference in yield could be due to some water solubility of the cyclopropanes. For example, special precautions have to be used when isolating diethyl formylmethylphosphonate from reaction mixtures, due to the very high water solubility of this compound.[31]

The effect of the nature of the stoichiometric base used was investigated next (Table 4), because this was found by other groups to have a significant influence on the outcome of the reaction.[17b,17c] However, the best results were still those obtained with triethylamine. We did not observe the rearrangement reported by Wang and co-workers when the reaction was performed in the presence of NaOAc, but obtained a similar product distribution to that observed when triethylamine was used.

The possibility of using a lower catalyst load was investigated next (Table 4, entries 9–11). As expected, as the proportion of catalyst was lowered, the reaction took longer. Although the diastereoselectivity for cyclopropane formation was not affected, the enantioselectivity of the major diastereoisomer gradually reduced, becoming only 88% when the reaction was performed with 1 mol-% catalyst. However a change from 5 to 1 mol-% caused a sharp decrease in the yield, as a result of competition by side product formation. When a catalyst load of 0.1 mol-% was used, some cyclopropane formation was still observed, however,

Table 4. The effect of the reaction conditions and the proportion of the reagents on the outcome of the reaction.[a]

Entry	Base	Catalyst [mol-%]	*T* [°C]	*t* [h]	Conv. [%][b]	Yield [%][c]	*dr* (**5a/5b**)[d]	*ee* (**5a**) [%][e]	*ee* (**5b**) [%][e]
1	Et_3N	20	room temp.	2.0	100	74	80:20	96	>99
2	DABCO	20	room temp.	2.25	98	63	81:19	96	>99
3	DBU	20	room temp.	2.0	100	22	82:18	86	>99
4	DIPEA	20	room temp.	2.0	47	52	81:19	99	>99
5	NaOAc	20	room temp.	2.0	85	57	78:22	95	>99
6	pyridine	20	room temp.	2.0	38	39	80:20	>99	>99
7	Et_3N	20	room temp.	2.0	100	74	80:20	96	>99
8	Et_3N	20	0	4.0	95	80	83:17	98	>99
9	Et_3N	10	room temp.	3.0	100	65	82:18	94	>99
10	Et_3N	5.0	room temp.	4.5	90	61	81:19	92	>99
11	Et_3N	1.0	room temp.	17.0	99	29	83:17	88	>99

[a] Reaction conditions (unless otherwise indicated): phosphonate **3a** (0.10 mmol), cinnamaldehyde (3.6 equiv.), base (1.1 equiv.), catalyst **IV** (0.2 equiv.), MeOH (0.30 mL), room temp. [b] Conversion: percentage of **3a** that reacted. [c] Yield relative to the amount reacted. Calculated from the ^{31}P NMR spectra, from the ratio of the signals using tetraethyl methylenediphosphonate as internal standard. [d] From the signal ratios in the ^{31}P NMR spectra. [e] Calculated from ^{31}P and ^{1}H NMR spectra from the ratio of the signals of the diastereoisomeric imines formed through reaction with L-Val-OMe.[30]

after 8 days nearly 20% of the phosphonate remained unreacted. With a catalyst load of 20 mol-%, the reaction was also tried at lower temperature (ice bath; Table 4, entry 8). Under these conditions, the combined yield of both diastereoisomers increased to 80%, and the diastereoselectivity improved slightly, as did the *ee*, which improved to 98% for the major diastereoisomer.

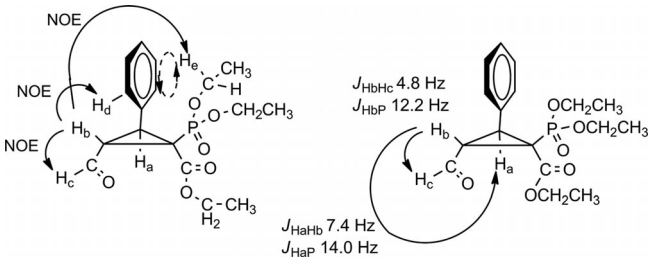
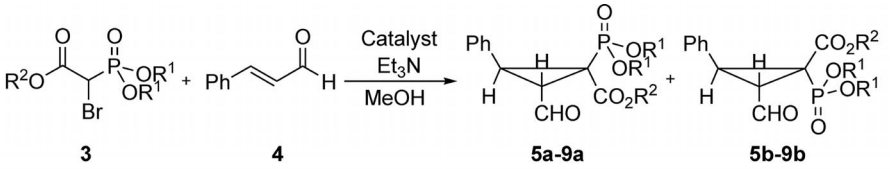


Figure 2. NOEs and coupling constants observed for the major diastereoisomer **5a**, which support the relative stereochemistry assignment.

The structural identity of cyclopropanes **5a** and **5b** was established by 1D and 2D NMR techniques, and confirmed by IR spectroscopy. 2D heteronuclear multiple-bond correlation (HMBC) experiments confirmed the connectivity between the ring carbon atoms. P–C coupling between the phosphorus atom and the carbon atom bearing the formyl group ($J_{P,C}$ = 2.5 Hz) and between the phosphorus atom and the proton at this ring position ($J_{P,H}$ = 12.2 Hz) also confirmed the connectivity. The elemental composition was confirmed by elemental analysis. NOESY experiments were used to establish the relative stereochemistry of the ring substituents. Hence, for the major diastereoisomer, cross peaks between H_b and H_d and H_e indicate that the formyl group, the phenyl group, and the phosphoryl ester group

Table 5. The scope of the cyclopropanation reaction.[a]



3 **4** **5a-9a** **5b-9b**

Entry	3	Major product	Minor product	*T* [°C]	*t* [h]	Yield[b] (**a**+**b**) [%]	Isolated yield (**a**+**b**) [%][c]	*dr* (**a**/**b**)[d]	*ee* (**a**) [%][e]	*ee* (**b**) [%][e]
1	**3a**			r.t.	2.0	74	n.d.	80:20	96	>99
2	**3a**			0	4.0	80	n.d.	83:17	98	>99
3	**3a**	**5a**	**5b**	0	4.0	n.d.	65	83:17	95	>99
4	**3b**			r.t.	1.5	72	n.d.	81:19	>99	>99
5	**3b**			0	3.5	83	n.d.	83:17	>99	>99
6	**3b**	**6a**	**6b**	0	4.5	n.d.	89	83:17	n.d.	>99
7	**3c**			r.t.	2.0	67	n.d.	80:20	94	>99
8	**3c**			0	4.5	65	n.d.	82:18	93	92
9	**3c**	**7a**	**7b**	0	4.0	n.d.	60	82:18	92	>99
10	**3d**			0	7.0	n.d.	47	70:30	>99	>99
11	**3d**	**8a**	**8b**	0	7.0	55	n.d.	68:32	>99	>99
12	**3e**			r.t.	2.0	65	n.d.	79:21	89	95
13	**3e**	**9a**	**9b**	0	4.5	n.d.	56	82:18	>94	>99

[a] Reaction conditions: phosphonates **3** (0.10 mmol), cinnamaldehyde (3.6 equiv.), base (1.1 equiv.), catalyst **IV** (0.2 equiv.), MeOH (0.30 mL). [b] Calculated from the ^{31}P NMR spectra, from the ratio of the signals using tetraethyl methylenediphosphonate as internal standard. n.d. = Not determined. [c] Yield of product isolated after chromatography. n.d. = Not determined. [d] From the signal ratios in ^{31}P NMR spectra. [e] Calculated from ^{31}P NMR and ^{1}H NMR spectra from the ratio of the signals of the diastereoisomeric imines formed through reaction with L-Val-OMe.[30]

are on the same side of the ring (Figure 2). The fact that the phenyl group and the phosphoryl ester group are in a *cis* relationship may also be indicated by the chemical shift of the phosphoryl methylene ester groups. In the ^{1}H NMR spectrum they appear as multiplets at 3.55–3.69 and 3.76–3.93 ppm, which is very much upfield from the typical chemical shift range of 4.0–4.2 ppm that is observed for many straight-chain phosphonates. This fact suggests that they are located in the shielding region of the aromatic ring. Although the cyclopropane ring has itself a considerable anisotropic effect, this difference in chemical shift has not been reported in other cyclopropylphosphonates that have a phenyl ring and a diethyl phosphonyl group with a *trans* relationship.[32] NOE difference experiments also confirmed this relative stereochemistry, as discussed below.

The NOESY spectrum of the minor diastereoisomer also showed cross peaks indicating a *trans* relationship between the formyl and the phenyl groups, and a cross peak between the proton geminal to the formyl group and the carboxyl ester methylene protons. The NOESY spectrum of the minor diastereoisomer also showed cross peaks indicating a *trans* relationship between the formyl and the phenyl groups. The relationship between the other two groups could not be established from this spectrum, however, by virtue of their diastereomeric relationship, their relative positions must be the inverse of those in the major diastereoisomer.

Using the optimised conditions, the synthesis of cyclopropylphosphonates with different substitution patterns was then undertaken to investigate the scope of the reaction. The structure of the phosphoryl ester groups as well as that of the carboxyl ester group was varied. The results obtained are shown in Table 5. Reactions performed at lower temperature were slower, as expected, but the yields were higher, varying from moderate to good. The diastereoselectivity did not vary much with a change in the substitution pattern of the reagents, except when the carboxyl ester group was *tert*-butyl. It seems that the steric bulk of this group and that of the phosphonyl group become less different in this case and the preference for the formation of one diastereoisomer over the other decreases. The enantioselectivities were very high, varying from 89 to >99%. In this case, the presence of bulkier ester substituents at either the carboxyl group or the phosphonyl group favoured enantioselection. The structural identity of the products was confirmed by 1D and 2D NMR spectroscopy techniques and by IR spectroscopy and elemental analysis as before. To confirm the stereochemical assignments obtained from NOESY experiments, NOE difference spectra were obtained. For cyclopropane **8a**, particularly strong NOE signals were observed between the nine protons of the *tert*-butyl ester group and the formyl group, the ring proton geminal to the phenyl group and the phosphoryl ester substituents. In some of the compounds this connectivity could not be observed, although a similar stereochemistry is assumed, since the reaction mechanism is the same in all

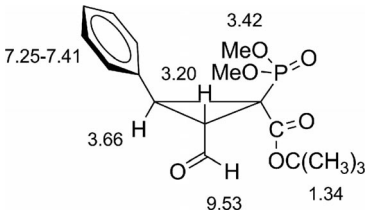


Figure 3. Chemical shifts of the major diastereoisomer **8a** in ppm.

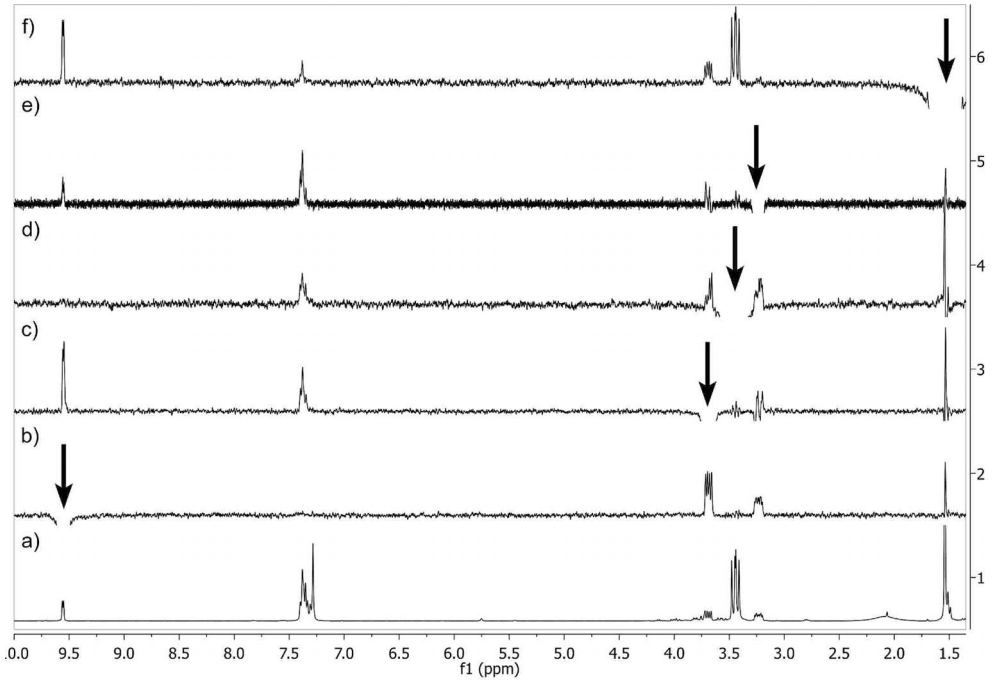


Figure 4. NOE difference spectra of **8a** recorded in $CDCl_3$. The arrows indicate the signals irradiated in each spectrum.

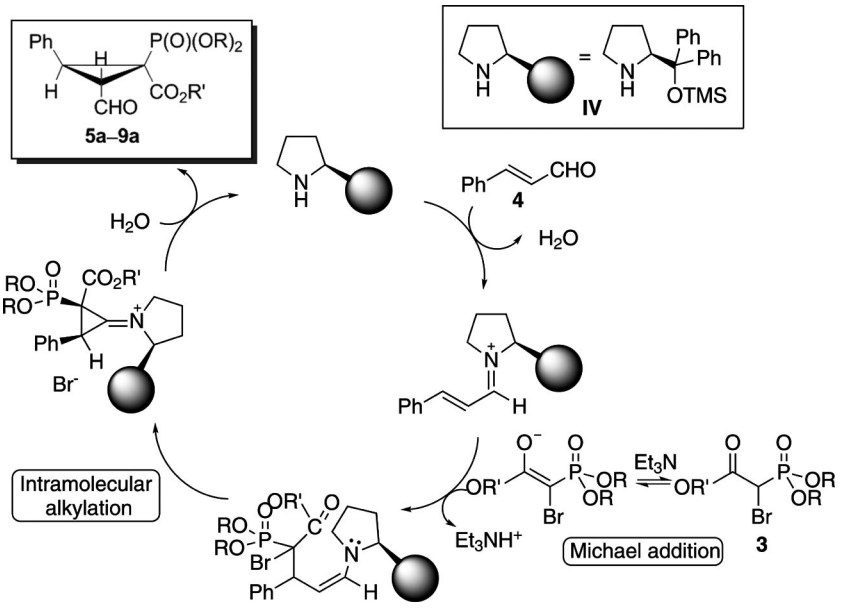


Figure 5. The mechanism proposed for the domino process leading to α-cyclopropylphosphonates.

cases. These experiments, summarised in Figure 3 and Figure 4, prove that the phenyl and the formyl group have a *trans* relationship, and that the *tert*-butyl carboxyl ester group is *cis* to the formyl group.

The mechanism proposed for the reaction is shown in Figure 5. Reaction of the chiral pyrrolidine with cinnamaldehyde gives rise to an iminium ion. Enantioselective Michael addition of the α-bromophosphono acetate to one of the enantiotopic faces results in the formation of a chiral enamine, which, through intramolecular nucleophilic substitution, expels bromide ion generating the cyclopropane ring. Upon iminium hydrolysis, the product is released as well as the catalyst, ready for another reaction cycle.

The mechanism of cyclopropanation reactions of cinnamaldehyde catalysed by (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether was studied in detail and documented by Córdova and co-workers[17a,17c] and by Wang and co-workers,[17b] as well as the configuration of the products obtained. From their reports and others published more recently,[17] it is known that the *Si* face of the chiral iminium intermediate is shielded by the bulky aryl groups of the catalyst. As a result, conjugate addition is stereoselective and takes place on the *Re* face, thus establishing the configuration of the first chiral centre. A similar process would take place with the bromo(phosphono)acetates. The enamine intermediate undergoes an intramolecular 3-*exo*-*tet* nucleophilic attack to form the cyclopropane ring, according to Baldwin's rules for ring closure. This implies that an angle of 180° is required for Walden inversion, and reaction as shown in **I** (Figure 6) will give the product.[35] Although there are two possibilities for enolate approach to the reacting enamine, **G** or **H**, only reaction as shown in **H** will give a major diastereoisomer with the phenyl and the phosphoryl groups with a *cis* relationship, and the formyl group *trans*, as observed for the major diastereoisomer, i.e. a (1*R*,2*S*,3*S*)-α-CPP.

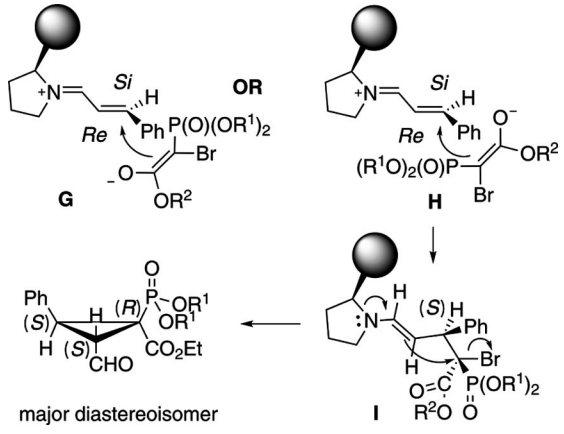


Figure 6. Determination of the absolute configuration of the products.

Conclusions

We have developed a novel method with which to synthesise highly substituted chiral α-cyclopropylphosphonates with three chiral centres including a quaternary centre. The method involves a "one-pot" domino Michael addition reaction/intramolecular alkylation between α,β-unsaturated aldehydes and bromophosphonoacetates that proceeds with a high degree of stereocontrol. Only two diastereoisomers are obtained, with good diastereoselectivities of up to 73:17 and very high enantioselectivities of more than 99%. Catalyst loads as low as 5 mol-% still give products in satisfactory yields, albeit with a drop in *ee* to 92%. This method produces cyclopropanes with a variety of substituents on the ring, which allows for further synthetic manipulation and conversion into more elaborate biologically active targets if so wished. Most of the compounds have not been described previously.

Experimental Section

General Information: All reactions were performed under an atmosphere of argon. The reagents were obtained from commercial suppliers and used without further purification. The solvents were purified by standard methods and distilled before use. For column chromatography, Merck silica gel 60 (230–400 mesh) was used, and for thin-layer chromatography, silica gel plates Merck 60 F254 were used. Optical rotations were measured with an AA-1000 Polarimeter from Optical Activity Ltd. with 1-mL, 0.5-dm cells. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer or with a Bruker Avance 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz, ^{31}P: 162 MHz). Chemical shifts are reported relative to TMS. ^{31}P NMR chemical shifts are reported relative to phosphoric acid, used as external standard. The assignment of signals in the ^{13}C NMR spectra was determined by DEPT experiments. NOE difference spectra were also obtained for the determination of the relative stereochemistry of the compounds. 2D spectra (COSY 45, HMQC, HMBC, NOESY) were used to help with structural determinations whenever necessary. For yield determination by NMR spectroscopy, the signal ratios obtained in a ^{31}P NMR spectrum relative to tetraethyl methylenediphosphonate, used as internal standard, were used. For the determination of the enantiomeric excesses, derivatisation with L-VAL-OMe was used. The values were calculated from the ratios of the signals observed in ^{31}P and ^{1}H NMR spectra of the diastereoisomeric imines formed through reaction with L-Val-OMe.[30] IR spectra were obtained with a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Elemental analyses were performed with a Thermo Finnigan Elemental Analyzer 1112 series, by the Laboratory for External Services of CQFB-Lab Associado/REQUIMTE, of the Department of Chemistry, FCT, UNL. Trialkyl phosphonoacetates were either purchased from commercial sources or were prepared from the corresponding trialkyl phosphites and α-bromoacetates through an Arbuzov reaction.[33]

General Procedure for the Synthesis of Bromophosphonoacetates 3a–e: Dialkyl dibromophosphonoacetates were prepared from the respective trialkyl phosphonoacetate, bromine and sodium hydroxide according to the method described by McKenna and Khawli for the synthesis of triethyl dibromophosphonoacetate.[29] It was found that the extent of dibromination varied between reactions and when mixtures of unreacted material, mono- and dibrominated phosphonoacetate were obtained, the dibromination was repeated on the crude product mixture. Alternatively, sodium hydride and bromine were used, as described for the synthesis of α-brominated diethyl diphenylphosphonoacetates by Olpp and Brückner.[27] In both cases, the crude products were then reduced to trialkyl monobromophosphonoacetates by $SnCl_2{\cdot}2H_2O$ in H_2O/EtOH as described by McKenna and Khawli for triethyl dibromophosphonoacetate.[29]

Triethyl Bromophosphonoacetate (3a):[29] Prepared from triethyl phosphonoacetate according to the general procedure.[29] The crude product was purified by column chromatography (silica gel; ethyl acetate–hexane, 2:1) as a colourless oil, yield 2.97 g (52%). ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, CH_3, COCCH_3), 1.38 (t, J = 7.0 Hz, 6 H, 2× CH_3, POCCH_3), 4.23–4.33 (m, 6 H, 3× CH_2, COCH_2, 2× POCH_2), 4.35 (overlapped t, $J_{H,P}$ = 14.0 Hz, CHP) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.85 (s, CH_3, OC*C*H_3), 16.27 (d, J = 6.0 Hz, CH_3, POC*C*H_3), 35.72 (d, $J_{C,P}$ = 145.9 Hz, CHP), 63.04 (s, CO*C*H_2), 64.59 (d, J = 6.6 Hz, POCH_2), 165.0 (d, $J_{C,P}$ = 1.0 Hz, C=O) ppm. ^{31}P NMR ($CDCl_3$): δ = 13.32 ppm. IR (neat): $\tilde{\nu}$ = 2982, 2937, 2910, 2871, 1755, 1740, 1734, 1654, 1648, 1636, 1559, 1540, 1522, 1507, 1475, 1469, 1444, 1392, 1368, 1262, 1161, 1131, 1096, 1049, 1025, 978, 865, 793, 755, 710, 665, 633 cm^{-1}. The NMR spectroscopic data were consistent with reported data.[29]

Ethyl Bromo(diisopropylphosphono)acetate (3b): Prepared from ethyl (diisopropylphosphono)acetate according to the general procedure. The crude product was purified by column chromatography (silica gel; ethyl acetate/hexane, 1:1 then ethyl acetate only) as a colourless oil, yield 0.338 g (26%). ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3, EtO), 1.32–1.40 (m, 12 H, 4× CH_3 of *i*Pr), 4.26 (q, J = 7.1 Hz, 2 H, CH_2 of EtO), 4.29 (d, J = 14.0 Hz, 1 H, CHP), 4.76–4.89 (m, 2 H, 2× CH of *i*Pr) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.88 (s, CH_3, COC*C*H_3), 23.56 (d, $J_{C,P}$ = 4.2 Hz, *i*Pr-CH_3), 23.62 (d, $J_{C,P}$ = 4.0 Hz, *i*Pr-CH_3), 24.05 (d, $J_{C,P}$ = 3.5 Hz, *i*Pr-CH_3), 24.13 (d, $J_{C,P}$ = 3.3 Hz, CH_3 of *i*Pr-CH_3), 36.53 (d, $J_{C,P}$ = 146.6 Hz, CHP), 62.87 (CH_2), 73.47 (d, $J_{C,P}$ = 5.5 Hz, POCH), 73.53 (d, $J_{C,P}$ = 5.2 Hz, POCH), 165.2 (C=O) ppm; ^{31}P NMR ($CDCl_3$): δ = 10.51 ppm. IR (neat): $\tilde{\nu}$ = 2981, 2935, 2914, 1737, 1650, 1467, 1453, 1386, 1378, 1265, 1178, 1149, 1124, 1102, 1008, 1000, 938, 902, 890, 833, 832, 755, 722, 666, 615 cm^{-1}. $C_{10}H_{20}BrO_5P$ (331.143): calcd. C 36.27, H 6.09; found C 35.00, H 6.05.

Trimethyl Bromophosphonoacetate (3c): Prepared from trimethyl phosphonoacetate according to the general procedure. The crude product was purified by column chromatography (silica gel; ethyl acetate/hexane, 2:1) as a colourless oil, yield 2.11 g (33%). ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, CH_3, COOMe), 3.89 (d, J = 4.4 Hz, 3 H, POCH_3), 3.91 (d, J = 4.4 Hz, 3 H, POCH_3), 4.40 (d, J = 14.2 Hz, 1 H, CHP) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.63 (d, $J_{C,P}$ = 147.6 Hz, CHP), 53.95 (s, CH_3, COO*C*H_3), 54.88–55.07 (2× d, 2× POCH_3), 165.4 (s, C=O) ppm. ^{31}P NMR ($CDCl_3$): δ = 14.93 ppm. IR (neat): $\tilde{\nu}$ = 3007, 2957, 2855, 1884, 1745, 1643, 1540, 1436, 1262, 1186, 1154, 1042, 900, 869, 830, 762, 779, 715, 632 cm^{-1}. $C_5H_{10}BrO_5P{\cdot}H_2O$ (279.093): calcd. C 21.88, H 4.33; found C 22.03, H 4.06.

***tert*-Butyl Bromo(dimethylphosphono)acetate (3d):** Prepared from *tert*-butyl (dimethylphosphono)acetate according to the general procedure. The crude product was purified by column chromatography (silica gel; diethyl ether/ethyl acetate/hexane, 1:1:1) as a colourless oil, yield 0.337 g (27%). ^{1}H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, 3× CH_3 of *t*Bu), 3.90 (d, J = 11.0 Hz, 3 H, 2× OCH_3), 4.31 (d, J = 13.6 Hz, 1 H, CHP) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.65 (s, 3× CH_3, *t*Bu-CH_3), 36.59 (d, $J_{C,P}$ = 146.2 Hz, CHP), 54.80 (apparent t, $J_{C,P}$ = 6.50 Hz, 2× OCH_3), 84.29 (s, Cq, *t*Bu-C), 163.7 (s, Cq, C=O) ppm. ^{31}P NMR ($CDCl_3$): δ = 15.69 ppm. IR (neat): $\tilde{\nu}$ = 2978, 2940, 2892, 2709, 1754, 1739, 1734, 1724, 1369, 1261, 1179, 1153, 1124, 1055, 1031, 830 cm^{-1}. $C_8H_{16}BrO_5P$ (302.98): calcd. C 31.71, H 5.32; found C 31.44, H 5.42.

Ethyl Bromo(dimethylphosphono)acetate (3e):[34] Prepared from ethyl (dimethylphosphono)acetate according to the general procedure.[29] The crude product was purified by column chromatography (silica gel; ethyl acetate/hexane, 2:1) as a colourless oil, yield 0.631 g (79%). ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_3 of EtO), 3.85 (d, J = 3.9 Hz, 3 H, OCH_3), 3.88 (d, J = 3.9 Hz, 3 H, OCH_3), 4.25 (q, J = 7.1 Hz, 2 H, CH_2 of EtO), 4.36 (d, J = 14.0 Hz, 1 H, CHP) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.75 (s, CH_3, OC*C*H_3), 34.92 (d, $J_{C,P}$ = 147.3 Hz, CHP), 54.89–54.73 (2× d, 2× POCH_3), 63.11 (s, CH_2), 164.7 (s, C=O) ppm. ^{31}P NMR ($CDCl_3$): δ = 15.14 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2922, 2853, 1753, 1741, 1734, 1723, 1464, 1458, 1452, 1387, 1368, 1263, 1178, 1139, 1045, 1031, 948, 872, 830, 783, 766, 666 cm^{-1}. $C_6H_{12}BrO_5P$ (275.035): calcd. C 26.20, H 4.40; found C 26.07, H 4.20.

General Procedure for the Domino Michael Addition/Intramolecular Alkylation Reaction: The phosphonate (0.10 mmol) was weighed into a reaction vessel, covered with a rubber septum and the cata-

lyst (0.020 mmol) dissolved in anhydrous methanol (0.30 mL) was added. The resulting solution was stirred under an atmosphere of argon, while cinnamaldehyde (0.36 mmol) was added dropwise. Finally, triethylamine (0.10 mmol) was added. The rubber septum was changed for a plastic stopper under an atmosphere of argon, and the reaction vessel was covered with aluminium foil for protection from light. The resulting solution was then stirred for the periods indicated in the tables. For low temperature reactions, the solution was cooled in an ice bath once the phosphonate and the catalyst were mixed and the reaction mixture was kept at this temperature thereafter. Once the reaction was complete, hydrochloric acid (1 M) was added, and the product was extracted four times into chloroform. The combined chloroform extracts were washed once with water, and the organic phase was separated and filtered through anhydrous sodium sulfate. The solvent was removed in a rotary evaporator to give the crude product, which was subsequently purified by plate or column chromatography as indicated for each compound.

Reaction times were determined on the basis of ^{31}P NMR spectroscopic analysis. For *ee* determinations, one drop of L-Val-OMe was added to an NMR tube containing the product, and a few minutes later the spectra were run. Imine formation was almost immediate. The chemical shifts in ^{31}P and ^{1}H NMR spectra were assigned based on those of racemic samples prepared by using equal amounts of D- and L-proline as catalyst.

Ethyl 1-(1-Diethoxyphosphoryl-2-formyl-3-phenyl)cyclopropanecarboxylate (5): Compound **5** was prepared from ethyl bromo(diethoxyphosphoryl)acetate and cinnamaldehyde, according to the general procedure. It was obtained as an 83:17 mixture of diastereoisomers, as determined by ^{31}P NMR spectroscopic analysis. After preparative thin-layer plate chromatography purification on silica gel, the pure diastereoisomers (69 mg, 65%) were obtained as a colourless oil. The enantiomeric excess was determined by ^{1}H and ^{31}P NMR spectroscopic analysis of the diastereoisomeric imines formed after in situ reaction with L-Val-OMe in CD_3CN.[30] For a racemic sample prepared in a similar way with equal amounts of D-proline plus L-proline as catalysts: ^{1}H NMR (400 MHz, CD_3CN): δ = 7.51 (d, J = 6.8 Hz, major), 7.56 (d, J = 6.8 Hz, major), 7.79 (d, J = 2.8 Hz, minor), 7.81 (d, J = 2.8 Hz, minor) ppm. ^{31}P NMR (162 MHz, CD_3CN): δ = 16.47 (major), 16.57 (major), 19.04 (minor), 19.10 (minor) ppm. Preparative thin-layer plate chromatography purification carried out twice in either case on the crude product (silica gel; acetone/$CHCl_3$, 1:4 or acetone/$CHCl_3$, 1:4, followed by acetone/$CHCl_3$, 1:6) provided the two diastereoisomers as separate compounds.

(1*R*,2*S*,3*S*)-(+)-5a (Major Diastereoisomer): $[\alpha]_D^{16}$ = +21.0 (c = 1.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.08 (overlapped t, J = 7.0 Hz, 3 H, $POCCH_3$), 1.11 (overlapped t, J = 7.1 Hz, 3 H, $POCCH_3$), 1.34 (t, J = 7.1 Hz, 3 H, $COCCH_3$), 3.23 (ddd, $J_{H,H}$ = 4.8, 7.4, $J_{H,P}$ = 12.2 Hz, 1 H, C*H*CHO), 3.55–3.69 (m, 1 H, POC*H*H), 3.73 (overlapped dd, $J_{H,H}$ = 7.4, $J_{H,P}$ = 14.0 Hz, 1 H, CHPh), 3.76–3.93 (overlapped m, 3 H, 2× $POCH_2$), 4.24–4.36 (m, 2 H, $COCH_2$), 7.28–7.38 (m, 5 H, Ph), 9.56 (d, J = 4.7 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.00 (s, CH_3, $COCCH_3$), 16.05 (d, $J_{C,P}$ = 6.1 Hz, CH_3, $POCCH_3$), 16.14 (d, $J_{C,P}$ = 6.3 Hz, CH_3, $POCCH_3$), 35.32 (d, $J_{C,P}$ = 3.4 Hz, CH, *C*HPh), 37.47 (d, $J_{C,P}$ = 2.5 Hz, CH, *C*HCHO), 37.84 (d, $J_{C,P}$ = 184.2 Hz, Cq, CP), 62.44 (d, $J_{C,P}$ = 6.1 Hz, CH_2, $POCH_2$), 62.67 (s, CH_2, $COCH_2$), 62.85 (d, $J_{C,P}$ = 6.7 Hz, CH_2, $POCH_2$), 127.8 (s, CH, *p*C-Ph), 128.1 (s, 2× CH, *m*C-Ph), 129.4 (s, 2× CH, *o*C-Ph), 132.8 (d, $J_{C,P}$ = 5.3 Hz, Cq, *i*C-Ph), 152.1 (d, $J_{C,P}$ = 6.3 Hz, Cq, COO), 197.0 (d, $J_{C,P}$ = 1.7 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 15.47 ppm. IR (neat): $\tilde{\nu}$ = 3058, 3022, 2982, 2932, 2906, 2870, 1732, 1718, 1706, 1654, 1647, 1636, 1603, 1583, 1560, 1542, 1498, 1474, 1448, 1424, 1390, 1367, 1262, 1232, 1181, 1163, 1123, 1097, 1052, 1022, 975, 917, 863, 798, 767, 721, 697, 665, 615, 594, 559 cm^{-1}. $C_{17}H_{23}O_6P{\cdot}1.5H_2O$ (372.354): calcd. C 54.84, H 6.77; found C 54.64, H 6.73.

(1*S*,2*S*,3*S*)-(+)-5b (Minor Diastereoisomer): ^{1}H NMR ($CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3 H, $COCCH_3$), 1.26 (t, J = 7.0 Hz, 3 H, $POCCH_3$), 1.38 (t, J = 7.1 Hz, 3 H, $POCCH_3$), 3.20 (ddd, $J_{H,H}$ = 5.4, 7.6, $J_{H,P}$ = 10.4 Hz, 1 H, C*H*CHO), 3.73 (dd, $J_{H,H}$ = 7.6, $J_{H,P}$ = 17.1 Hz, 1 H, CHPh), 3.80 (q, J = 7.1 Hz, 2 H, $COCH_2$), 4.08 (m, 2 H, $POCH_2$), 4.20–4.34 (m, 2 H, $POCH_2$), 7.10–7.29 (m, 5 H, Ph), 9.66 (d, J = 5.4 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.57 (s, CH_3, $COCCH_3$), 16.26 (d, $J_{C,P}$ = 6.0 Hz, CH_3, $POCCH_3$), 16.44 (d, $J_{C,P}$ = 6.4 Hz, CH_3, $POCCH_3$), 34.23 (d, $J_{C,P}$ = 2.6 Hz, CH, *C*HPh), 37.49 (d, $J_{C,P}$ = 184.3 Hz, Cq, CP), 38.17 (d, $J_{C,P}$ = 1.5 Hz, CH, *C*HCHO), 61.95 (s, CH_2, $COCH_2$), 63.23 (d, $J_{C,P}$ = 6.2 Hz, CH_2, $POCH_2$), 63.46 (d, $J_{C,P}$ = 6.2 Hz, CH_2, $POCH_2$), 128.0 (s, CH, *p*C-Ph), 128.5 (s, 4× CH, *o*C-Ph, *m*C-Ph), 132.6 (d, $J_{C,P}$ = 2.2 Hz, Cq, *i*C-Ph), 164.7 (d, $J_{C,P}$ = 6.3 Hz, Cq, COO), 198.3 (d, $J_{C,P}$ = 3.3 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 18.92 ppm.

Ethyl 1-(2-Formyl-1-diisopropoxyphosphoryl-3-phenyl)cyclopropanecarboxylate (6): Prepared from ethyl bromo(diisopropoxyphosphoryl)acetate and cinnamaldehyde, according to the general procedure. It was obtained as a 83:17 mixture of diastereoisomers as determined by ^{31}P NMR spectroscopic analysis. Preparative thin-layer plate chromatography purification carried out twice in each case (silica gel; acetone/$CHCl_3$, 1:4 or acetone/$CHCl_3$, 1:6) provided the two diastereoisomers as separate compounds. After preparative thin-layer plate chromatography purification on silica gel, the pure diastereoisomers (34 mg, 89%) were obtained as a colourless oil. The enantiomeric excess was determined by ^{1}H NMR and ^{31}P NMR spectroscopic analysis of the diastereoisomeric imines formed after in situ reaction with L-Val-OMe in CD_3CN.[30] For a racemic sample prepared in a similar way with equal amounts of D-proline plus L-proline as catalysts: ^{1}H NMR (400 MHz, CD_3CN): δ = 7.50 (d, J = 7.0 Hz, major), 7.56 (d, J = 6.8 Hz, major), 7.85 (d, J = 7.4 Hz, minor), 7.87 (d, J = 7.4 Hz, minor) ppm. ^{31}P NMR (162 MHz, CD_3CN): δ = 15.02 (major), 15.02 (major), 16.90 (minor), 17.01 (minor) ppm.

(1*R*,2*S*,3*S*)-(+)-6a (Major Diastereoisomer): $[\alpha]_D^{16}$ = +27.0 (c = 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, J = 6.2 Hz, 3 H, *i*Pr-CH_3), 1.08 (d, J = 6.2 Hz, 3 H, *i*Pr-CH_3), 1.10 (d, J = 6.3 Hz, 3 H, *i*Pr-CH_3), 1.18 (d, J = 6.2 Hz, 3 H, *i*Pr-CH_3), 1.30 (t, J = 7.2 Hz, 3 H, $COCCH_3$), 3.22 (ddd, $J_{H,H}$ = 4.8, 7.4, $J_{H,P}$ = 12.3 Hz, 1 H, C*H*CHO), 3.63 (dd, $J_{H,H}$ = 7.4, $J_{H,P}$ = 14.0 Hz, 1 H, CHPh), 4.15–4.34 (m, 3 H, $COOCH_2$, POC*H*), 4.48–4.61 (m, 1 H, POC*H*), 7.18–7.3 (m, 3 H, Ph-H), 7.33 (d, J = 7.0 Hz, 2 H, Ph-H), 9.51 (dd, J = 0.8, 4.8 Hz, 1 H, CCHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.99 (s, CH_3, $COCCH_3$), 23.43 (d, $J_{C,P}$ = 5.1 Hz, *i*Pr-CH_3), 23.50 (d, $J_{C,P}$ = 5.9 Hz, *i*Pr-CH_3), 23.71 (d, $J_{C,P}$ = 3.5 Hz, *i*Pr-CH_3), 23.96 (d, $J_{C,P}$ = 4.0 Hz, *i*Pr-H_3), 35.48 (d, $J_{C,P}$ = 3.7 Hz, CH, *C*HPh), 37.28 (d, $J_{C,P}$ = 1.9 Hz, CH, *C*HCHO), 38.59 (d, $J_{C,P}$ = 183.7 Hz, Cq, CP), 62.47 (s, CH_2, $COCH_2$), 71.46 (d, $J_{C,P}$ = 6.8 Hz, POCH), 71.75 (d, $J_{C,P}$ = 6.2 Hz, POCH), 127.7 (s, CH, *p*C-Ph), 127.9 (s, 2× CH, *m*C-Ph), 129.6 (s, 2× CH, *o*C-Ph), 132.7 (d, $J_{C,P}$ = 5.3 Hz, Cq, *i*C-Ph), 167.3 (d, $J_{C,P}$ = 5.6 Hz, Cq, COO), 197.2 (s, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 13.61 ppm. IR: $\tilde{\nu}$ = 3021, 3004, 2980, 2935, 2927, 1738, 1730, 1714, 1605, 1560, 1541, 1499, 1465, 1453, 1386, 1375, 1257, 1234, 1178, 1142, 1103, 1010, 993, 950, 913, 900, 867, 845, 771, 697, 666, 615, 594, 564 cm^{-1}. $C_{19}H_{27}O_6P{\cdot}H_2O$ (400.408): calcd. C 56.99, H 7.30; found C 56.73, H 6.25.

(1*S*,2*S*,3*S*)-(+)-6b (Minor Diastereoisomer): ^{1}H NMR ($CDCl_3$): δ = 0.84 (t, J = 7.1 Hz, 3 H, $COCCH_3$), 1.23 (d, J = 6.1 Hz, 3 H, *i*Pr-CH_3), 1.26 (d, J = 6.1 Hz, 3 H, *i*Pr-CH_3), 1.38 (app. t, J = 7.7 Hz, 6 H, 2× *i*Pr-CH_3), 3.14–3.25 (m, 1 H, C*H*CHO), 3.70 (dd, $J_{H,H}$ = 7.5, $J_{H,P}$ = 17.2 Hz, 1 H, CHPh), 3.81 (q, J = 7.1 Hz, 3 H, COOCH_2), 4.54–4.70 (m, 1 H, POC*H*), 4.75–4.90 (m, 1 H, POC*H*), 7.14 (d, J = 6.6 Hz, 2 H, Ph-H), 7.15–7.30 (m, 3 H, Ph-H), 9.69 (d, J = 5.3 Hz, 1 H, CCHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.65 (s, CH_3, COCCH_3), 23.78 (d, $J_{C,P}$ = 4.6 Hz, *i*Pr-CH_3), 23.91 (d, $J_{C,P}$ = 4.1 Hz, *i*Pr-CH_3), 24.04 (d, $J_{C,P}$ = 4.3 Hz, *i*Pr-CH_3), 24.10 (d, $J_{C,P}$ = 4.9 Hz, *i*Pr-H_3), 34.20 (d, $J_{C,P}$ = 2.5 Hz, CH, *C*HPh), 38.38 (s, CH, *C*HCHO), 38.55 (d, $J_{C,P}$ = 185.7 Hz, Cq, CP), 61.81 (s, CH_2, CO*C*H_2), 72.07 (d, $J_{C,P}$ = 6.3 Hz, POCH), 72.47 (d, $J_{C,P}$ = 6.7 Hz, POCH), 128.0 (s, CH, *p*C-Ph), 128.4 (s, 2× CH, *m*C-Ph), 128.5 (s, 2× CH, *o*C-Ph), 132.8 (s, Cq, *i*C-Ph), 164.9 (s Cq, COO), 198.7 (d, $J_{C,P}$ = 3.2 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 16.71 ppm.

Methyl 1-(2-Formyl-1-dimethoxyphosphoryl-3-phenyl)cyclopropanecarboxylate (7): Prepared from methyl bromo(dimethoxyphosphoryl)acetate and cinnamaldehyde, according to the general procedure. It was obtained as a 82:18 mixture of diastereoisomers, as determined by ^{31}P NMR spectroscopic analysis. After preparative thin-layer plate chromatography purification on silica gel, the pure diastereoisomers (63 mg, 60%) were obtained as a colourless oil. The enantiomeric excess was determined by ^{1}H and ^{31}P NMR spectroscopic analysis of the diastereoisomeric imines formed after in situ reaction with L-Val-OMe in CD_3CN.[30] For a racemic sample prepared in a similar way with equal amounts of D-proline plus L-proline as catalysts: ^{1}H NMR (400 MHz, CD_3CN): δ = 7.55 (d, J = 6.5 Hz, major), 7.60 (d, J = 6.4 Hz, major), 7.77 (app. t, J = 6.6 Hz, minor) ppm. ^{31}P NMR (162 MHz, CD_3CN): δ = 19.22 (major), 19.32 (major), 21.76 (minor), 21.84 (minor) ppm. Preparative thin-layer plate chromatography purification carried out twice in each case (silica gel, ethyl acetate only or acetone/$CHCl_3$, 1:6) provided the two diastereoisomers as separate compounds.

(1*R*,2*S*,3*S*)-(+)-7a (Major Diastereoisomer): $[\alpha]_D^{16}$ = +19.2 (c = 0.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 3.23 (ddd, $J_{H,H}$ = 4.6, 7.5, $J_{H,P}$ = 12.1 Hz, 1 H, C*H*CHO), 3.32 (d, $J_{H,P}$ = 11.1 Hz, 3 H, $POCH_3$), 3.45 (d, $J_{H,P}$ = 11.3 Hz, 3 H, $POCH_3$), 3.75 (dd, $J_{H,H}$ = 7.5, $J_{H,P}$ = 14.1 Hz, 1 H, CHPh), 3.85 (s, 3 H, COOCH_3), 7.25–7.40 (m, 5 H, Ph), 9.59 (dd, J = 0.8, 4.6 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.45 (d, $J_{C,P}$ = 3.2 Hz, CH, *C*HPh), 37.34 (d, $J_{C,P}$ = 186.6 Hz, Cq, CP), 37.41 (d, $J_{C,P}$ = 2.7 Hz, CH, *C*HCHO), 52.79 (d, $J_{C,P}$ = 6.1 Hz, $POCH_3$), 53.42 (d, $J_{C,P}$ = 6.6 Hz, $POCH_3$), 53.56 (s, COOCH_3), 127.9 (s, CH, *p*C-Ph), 128.2 (s, 2× CH, *m*C-Ph), 129.3 (s, 2× CH, *o*C-Ph), 132.7 (d, $J_{C,P}$ = 5.3 Hz, Cq, *i*C-Ph), 167.5 (d, $J_{C,P}$ = 6.6 Hz, Cq, COO), 196.7 (s, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 18.13 ppm. IR (neat): $\tilde{\nu}$ = 3060, 3028, 2956, 2853, 1767, 1729, 1657, 1648, 1639, 1627, 1588, 1559, 1540, 1498, 1448, 1436, 1385, 1355, 1262, 1232, 1196, 1184, 1154, 1124, 1094, 1034, 992, 924, 870, 836, 788, 775, 730, 698, 665, 646, 614, 589, 559 cm^{-1}. $C_{14}H_{17}O_6P$ (312.258): calcd. C 53.85, H 5.49; found C 53.52, H 5.08.

(1*S*,2*S*,3*S*)-(+)-7b (Minor Diastereoisomer): ^{1}H NMR ($CDCl_3$): δ = 3.29 (ddd, $J_{H,H}$ = 5.3, 7.6, $J_{H,P}$ = 10.6 Hz, 1 H, C*H*CHO), 3.43 (s, 3 H, COOCH_3), 3.79 (overlapped d, $J_{H,P}$ = 8.4 Hz, 3 H, $POCH_3$), 3.78–3.85 (overlapped m, 1 H, CHPh), 3.97 (d, $J_{H,P}$ = 11.3 Hz, 3 H, $POCH_3$), 7.19–7.35 (m, 5 H, Ph), 9.71 (dd, J = 5.0 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.31 (d, $J_{C,P}$ = 2.6 Hz, CH, *C*HPh), 36.64 (d, $J_{C,P}$ = 186.0 Hz, Cq, CP), 38.24 (s, CH, *C*HCHO), 52.90 (s, COOCH_3), 53.60 (d, $J_{C,P}$ = 6.3 Hz, $POCH_3$), 53.94 (d, $J_{C,P}$ = 6.2 Hz, $POCH_3$), 128.2 (s, CH, *p*C-Ph), 128.4 (s, 2× CH, *m*C-Ph), 128.6 (s, 2× CH, *o*C-Ph), 132.3 (s, Cq, *i*C-Ph), 156.1 (d, $J_{C,P}$ = 6.4 Hz, Cq, COO), 197.9 (s, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 21.73 ppm.

***tert*-Butyl 1-(2-Formyl-1-dimethoxyphosphoryl-3-phenyl)cyclopropanecarboxylate (8):** Prepared from *tert*-butyl bromo(dimethoxyphosphoryl)acetate and cinnamaldehyde, according to the general procedure. It was obtained as a 68:32 mixture of diastereoisomers, as determined by ^{31}P NMR spectroscopic analysis. After preparative thin-layer plate chromatography purification on silica gel, the pure diastereoisomers (48 mg, 47%) were obtained as a colourless oil. The enantiomeric excess was determined by ^{1}H and ^{31}P NMR spectroscopic analysis of the diastereoisomeric imines formed after in situ reaction with L-Val-OMe in CD_3CN.[30] For a racemic sample prepared in a similar way with equal amounts of D-proline plus L-proline as catalysts: ^{1}H NMR (400 MHz, CD_3CN): δ = 7.44 (d, J = 7.1 Hz, major), 7.46 (d, J = 7.2 Hz, major), 7.75 (d, J = 5.0 Hz, minor), 7.76 (d, J = 4.9 Hz, minor) ppm. ^{31}P NMR (162 MHz, CD_3CN): δ = 19.74 (major), 19.77 (major), 22.57 (minor), 22.72 (minor) ppm. Preparative thin-layer plate chromatography purification carried out twice in either case on the crude product (silica gel, acetone/$CHCl_3$, 1:4 or acetone/$CHCl_3$, 1:4, followed by acetone/$CHCl_3$, 1:6) provided the two diastereoisomers as separate compounds.

(1*R*,2*S*,3*S*)-(+)-8a (Major Diastereoisomer): $[\alpha]_{25}^{D}$ = –11.6 (c = 1.78, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.34 [s, 9 H, $COC(CH_3)_3$], 3.20 (ddd, $J_{H,H}$ = 4.7, 7.2, $J_{H,P}$ = 12.0 Hz, 1 H, C*H*CHO), 3.42 (app. t, $J_{H,P}$ = 11.5 Hz, 6 H, 2× POCH_3), 3.66 (dd, $J_{H,H}$ = 7.3, $J_{H,P}$ = 14.6 Hz, 1 H, CHPh), 7.25–7.41 (m, 5 H, Ph), 9.53 (dd, J = 4.6 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.83 (s, 3× OCCH_3), 34.51 (d, $J_{C,P}$ = 3.3 Hz, CH, *C*HPh), 36.99 (d, $J_{C,P}$ = 2.5 Hz, CH, *C*HCHO), 38.89 (d, $J_{C,P}$ = 183.8 Hz, Cq, CP), 52.79 (d, $J_{C,P}$ = 6.0 Hz, $POCH_3$), 53.18 (d, $J_{C,P}$ = 6.6 Hz, $POCH_3$), 83.85 [s, CO$C(CH_3)_3$], 127.8 (s, CH, *p*C-Ph), 128.2 (s, 2× CH, *m*C-Ph), 129.3 (s, 2× CH, *o*C-Ph), 132.9 (d, $J_{C,P}$ = 5.5 Hz, Cq, *i*C-Ph), 165.6 (d, $J_{C,P}$ = 5.9 Hz, Cq, COO), 196.6 (d, $J_{C,P}$ = 1.9 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 18.82 ppm. IR (neat): $\tilde{\nu}$ = 2980, 2956, 2928, 2852, 1715, 1647, 1654, 1636, 1560, 1542, 1508, 1498, 1457, 1451, 1420, 1394, 1369, 1285, 1257, 1192, 1156, 1120, 1052, 1034, 942, 912, 836, 806, 775, 733, 697, 664 cm^{-1}. $C_{17}H_{23}O_6P$ (354.339): calcd. C 57.63, H 6.54; found C 57.55, H 6.66.

(1*S*,2*S*,3*S*)-(+)-8b (Minor Diastereoisomer): ^{1}H NMR ($CDCl_3$): δ = 1.01 [s, 9 H, $COC(CH_3)_3$], 3.10–3.20 (m, 1 H, C*H*CHO), 3.66–3.75 (overlapped m, 1 H, C*H*Ph), 3.72 (overlapped d, $J_{H,P}$ = 11.3 Hz, 3 H, POCH_3), 3.91 (d, $J_{H,P}$ = 11.2 Hz, 3 H, POCH_3), 7.15–7.35 (m, 5 H, Ph), 9.63 (d, $J_{H,H}$ = 5.4 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.28 (s, 3× OCCH_3), 33.86 (d, $J_{C,P}$ = 2.6 Hz, CH, *C*HPh), 37.40 (d, $J_{C,P}$ = 184.5 Hz, Cq, CP), 37.58 (d, $J_{C,P}$ = 1.3 Hz, CH, *C*HCHO), 53.37 (d, $J_{C,P}$ = 6.2 Hz, $POCH_3$), 53.68 (d, $J_{C,P}$ = 6.1 Hz, $POCH_3$), 83.05 [s, CO$C(CH_3)_3$], 128.0 (s, CH, *p*C-Ph), 128.4 (s, 2× CH, *m*C-Ph), 128.8 (s, 2× CH, *o*C-Ph), 132.4 (d, $J_{C,P}$ = 2.2 Hz, Cq, *i*C-Ph), 163.1 (d, $J_{C,P}$ = 6.3 Hz, Cq, COO), 198.3 (d, $J_{C,P}$ = 3.3 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 22.63 ppm.

Ethyl 1-(2-Formyl-1-dimethoxyphosphoryl-3-phenyl)cyclopropanecarboxylate (9): Prepared from ethyl bromo(dimethoxyphosphoryl)acetate and cinnamaldehyde, according to the general procedure. It was obtained as a 82:18 mixture of diastereoisomers, as determined by ^{31}P NMR spectroscopic analysis. After preparative thin-layer plate chromatography purification on silica gel, the pure diastereoisomers (32 mg, 56%) were obtained as a colourless oil. The enantiomeric excess was determined by ^{1}H and ^{31}P NMR spectroscopic analysis of the diastereoisomeric imines formed after in situ reaction with L-Val-OMe in CD_3CN.[30] For a racemic sample pre-

pared in a similar way with equal amounts of D-proline plus L-proline as catalysts: ^{1}H NMR (400 MHz, CD_3CN): δ = 7.53 (d, J = 6.6 Hz, major), 7.56 (d, J = 6.6 Hz, major), 7.77 (app. t, J = 6.7 Hz, minor) ppm. ^{31}P NMR (162 MHz, CD_3CN): δ = 19.28 (major), 19.36 (major), 21.89 (minor), 21.97 (minor) ppm. Preparative thin-layer plate chromatography purification carried out twice (silica gel; acetone/$CHCl_3$, 1:4) provided the major diastereoisomers as a separate compound. Preparative thin-layer plate chromatography purification carried out twice (silica gel; acetone/$CHCl_3$, 1:4, then EtOAc only) provided the minor diastereoisomer as a separate compound (plus < 10% major diastereoisomer).

(1*R*,2*S*,3*S*)-(+)-9a (Major Diastereoisomer): $[\alpha]_D^{21}$ = +20.0 (c = 0.94, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3 H, $COCCH_3$), 3.23 (ddd, $J_{H,H}$ = 4.6, 7.5, $J_{H,P}$ = 12.1 Hz, 1 H, C*H*CHO), 3.34 (d, $J_{H,P}$ = 11.0 Hz, 3 H, $POCH_3$), 3.47 (d, $J_{H,P}$ = 11.3 Hz, 3 H, $POCH_3$), 3.75 (dd, $J_{H,H}$ = 7.4, $J_{H,P}$ = 14.1 Hz, 1 H, CHPh), 4.28–4.33 (m, 2 H, OCH_2), 7.25–7.40 (m, 5 H, Ph), 9.57 (dd, J = 4.6 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.99 (s, $COCCH_3$), 35.21 (d, $J_{C,P}$ = 3.3 Hz, CH, *C*HPh), 37.37 (d, $J_{C,P}$ = 2.7 Hz, CH, *C*HCHO), 37.56 (d, $J_{C,P}$ = 186.1 Hz, Cq, CP), 52.78 (d, $J_{C,P}$ = 6.1 Hz, $POCH_3$), 53.38 (d, $J_{C,P}$ = 6.7 Hz, $POCH_3$), 62.79 (s, $COOCH_3$), 127.9 (s, CH, *p*C-Ph), 128.2 (s, 2× CH, *m*C-Ph), 129.4 (s, 2× CH, *o*C-Ph), 132.8 (d, $J_{C,P}$ = 5.3 Hz, Cq, *i*C-Ph), 166.9 (d, $J_{C,P}$ = 6.5 Hz, Cq, COO), 196.7 (s, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 18.27 ppm. IR (neat): $\tilde{\nu}$ = 3059, 3048, 2981, 2957, 2852, 2800, 2743, 1730, 1713, 1643, 1603, 1499, 1469, 1448, 1422, 1391, 1367, 1263, 1211, 1181, 1153, 1100, 1033, 943, 916, 862, 835, 801, 776, 698, 665, 624, 614, 594, 559 cm^{-1}. $C_{15}H_{19}O_6P{\cdot}1.25\ H_2O$ (348.814): calcd. C 51.65, H 6.21; found C 51.67, H 5.94.

(1*S*,2*S*,3*S*)-(+)-9b (Minor Diastereoisomer): ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 7.1 Hz, 3 H, $COCCH_3$), 3.22–3.36 (m, 1 H, C*H*CHO), 3.79 (overlapped d, $J_{H,P}$ = 11.0 Hz, 3 H, $POCH_3$), 3.72–3.92 (overlapped m, 3 H, CHPh, $COCH_2$), 3.97 (d, $J_{H,P}$ = 11.1 Hz, 3 H, $POCH_3$), 7.15–7.35 (m, 5 H, Ph), 9.71 (d, $J_{H,H}$ = 5.2 Hz, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.54 (s, $COCCH_3$), 34.23 (s, CH, *C*HPh), 36.61 (d, $J_{C,P}$ = 186.0 Hz, Cq, CP), 38.03 (s, CH, *C*HCHO), 53.56 (d, $J_{C,P}$ = 6.3 Hz, $POCH_3$), 53.76 (d, $J_{C,P}$ = 6.2 Hz, $POCH_3$), 62.09 (s, $COOCH_3$), 128.2 (s, CH, *p*C-Ph), 128.52 (s, 2× CH, *m*C-Ph), 128.53 (s, 2× CH, *o*C-Ph), 132.3 (d, $J_{C,P}$ = 2.1 Hz, Cq, *i*C-Ph), 164.6 (s, Cq, COO), 198.0 (d, $J_{C,P}$ = 3.5 Hz, Cq, CHO) ppm. ^{31}P NMR ($CDCl_3$): δ = 21.88 ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all compounds synthesised, as well as examples of ^{31}P and ^{1}H NMR spectra of racemic imine standards and those of the chiral compounds used to determine enantiomeric excess values.

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