Tetrahedron 67 (2011) 2849–2857

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

(2-Formyl-1-phenylcyclopropyl)phosphonates as building blocks for (2-aminomethyl-cyclopropyl)phosphonates

Ahmed El-Gokha, Gerhard Maas *

Institute of Organic Chemistry I, University of Ulm, Albert-Einstein-Allee 11, D-89081 Ulm, Germany

ARTICLE INFO

Article history:
Received 29 November 2010
Received in revised form 18 February 2011
Accepted 23 February 2011
Available online 1 March 2011

Keywords:
Acceptor-substituted cyclopropanes
Amino acids
(Aminoalkyl)phosphonates
Cyclopropylphosphonates
Organocatalysis

ABSTRACT

A diastereomeric mixture of dimethyl (2-formyl-2-methyl-1-phenylcyclopropyl)phosphonate ((*Z*)-**6**, (*E*)-**6**) was obtained by thermally induced cyclopropanation of α-methylacrolein with α-diazobenzylphosphonate **5**. Application of proline or proline-derived organocatalysts accelerated the reaction, but had a minor effect on the *Z*/*E* ratio of **6**. By reaction with benzylamine or methyl esters of glycine, (*S*)-alanine, and (*S*)-phenylalanine, the *Z*/*E*-mixture of **6** was converted into cyclopropylaldimines, which after reduction gave the corresponding *N*-substituted (2-aminomethyl-cyclopropyl)phosphonates.

1. Introduction

2-Amino- and 2-aminomethyl-substituted cyclopropylphosphonate acids and their derivatives have only recently started to receive attention in terms of synthesis or biological activity studies. These molecular structures combine several interesting features. Firstly, the cyclopropane motif is found in many naturally occurring and synthetic biologically active compounds.[1] A cyclopropane ring often acts as a molecular subunit with a particular reactivity; moreover, its incorporation into a flexible alkyl chain imposes conformational constraints, as only two defined geometries at the three-membered ring are available in 1,2-disubstituted cyclopropanes. Secondly, there is a long-standing interest in phosphonic acids and their derivatives as analogues of natural organophosphates.[2] Thirdly, (1-aminoalkyl)phosphonic acids and derivatives have been studied widely as analogues of natural and non-natural amino acids. On the other hand, the biological activity of higher (aminoalkyl)phosphonates, i.e., those which have two or more carbon atoms between the two functional groups, apparently has received less attention (but see 2-amino-4-phosphonobutanoic acid, a phosphono analogue of glutamic acid,[3] and its derivatives).

Fig. 1 shows the chemical structures of some (2-aminomethyl-cyclopropyl)phosphonates, which have recently appeared in the literature. 2-(Aminomethyl)cyclopropane-1,1-bisphosphonate **1**[4] was designed as a modification of some ω-aminoalkane-1,1-bisphosphonates, which as part of methotrexate-bisphosphonate prodrugs showed interesting therapeutic activity toward bone diseases.[5] (2-Aminomethyl-cyclopropyl)phosphonate **2**[6] is structurally related to the antidepressant Minalcipran (Ixel, (±)-(*Z*)-*N*,*N*-diethyl-2-aminomethyl-1-phenyl-cyclopropanecarboxamide). 2-[(*N*-Hydroxy)carbamoylmethyl]cyclopropyl-phosphonic acids **3** are synthetic cyclopropano analogues of the natural antibiotics

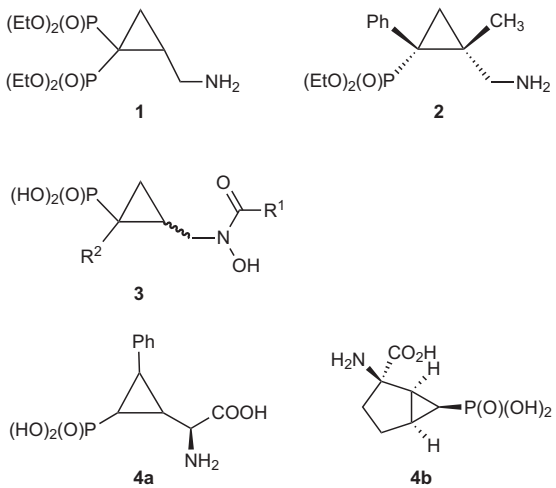


Fig. 1. Some known (2-aminomethyl-cyclopropyl)-phosphonic acids and -phosphonates.

* Corresponding author. E-mail address: gerhard.maas@uni-ulm.de (G. Maas).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.02.068

fosmidomycin and FR-900098, which have high antimalarial activity. One derivative of **3** (R=Me, R′=H, (1*R*, 2*S*)-enantiomer) was equally effective in vitro as fosmidomycin in inhibiting the growth of *Plasmodium falciparum*.[7]

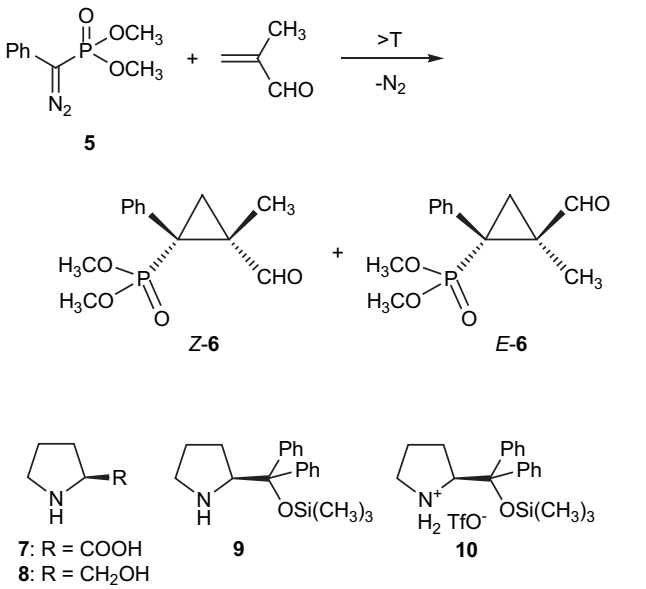
Stereocontrolled syntheses of the conformationally constrained γ-aminophosphonic acid **4a**[8] and of the bicyclic analogue **4b**[9] have been published lately; these compounds are of interest as potential selective mGluRs agonists. (2*R*)-2-(2′-Phosphonocyclopropyl)alanine, structurally related to **4a**, has been designed as a competitive antagonist for the NMDA receptor.[10]

Diverse synthetic approaches were used to prepare compounds **1**–**4**. Michael addition/ring-closure strategies (halo-substituted carbanion addition to acceptor-substituted alkenes,[4,8] electrochemical reduction of diethyl α,α-dichlorobenzylphosphonate in the presence of Michael acceptors,[6] phosphoryl sulfonium ylides, and 2-(*p*-tolylsulfinyl)cyclopent-2-enone[9]) were used to prepare cyclopropylphosphonates bearing acceptor groups (COOR, CN, COR) at C-2 that were further elaborated to give the aminomethyl moieties of **1**, **2**, **4a**, and **4b**. Construction of the cyclopropylphosphonate moiety by intramolecular opening of (3,4-epoxybutyl)phosphonates was another strategy.[7,8]

We describe here a different approach to (2-aminomethylcyclopropyl)phosphonates, which uses a reductive amination of (2-formylcyclopropyl)phosphonates as the key step. This method is very well suited to connect the phosphonic ester moiety with an N-linked α-aminoacid ester through a cyclopropane ring. To the best of our knowledge, such compounds have not been prepared before.

2. Results and discussion

For the purpose of the present study, we considered the diastereomeric (2-formylcyclopropyl)phosphonates (*Z*)- and (*E*)-**6** as suitable building blocks. It is well known that inter- and intramolecular cyclopropanation can be achieved by photochemically[11] or transition-metal[12] induced carbene transfer from α-diazophosphonates to sufficiently electron-rich olefinic bonds. With acroleins as olefinic substrates, however, these strategies are likely to fail.[13] In contrast, the thermally induced reaction of α-diazobenzylphosphonate **5** and methacrolein in toluene gave cyclopropanes (*Z*)- and (*E*)-**6** in good yield, albeit with low diastereoselectivity (Scheme 1 and Table 1, entry 1). Toluene was found to be the best solvent, compared to acetonitrile (lower yields) and methanol (mostly unspecific decomposition). The transformation likely proceeds through a 1-pyrazoline, formed by [3+2]-cycloaddition, which undergoes ring contraction with elimination of N_2 under the reaction conditions. In a number of other cases, the 1-pyrazolines, obtained from mono- and disubstituted diazomethane derivatives, could be isolated and submitted to this ring contraction at elevated temperatures.[14]



Scheme 1. Cyclopropanation of methacrolein with **5** and tested organocatalysts **7**–**10**.

Although the yield of cyclopropanes **6** under optimized conditions (toluene, 80 °C, 36 h) was satisfactory, the long reaction time and low diastereoselectivity led us to investigate the possibilities of iminium ion activation of methacrolein. Iminium activation of α,β-unsaturated aldehydes and ketones toward various reactions,[15] including Michael addition/ring-closure reactions[16] and 1,3-dipolar cycloaddition reactions,[17] is well known nowadays.

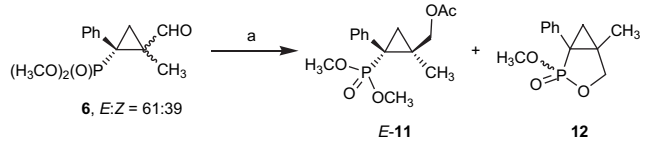
The results obtained with (*S*)-proline (**7**), (*S*)-prolinol (**8**), and (*S*)-pyrrolidines **9** and **10** as organocatalysts are shown in Table 1. All four pyrrolidine derivatives accelerate the cyclopropanation reaction, but **9** and **10** give the best results. Compared to the uncatalyzed reaction in toluene, a quantitative conversion was achieved in the presence of **10** in about one third of the reaction time and with more or less the same cyclopropane yield (entry 11). Toluene and acetonitrile are both suitable solvents, but toluene had some advantage in terms of yield under comparable conditions. With methanol as solvent, the conversion and cyclopropane yield was not much inferior to the reaction in toluene, when (*S*)-proline was used as a catalyst (entries 3 and 5); with all other catalysts, unspecific decomposition pathways as in the uncatalyzed reaction took over.

Table 1
Formation of cyclopropanes **6** from α-diazophosphonate **5** and methacrolein under various conditions

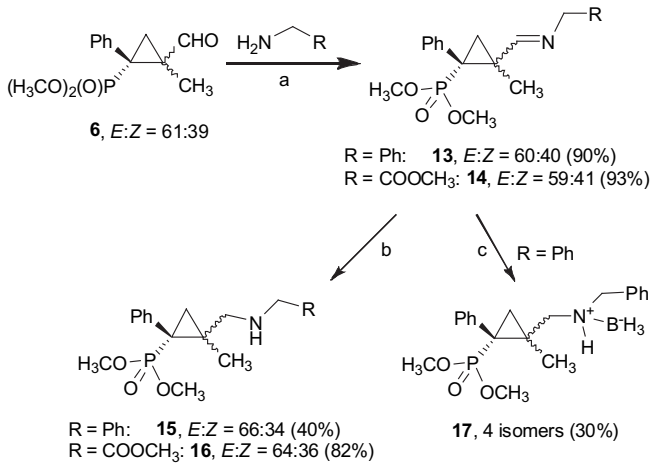
Entry	Solvent	Organocatalyst[a]	Temperature (°C)/Reaction time (h)	Conversion of **5**(%)[b]	Yield[b] of *E*/*Z*-**6** (%)	Ratio[c] *E*-**6**/*Z*-**6**
1	Toluene	None	80/36	quant.	72[d]	56/44
2	Toluene	None	63/24	13[d]	67[d]	
3	Toluene	**7**	63/24	66[d]	67[d]	59/41
4	Acetonitrile	**7**	81/12	95[e]	44[e]	59/41
5	Methanol	**7**	63/24	58[d]	52[d]	58/42
6	Toluene	**8**	63/24	80[d]	46[d]	67/33
7	Acetonitrile	**8**	81/12	quant.	41[e]	62/38
8	Toluene	**9**	63/24	96[e]	59[e]	61/39
9	Acetonitrile	**9**	81/12	quant.	54[e]	61/39
10	Toluene	**10**	63/24	quant.	56[d]	65/35
11	Toluene	**10**	81/12	quant.	74[e]	62/38
12	Acetonitrile	**10**	81/12	quant.	62[d]	60/40

[a] Reactions were carried out using 1 equiv of diazophosphonate **5** and 1.5 equiv of methacrolein; the organocatalyst was applied at 40 mol % relative to methacrolein.
[b] Conversion and yield are based on converted diazophosphonate **5**.
[c] Determined from the ^{1}H NMR spectra of the crude product mixture.
[d] Yield of isolated product after chromatographic work-up.
[e] Determined from the ^{1}H NMR spectra of the crude product mixture after addition of a defined quantity of *p*-iodoanisole as the reference.

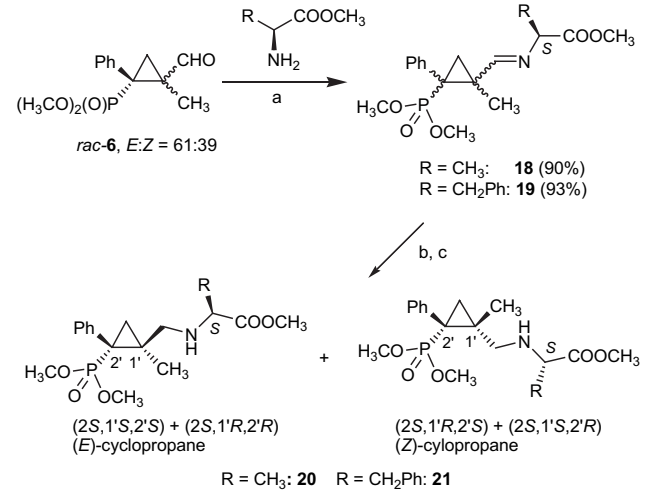
The diastereoselectivity of the cyclopropanation reaction changed only slightly in favor of (*E*)-**6** in the organocatalyzed reactions. The steric bulk of the side chain in pyrrolidines **9** and **10** has no appreciable influence on the diastereomeric ratio. Asymmetric induction by the chiral organocatalysts **7**–**10** appears to be negligible. While we were not able to resolve the optical antipodes of (*E*)- and (*Z*)-**6** by analytical HPLC at a chiral stationary phase [(*S*,*S*) Whelk-O 1, Regis Technologies] or by the use of a chiral NMR shift reagent, we could determine by NMR (^{1}H, ^{31}P) integration the ratio of the four diastereomers of imines **15** and **16** as well as amine **21** (Schemes 3 and 4). This allows us to conclude that cyclopropanes (*E*)- and (*Z*)-**6** in the presence of **10** as catalyst are formed with ee values of about 3–5 and 0%, respectively.



Scheme 2. Reduction of (*E*)- and (*Z*)-**6**; a: (1) $NaBH_4$, THF, 0 °C; (2) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2.



Scheme 3. Conditions: a: benzylamine or methyl glycinate hydrochloride/$NaHCO_3$, Na_2SO_4, CH_2Cl_2, reflux, 4 h; b: H_2, Pd/C, methanol, rt, 1.5 h; c: (1) $NaBH_4$, THF, 0 °C; (2) 2 M aqueous HCl.



Scheme 4. Conditions: a: methyl (*S*)-alaninate hydrochloride/$NaHCO_3$ or methyl (*S*)-phenylalaninate, Na_2SO_4, CH_2Cl_2, reflux, 4 h; b: H_2, Pd/C, methanol, 1.5 h; c: chromatographic separation.

A rationalization for the low level of stereoselectivity in the iminium-activated cyclopropanation reactions remains speculative, as long as the detailed reaction mechanism is not known. Iminium activation of the α,β-unsaturated aldehyde lowers the LUMO energy level and therefore should accelerate both the concerted [3+2] cycloaddition of the diazo dipole and the conjugate addition by the nucleophilic diazo carbon atom yielding a diazonium/enamine intermediate. The cycloaddition process yields a 1-pyrazoline, which then can undergo a thermal ring contraction with elimination of N_2. Both stepwise and concerted pathways are available for the latter step, depending on the substituents at the pyrazoline ring and the reaction temperature.[18] It has been reported that 3,3-disubstituted 1-pyrazolines with an acceptor group at C-3 are thermally converted into cyclopropanes in a completely stereoselective manner, and a concerted N_2 elimination proceeding through a polar transition state has been proposed.[14c,18b,c] If we adopt the 1-pyrazoline pathway with two concerted steps ([3+2] cycloaddition and ring contraction) to form cyclopropane **6**, the low stereoselectivity originates already in the cycloaddition step involving diazophosphonate **5** and the α,β-unsaturated iminium compound (Fig. 2).[19] In the proposed transition state, the regioselective approach of the diazo compound to the olefinic bond is not expected to entail an appreciable diastereoselectivity due to the absence of major steric interactions with the dipolarophile. Because of the small steric demand of the diazo dipole, which has no substituent at the terminal nitrogen atom, a high π-facial selectivity for either the *Re*- or the *Si*-side of the dipolarophile is also not likely.

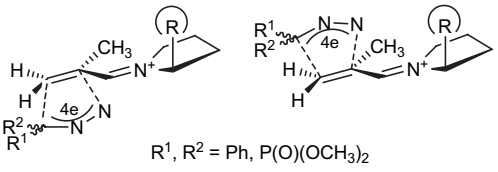


Fig. 2. Proposed transition states for pyrazoline formation in the iminium-activated reactions.

Maruoka and co-workers have reported that *tert*-butyl phenyldiazoacetate, a structural analogue of **1**, reacts with methacrolein to give the tetrasubstituted (2-formylcyclopropyl)carboxylate with high *E*-selectivity in the presence of certain Lewis and Brønsted acids.[20] Whether or not this transformation occurs by a stepwise mechanism that includes the initial nucleophilic addition of the diazoester at the activated methacrolein, is not yet clear. Due to the lability of diazophosphonate **5** toward $TiCl_4$ and triflic acid, we were not able to achieve the analogous transformations.

The diastereomeric mixture of (*Z*)- and (*E*)-**6** could not be separated by crystallization. Chromatographic separation with silica gel as stationary phase was also unsuccessful due to almost identical R_f values. In contrast, chromatography over alumina allowed to isolate the pure *E*-isomer, albeit in reduced yield, while only traces of the Z-isomer could be recovered. Unexpectedly, attempted chromatographic separation of imines (*Z*)- and (*E*)-**13** furnished a fraction consisting of aldehyde (*Z*)-**6** only. The configuration of (*Z*)- and (*E*)-**6** is based on several NMR arguments (Fig. 3). The

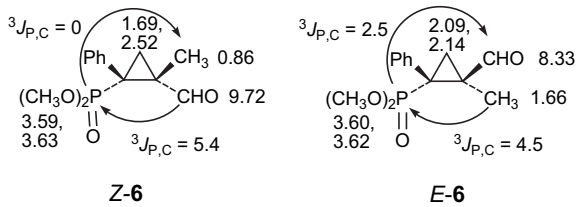


Fig. 3. NMR data for cyclopropanes (*Z*)- and (*E*)-**6** (δ_H values [ppm] and $^3J_{C,P}$ coupling constants [Hz]).

methyl and formyl protons are shielded (lower δ values) when these groups are located on the same side of the cyclopropane ring as the phenyl ring; the observation of nuclear Overhauser effects confirms this assignment. In line with these results, the known relationship,[6,21] $^3J^{cis}(P,C) > {}^3J^{trans}(P,C)$ for the magnitude of the coupling constant between the P nucleus and a C nucleus at the neighboring cyclopropane ring position, is fulfilled.

In a chemical experiment (Scheme 2), a diastereomeric mixture of **6** enriched in the (*E*)-isomer was subjected to borohydride reduction and after acetylation and chromatographic separation, cyclopropane (*E*)-**11** and the bicyclic phosponate **12** (63:37 mixture of the two *P*-epimers, major isomer partially separated) was obtained. The yields of (*E*)-**11** (59%) and **12** (38%) indicate that each isomer of **6** was converted almost quantitatively into the corresponding product. Bicyclic phosphonates similar to **12** have been obtained earlier by electrophile-induced cyclization of (2-vinylcyclopropyl)phosphonates[22] and by intramolecular cyclopropanation of alkenyl α-diazophosphonates.[12a,b]

For the reductive amination of cyclopropane carbaldehyde **6**, we chose a two-step procedure via the corresponding cyclopropane aldimines.[23,24] Condensation of a *Z*,*E*-mixture of **6** with benzylamine and methyl glycinate, respectively, gave the expected cyclopropylimines **13** and **14** in high yield (Scheme 3). In both cases, the resulting *Z*,*E*-mixture was not separated chromatographically to avoid partial hydrolysis. Catalytic hydrogenation converted the imines into the desired *N*-substituted (2-aminomethyl-cyclopropyl) phosphonates **15** and **16**, respectively.

In an analogous manner, the reaction of aldehyde **6** with the methyl esters of (*S*)-alanine and (*S*)-phenylalanine provided aldimines **18** and **19**, respectively, as a mixture of four diastereoisomers (Scheme 4). Catalytic hydrogenation then yielded the *N*-cyclopropylmethyl-aminoacid esters **20** and **21**, which were again obtained as the full set of four diastereoisomers. Their ratio on the one hand corresponded exactly to the original *E*/*Z* ratio of **6**, and on the other hand indicated that, when aldehyde **6** was prepared with (*S*)-proline as catalyst, both the *E*- and the *Z*-cylopropanes were formed with almost no enantioselectivity, as was already stated above. Chromatographic separation of **20** allowed only a fraction of the two *Z*-isomers to be separated from the mixture, but in the case of **21**, a mixture each of the two major isomers (with *E*-configuration at the cyclopropane ring) and of the two minor ones (*Z*-cyclopropanes) could be obtained.

Reduction of imine **13** with $NaBH_4$ gave rise to the amine–borane adduct **17** (Scheme 3). Due to the formation of a stereogenic center at the nitrogen atom, a mixture of four diastereoisomers was obtained, which could be separated easily by chromatography to give the two individual *Z*-cyclopropane isomers and a mixture of the two *E*-cyclopropanes.

The configurational assignment (*E* and *Z* isomers) of the prepared cyclopropylimines and (aminomethyl)cyclopropanes follows the same NMR-based arguments as discussed above for **6** (in addition to the unchanged *E*/*Z* ratio compared with the precursor aldehydes, of course). The difference in the coupling constants $^3J_{cis}(P,C)$ and $^3J_{trans}(P,C)$ is again typical (Fig. 4). The expected *E*-configuration at the imine C=N bond is supported in all cases by NMR (NOE) experiments.

In conclusion, we have developed a short and convenient synthesis for (2-aminomethyl-cyclopropyl)phosphonates, which uses the cyclopropanation of methacrolein with a readily accessible α-diazo-benzylphosphonate as the introductory step. Reductive amination of the resulting cyclopropane carbaldehyde can also be used to connect the structural moieties of a cyclopropylphosphonate and an α-aminoacid through C–N bond formation. The moderate stereoselectivity of the cyclopropanation step, even under conditions of proline-based iminium catalysis, may be considered as a drawback. However, this allows the parallel synthesis of several diastereoisomers of targeted (2-phosphono-cyclopropylmethylamino)carboxylic acid esters, such as **16**, **20**, and **21**, which can then be submitted to initial biological tests.

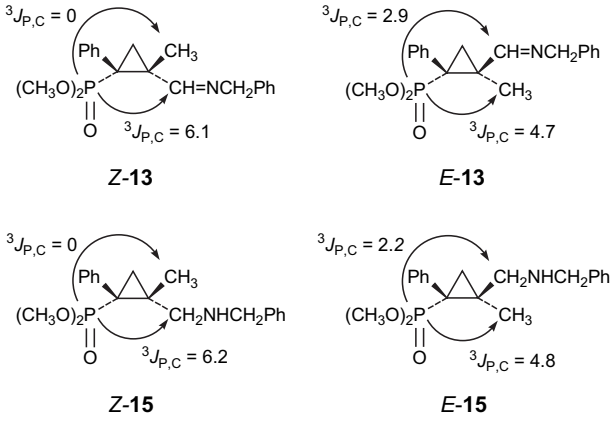


Fig. 4. $^3J_{C,P}$ coupling constants [Hz] involving a cyclopropane ring bond in **13** and **15**.

3. Experimental part

3.1. General information

NMR spectra: Bruker Avance 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.62 MHz; ^{31}P: 161.98 MHz; ^{11}B: 128.38 MHz). All spectra were recorded on $CDCl_3$ solutions. Chemical shifts (δ values [ppm]) were referenced to the solvent peak for ^{1}H ($CHCl_3$: δ=7.26 ppm) and ^{13}C ($CDCl_3$: δ=77.00 ppm) NMR spectra, to external 85% H_3PO_4 (δ_P=0 ppm) for ^{31}P NMR spectra, and to external BF_3 etherate (δ_B=0 ppm) for ^{11}B NMR spectra. When necessary, ^{13}C signal assignments were derived from H,H COSY, HSQC, and HMBC spectra. IR spectra were taken from KBr pellets or samples films on NaCl disks, using a Bruker Vector 22 spectrometer and processing software Opus NT; wavenumbers [cm^{-1}] are given. Elemental analyses: Elementar Vario EL and Elementar Vario Micro Cube instruments. Mass spectra: CI spectra were recorded on a Finnigan MAT SSQ 7000 spectrometer, high-resolution ESI mass spectra on an FT-ICR (Bruker APEX IV) instrument. All melting points are uncorrected and were measured on a Büchi B-540 apparatus (heating rate 1 °C/min). Column chromatography was usually performed using medium pressure chromatography with Merck Lobar columns in size A, B, and C on silica gel 60 (particle size 0.040–0.063 mm). In other cases, column chromatography at hydrostatic pressure was applied using either silica gel 60 (particle size 0.063–0.2 mm, Merck) or aluminum oxide 90 (active neutral, particle size 0.063–0.2 mm, Merck) as the stationary phase. The weight of the latter phase was 100–150 g per 1 g of the crude product. Solvents were purified and dried by usual techniques. Methacrolein was used as purchased (97% GC purity, stabilized with hydroquinone). Organocatalysts were prepared according to published procedures and purified by column chromatography.

3.2. Dimethyl (2-formyl-2-methyl-1-phenylcyclopropyl) phosphonate ((*Z*)-6, (*E*)-6)

(a) *Uncatalyzed reaction*. In a round-bottom flask equipped with a reflux condenser, a stirred solution of α-methylacrolein (2.30 g, 33.2 mmol) and dimethyl α-diazobenzylphosphonate[25] (**5**, 5.00 g, 22.1 mmol) in dry toluene (10 mL) was heated at 80 °C for 36 h. The solvent was removed in vacuo, and the residue was submitted to column chromatography over silica gel (eluent: ethyl acetate/

cyclohexane (4:6)) to furnish **6** as a viscous yellow oil (4.26 g, 72% yield; mixture of diastereomers, *E*/*Z*=56:44).

(b) *Organocatalytic reactions*. To a stirred solution of α-methylacrolein (0.23 g, 3.32 mmol, 1.50 equiv) in the solvent (10 mL), the catalyst (40 mol % based on methacrolein) was added followed by diazo compound **5** (0.50 g, 2.21 mmol, 1.00 equiv). For reaction temperature and time, see Table 1. The ratio of diastereomers (*Z*)- and (*E*)-**6** was determined from the ^{1}H NMR spectra of the crude product mixture. The crude product was purified by column chromatography over silica gel (eluent: ethyl acetate/cyclohexane (4:6)) or by Lobar column chromatography (eluent: ethyl acetate/cyclohexane (1:1)) to afford a mixture of (*E*)- and (*Z*)-**6**.

Efforts to separate the diastereomeric mixture of (*Z*)- and (*E*)-**6** by chromatography over silica gel failed because of almost identical R_f values with different eluents. Preparative layer chromatography of the mixture (100 mg) over alumina (alumina 60 F_{254}, 1.5 mm, 20×20 cm plate) with chloroform/ether (7:3) as eluent gave 78 mg (39%) of (*E*)-**6** as an oil (R_f=0.4), while (*Z*)-**6** had R_f=0 and could be recovered only in traces. Colorless crystals of (*E*)-**6** were obtained from CH_2Cl_2/*n*-pentane, mp 186 °C.

A sample of (*Z*)-**6** was obtained unexpectedly as the only identified fraction, when imine **13** was submitted to column chromatography (silica gel, eluent ethyl acetate/cyclohexane). After evaporation of the solvent, an oil remained (25% yield), which was dissolved in chloroform. After addition of *n*-pentane, colorless crystals of (*Z*)-**6** were obtained, mp 102 °C.

Spectroscopic and analytical for (*E*)-**6**: IR (NaCl, film): ν=1712 (s, C=O), 1492 (m), 1448 (m), 1249 (s, P=O), 1182 (m), 1109 (m), 1030 (vs, br, POC), 951 (m), 904 (m), 828 (m), 703 (m) cm^{-1}. ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR ($CDCl_3$): δ=12.40 (d, *J*=4.5 Hz, 2-CH_3), 22.84 (d, *J*=1.1 Hz, C-3), 33.64 (d, *J*=187.0 Hz, C-1), 35.56 (d, *J*=2.2 Hz, C-2), 52.87 (d, *J*=7.0 Hz, $POCH_3$), 53.07 (d, *J*=6.5 Hz, $POCH_3$), 127.82 (d, *J*=2.8 Hz), 128.51, 129.48, 143.19 (all C–Ph), 200.02 (d, *J*=2.5 Hz, CHO) ppm. (*Z*)-**6**: IR (NaCl, film): ν=1704 (s, C=O), 1492 (m), 1448 (m), 1249 (s, P=O), 1182 (m), 1107 (m), 1030 (vs, br, POC), 949 (m), 909 (m), 838 (m), 703 (m) cm^{-1}. ^{13}C{^{1}H} NMR ($CDCl_3$): δ=14.80 (2-CH_3), 23.87 (d, *J*=1.7 Hz, C-3), 33.79 (d, *J*=185.3 Hz, C-1), 37.87 (d, *J*=1.0 Hz, C-2), 53.12 (d, *J*=6.5 Hz, $POCH_3$), 53.18 (d, *J*=6.5 Hz, $POCH_3$), 127.86 (d, *J*=2.5 Hz), 128.78, 131.40, 134.24 (d, *J*=1.3 Hz) (C_{Ph}), 201.26 (d, *J*=5.4 Hz, CHO) ppm. Data for the mixture: ^{31}P NMR ($CDCl_3$): δ=25.28 ((*E*)-**6**), 27.05 ((*Z*)-**6**) ppm. MS (CI, 100 eV): *m*/*z* (%)=269 (100, [M+H]), 251 (12), 159 (100). Anal. Calcd for $C_{13}H_{17}O_4P$ (268.25 g/mol): C 58.21, H 6.39. Found: C 58.17, H 6.46.

3.3. Reduction of cyclopropane carbaldehyde 6

A solution of a diastereomeric mixture of **6** (0.60 g, 2.20 mmol, *E*/*Z*=61:39) in THF (5 mL) was cooled at 0 °C and $NaBH_4$ (0.13 g, 3.4 mmol) was added. The reaction mixture was stirred overnight. HCl (2 M aqueous) was added dropwise in the cold to the reaction mixture until no effervescence was observed. The aqueous layer was extracted with 3×5 mL of dichloromethane, and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product (0.63 g), triethylamine (0.34 g, 3.40 mmol), and DMAP (0.01 g, 0.10 mmol) were dissolved in dry dichloromethane (5 mL). Acetic anhydride (0.34 g, 3.40 mmol) was added, the reaction mixture was stirred for 3 h at room temperature, and 5 mL of aqueous HCl (2 M) was added followed by saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was stirred vigorously for 30 min to destroy excess acetic anhydride. The organic layer was separated and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography over silica gel (135 g) with a 6:4 mixture of cyclohexane and ethyl acetate to afford first the major isomer of compound **12** followed by a mixture of the two *P*-epimers of **12** [total yield of **12**: 0.20 g (38%); molar ratio=63:37 as determined by ^{1}H NMR of the reaction mixture], then cyclopropane (*E*)-**11** as a very viscous colorless oil (0.41 g, 59%).

Data for (*E*)-(2-dimethoxyphosphoryl-1-methyl-2-phenylcyclopropyl)methyl acetate ((*E*)-**11**): IR (NaCl): ν=1738 (s, C=O), 1247 (s, P=O), 1068 (s), 1018 (s, br, POC), 828 (s), 761 (s), 706 (s) cm^{-1}. ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR: δ=17.28 (d, *J*=4.8 Hz, $C_{cp}CH_3$), 20.72 ($COCH_3$), 22.18 (d, *J*=2.6 Hz, $C_{cp}H_2$), 26.15 (d, *J*=1.7 Hz, $C_{cp}CH_3$), 32.73 (d, *J*=185.9 Hz, $C_{cp}P$), 52.73 (d, *J*=7.0 Hz, $POCH_3$), 52.82 (d, *J*=6.4 Hz, $POCH_3$), 69.59 (d, *J*=2.2 Hz, CH_2OAc), 127.48 (d, *J*=2.6 Hz), 127.86 (d, *J*=2.5 Hz), 128.57 (d, *J*=1.8 Hz), 129.89 (d, *J*=5.3 Hz), 131.46 (d, *J*=2.9 Hz), 135.68 (d, *J*=1.1 Hz) ($6C_{Ph}$), 170.68 (C=O) ppm. ^{31}P NMR: δ=29.12 ppm. MS (CI, 100 eV): *m*/*z* (%)=313 (32, [M+H]), 281 (8), 253 (100). Anal. Calcd for $C_{15}H_{21}O_5P$ (312.32 g/mol): C 57.69, H 6.78. Found: C 57.36, H 6.72.

Data for 2-methoxy-5-methyl-1-phenyl-3-oxa-2-phosphabicyclo[3.1.0]hexane 2-oxide (**12**): IR (NaCl) for diastereomeric mixture: ν=1498 (m), 1447 (m), 1230 (vs, P=O), 1060 (s), 1046 (s), 1023 (vs), 995 (vs), 953 (m), 924 (m), 841 (vs), 830 (vs), 786 (s), 700 (s) cm^{-1}. ^{1}H NMR, major isomer: δ=1.01 (s, 3H, CH_3), 1.35 (dd, $J_{P,H}$=13.7 Hz, $J_{H,H}$=5.3 Hz, 1H, $C_{cp}HH$), 1.49 (dd, $J_{P,H}$=13.8 Hz, $J_{H,H}$=5.3 Hz, 1H, $C_{cp}HH$), 3.69 (d, *J*=11.1 Hz, 3H, $POCH_3$), 4.14 (d, *J*=9.1 Hz, 1H, C*H*H-cyclic), 4.18–4.21 (m, 1H, CH*H*-cyclic), 7.24–7.42 (m, $5H_{Ph}$) ppm; minor isomer: δ=1.08 (s, 3H, CH_3), 1.23 (dd, $J_{P,H}$=13.6 Hz, $J_{H,H}$=5.5 Hz, 1H, $C_{cp}HH$), 1.70 (dd, $J_{P,H}$=13.8 Hz, $J_{H,H}$=5.5 Hz, 1H, $C_{cp}HH$), 3.65 (d, *J*=10.8 Hz, 3H, $POCH_3$), 4.01 (d, *J*=9.0 Hz, 1H, C*H*H-cyclic), 4.12–4.17 (m, 1H, CH*H*-cyclic), 7.27–7.41 (m, 5H, H_{Ph}) ppm. ^{13}C{^{1}H} NMR, major isomer: δ=15.14 (d, *J*=1.5 Hz, CH_3), 19.63 (d, *J*=2.7 Hz, $C_{cp}H_2$), 26.87 (d, *J*=169.6 Hz, PC_{cp}), 30.67 (d, *J*=8.2 Hz, $C_{cp}CH_3$), 53.69 (d, *J*=6.0 Hz, $POCH_3$), 70.26 (d, *J*=8.5 Hz, $POCH_2$), 127.39 (d, *J*=2.5 Hz), 128.37 (d, *J*=1.9 Hz), 130.89 (d, *J*=4.4 Hz), 132.40 (d, *J*=5.3 Hz) (all C_{Ph}) ppm; minor isomer: δ=15.48 (d, *J*=1.5 Hz, CH_3), 19.36 ($C_{cp}H_2$), 26.73 (d, *J*=171.3 Hz, PC_{cp}), 29.06 (d, *J*=6.9 Hz, $C_{cp}CH_3$), 53.37 (d, *J*=6.9 Hz, $POCH_3$), 70.19 (d, *J*=6.4 Hz, $POCH_2$), 127.66 (d, *J*=2.6 Hz), 128.44 (d, *J*=2.1 Hz), 131.37 (d, *J*=4.2 Hz), 132.12 (d, *J*=3.8 Hz) (all C_{Ph}) ppm. ^{31}P NMR: δ=43.21 (minor), 43.82 ppm (major). Anal. Calcd for $C_{12}H_{15}O_3P$ (238.22 g/mol): C 60.50, H 6.35. Found: C 60.26, H 6.39.

3.4. Cyclopropylaldimines 13, 14, 18, and 19

*3.4.1. Dimethyl 2-benzyliminomethyl-2-methyl-1-phenylcyclopropane-1-phosphonate (**13**).* A diastereomeric mixture of **6** (2.00 g, 7.46 mmol, *E*/*Z*=60:40) in dichloromethane (10 mL) was placed in a 50 mL round-bottom flask under argon atmosphere. Benzylamine (0.80 g, 7.46 mmol) was added followed by Na_2SO_4 (3.18 g, 22.4 mmol). The reaction mixture was heated at reflux for 4 h, then filtered. The volatiles were removed at 0.021 mbar/45 °C to afford pure **13** as a highly viscous yellow oil (*E*/*Z*=60:40). Yield: 2.42 g (90%). Due to hydrolysis, a chromatographic separation of the diastereomeric mixture was not possible (see Section 3.2).

IR (NaCl): ν=1655 (s, C=N), 1601 (m), 1495 (s), 1447 (s), 1390 (m), 1248 (vs, P=O), 1182 (m), 1109 (m), 1029 (vs, br, POC), 955 (m), 825 (s), 827 (s), 769 (m), 735 (s), 701 (s) cm^{-1}. ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR, (*E*)-**13**: δ=15.77 (d, *J*=4.7 Hz, $C_{cp}CH_3$), 23.56 (d, *J*=2.2 Hz, $C_{cp}H_2$), 30.49 (d, *J*=1.6 Hz, $C_{cp}C$=N), 32.12 (d, *J*=186.0 Hz, PC_{cp}), 52.39–52.72 ($POCH_3$ both isomers), 64.08 (CH_2Ph), 126.47, 127.10 (d, *J*=2.7 Hz), 127.60, 127.82 (br s), 127.97, 128.12, 128.28, 129.51 (br s), 132.07 (br s), 135.59 (d, *J*=0.7 Hz), 138.68 (all C_{Ph}), 167.07 (d, *J*=2.9 Hz, C=N); (*Z*)-**13**: δ=18.33 (CH_3), 24.55 (d, *J*=1.9 Hz, $C_{cp}H_2$), 31.52 (d, *J*=1.7 Hz, C_{cp}C=N), 32.12 (d, *J*=184.0 Hz, PC_{cp}), 52.39–52.72 ($POCH_3$ both isomers), 64.37 (CH_2Ph), 126.49, 127.20 (d, *J*=2.4 Hz), 127.39, 127.64, 128.07, 128.24 (br s), 128.24 (br s), 131.64 (br s), 128.30, 135.37 (d, *J*=1.4 Hz), 139.44 (all C_{Ph}), 168.02 (d, *J*=6.1 Hz, C=N) ppm. ^{31}P NMR: δ=27.66 (*E*), 28.68 (*Z*) ppm. Anal. Calcd for $C_{20}H_{24}NO_3P$ (357.38 g/mol): C 67.21, H 6.77, N 3.92. Found: C 66.90, H 6.81, N 3.90.

Table 2
^{1}H NMR data for cyclopropylphosphonates prepared in this study ($CDCl_3$, 400.13 Hz, δ values [ppm], coupling constants J [Hz] are given in parentheses (cp=cyclopropane))

Com-pound	$C_{cp}CH_3$	$C_{cp}HH$[a]	$C_{cp}HH$[a]	$P(OCH_3)_2$[b]	CH=O or CH=N or $C_{cp}CH_2N$	Other signals
(*Z*)-**6**	0.86 s	1.69 (11.9, 5.3)	2.52 (18.3, 5.3)	3.59 (10.7), 3.63 (10.9)	9.72 s	7.26–7.33 (m, $5H_{Ph}$)
(*E*)-**6**	1.66 s	2.09 (13.0, 5.3)	2.14 (9.2, 5.3)	3.60 (10.7), 3.62 (10.9)	8.33 s	7.26–7.33 (m, $5H_{Ph}$)
(*E*)-**11**	1.61 s	1.41 (10.4, 5.0)	1.68 (17.0, 5.0)	3.57 (10.6), 3.62 (10.8)		1.99 (s, 3H, $C(O)CH_3$), 3.44/3.62 (AB quartet, J=11.5 Hz, 2H, CH_2OAc), 7.17–7.31 (m, $4H_{Ph}$), 7.47–7.50 (m, $1H_{Ph}$)
(*Z*)-**13**	0.91 s	1.48 (11.3, 5.0)	2.12 (18.2, 5.0)	3.43 (10.6), 3.45 (10.8)	8.09 s	4.57/4.61 (AB quartet, J=14.8 Hz, 2H, CH_2Ph), 6.87–7.42 (m, $10H_{Ph}$)
(*E*)-**13**	1.70 s	1.76 (11.4, 5.0)	1.90 (17.2, 5.0)	3.48 (10.7), 3.54 (10.9)	6.61 s	4.21 (s, 2H, CH_2Ph), 6.87–7.42 (m, $10H_{Ph}$)
(*Z*)-**14**	0.93 s	1.54 dd (11.4, 5.1)	2.15 (18.3, 5.1)	3.47 (10.9), 3.61 (10.9)	8.03 s	4.19–4.27 (AB quartet, 2H, NCH_2CO), 3.68 (s, CO_2CH_3), 7.19–7.27 (m, $5H_{Ph}$)
(*E*)-**14**	1.72 s	1.78 (11.5, 5.3)	1.97 (17.2, 5.1)	3.53 (10.6), 3.58 (10.8)	6.49 s	3.61 (s, CO_2CH_3), 3.78/3.91 (AB quartet, J=15.9 Hz, NCH_2CO), 7.19–7.27 (m, $5H_{Ph}$)
(*Z*)-**15**	0.90 s	1.23 (9.7, 4.8)	1.73 ([c], 4.8)	3.47 (10.6), 3.52 (10.8)	2.98/3.07 (12.1[d])	3.87/3.90 (AB quartet, J=13.4 Hz, CH_2Ph), 7.12–7.57 (m, $10H_{Ph}$)
(*E*)-**15**	1.66 s	1.36 (10.2, 4.3)	1.68 (m, [c], 4.0)	3.53 (10.8), 3.66 (10.9)	2.07/2.22 (12.4[d])	3.41/3.57 (AB quartet, J=13.4 Hz, CH_2Ph), 7.12–7.57 (m, $10H_{Ph}$)
(*Z*)-**16**	0.72 s	1.09 (9.8, 4.7)	1.60 (18.0, 4.6)	3.41 (10.8), 3.44 (10.8)	2.83/3.01 (12.1[d])	1.68 (br s, NH), 3.29–3.36 (m, 2H, CH_2CO), 3.58 (s, 3H, CO_2CH_3), 7.02–7.39 (m, $5H_{Ph}$)
(*E*)-**16**	1.51 s	1.23 (10.2, 4.8)	1.54 (17.3, 4.8)	3.38 (10.9), 3.50 (10.9)	1.77/2.13 (12.1[d])	1.68 (br s, NH), 2.95/3.05 (AB quartet, J=17.2 Hz, CH_2CO), 3.45 (s, 3H, CO_2CH_3), 7.02–7.39 (m, $5H_{Ph}$)
(*Z*)-**17 I**[e]	0.92 s	1.34 (10.6, 5.2)	1.92 (18.3, 5.2)	3.48 (10.7), 3.53 (10.7)	3.13 dd (13.3, 4.7), 3.30 dd(13.3, 8.4)	1.18–2.16 (very broad, 3H, NBH_3), 3.88 (dd, J=13.2, 6.0 Hz, 1H, *CH*HPh), 4.08 (dd, J=13.2, 5.6 Hz, 1H, CH*H*Ph), 5.00 (unresolved m, 1H, N^+H), 7.12–7.56 (m, $10H_{Ph}$)
(*Z*)-**17 II**[e]	0.90 s	1.37 (11.5, 5.8)	1.92 (13.4, 5.8)	3.44 (10.9), 3.58 (10.6)	3.04 dd (13.4, 8.5), 3.46 dd (13.4, 4.1)	1.26–2.01 (very broad, 3H, NBH_3), 3.89 (dd, J=12.9 Hz, J=5.9 Hz, 1H, *CH*HPh), 4.01 (dd, J=12.9, 6.1 Hz, 1H, CH*H*Ph), 4.67 (unresolved m, 1H, N^+H), 7.12–7.44 (m, $10H_{Ph}$)
(*E*)-**17 I**[e]	1.66 s	1.92 (11.0, 5.6)	1.81 (17.2, 5.4)	3.50 (10.9), 3.54 (10.9)	1.31 d (12.3), 2.69 d (12.4)	1.21–2.05 (very broad, 3H, NBH_3), 3.29 (dd, J=13.7, 9.3 Hz, 1H, *CH*HPh), 3.94 (unresolved m, 1H, CH_2N^+H), 4.11 (dd, J=13.7, 2.8 Hz, 1H, CH*H*Ph), 6.81–7.37 (m, $10H_{Ph}$)
(*E*)-**17 II**[e]	1.37	0.66 (10.4, 5.3)	1.55 (17.6, 5.2)	3.44 (10.9), 3.60 (10.9)	1.71 dd (17.6, 5.9), 3.02 dd (13.6, 3.4)	1.21–2.05 (very broad, 3H, NBH_3), 3.62 (dd, partially covered, 1H, *CH*HPh), 3.80 (dd, J=13.1, 5.3 Hz, 1H, CH*H*Ph), 3.96 (unresolved m, 1H, N^+H), 6.81–7.37 (m, $10H_{Ph}$)
(*Z*)-**20 I**[e]	0.78 s	1.13 (9.7, 4.7)	1.64 (18.0, 4.7)	3.51 (10.9)	2.93/2.95 (12.0[d])	1.28 (d, J=7.1 Hz, $NCHCH_3$), 1.96 (br, NH), 3.37 (q, J=6.8 Hz, 1H, CHCO), 3.655 (s, 3H, CO_2CH_3), 7.08–7.38 (m, $5H_{Ph}$)
(*Z*)-**20 II**[e]	0.78 s	1.15 (9.8, 4.7)	1.67 (18.0, 4.7)	3.50 (10.7), 3.51 (10.6)	2.81/3.04 (12.0[d])	1.26 (d, J=6.8 Hz, $NCHCH_3$), 1.91 (br, NH), 3.32 (q, J=7.1 Hz, 1H, CHCO), 3.662 (s, 3H, CO_2CH_3), 7.08–7.38 (m, $5H_{Ph}$)
(*E*)-**20 I**[f]	1.55 s	1.23 m	1.64 (18.0, 4.6)	3.49 (10.6), 3.56 (10.8)	1.90–2.00 m	1.05 (d, J=7.1 Hz, $NCHCH_3$), 1.71–1.83 (br s, NH), 2.85 (q, J=7.1 Hz, 1H, CHCO), 3.64 (s, 3H, CO_2CH_3), 7.08–7.38 (m, $5H_{Ph}$)
(*E*)-**20 II**[f]	1.55 s	1.24 m	1.66 (18.0, 4.7)	3.48 (10.9), 3.52 (10.9)	1.90–2.00 m	1.28 (d, J=7.1 Hz, $NCHCH_3$), 1.71–1.83 (br, NH), 3.30 (q, J=7.1 Hz, 1H, CHCO), 3.65 (s, 3H, CO_2CH_3), 7.08–7.38 (m, $5H_{Ph}$)
(*Z*)-**21 I**	0.72 s	1.10 (9.8, 4.7)	1.58–1.65 m	3.38–3.50	2.75/3.07 (12.3[d])	2.10 (br, NH), 2.92 (d, 2H, CH_2Ph), 3.52 ([c], 1H, CHCO), 3.58 (s, 3H, CO_2CH_3), 7.02–7.36 (m, $10H_{Ph}$)
(*Z*)-**21 II**	0.69 s	1.10 (9.8, 4.7)	1.58–1.65 m	3.38–3.50	2.93/2.96 (13.2[d])	2.10 (br, NH), 2.92 (d, 2H, CH_2Ph), 3.44 ([c], 1H, CHCO), 3.59 (s, 3H, CO_2CH_3), 7.02–7.36 (m, $10H_{Ph}$)
(*E*)-**21 I**	1.50 s	1.17 (10.1, 4.7)	1.52–1.57 m	3.41 (10.9), 3.52 (10.9)	1.83/2.03 (12.1[d])	1.49 (br, NH), 2.65–2.74 (m, 2H, CH_2Ph), 3.16 (t, J=6.6 Hz, CHCO), 3.40 (s, 3H, CO_2CH_3), 7.01–7.41 (m, $10H_{Ph}$)
(*E*)-**21 II**	1.44 s	1.23 (10.2, 4.8)	1.57–1.59 m	3.42 (10.6), 3.52 (10.6)	1.72/2.16 (12.4[d])	1.49 (br, NH), 2.65–2.74 (m, 2H, CH_2Ph), 3.07 (t, J=6.6 Hz, CHCO), 3.36 (s, 3H, CO_2CH_3), 7.01–7.41 (m, $10H_{Ph}$)

[a] Signals appear as doublet of doublets, if not stated otherwise. Coupling constants are given in the order $^3J_{P,H}$, $^3J_{H,H}$.
[b] Doublets in all cases, $^3J_{P,H}$ is given.
[c] Not determined due to signal overlap.
[d] AB quartet.
[e] Two diastereoisomers of (*Z*)-, and two of (*E*)-cyclopropane were obtained.
[f] Signals of the two isomers of (*Z*)-cyclopropane and the two isomers of (*E*)-cyclopropane overlap partially.

*3.4.2. Methyl 2-(2-dimethoxyphosphoryl-1-methyl-2-phenylcyclopropyl-1-methylimino)acetate (**14**).* A diastereomeric mixture of **6** (0.50 g, 1.86 mmol, *E*/*Z*=60:40) was dissolved in dry dichloromethane (10 mL) under argon. Methyl glycinate hydrochloride (0.25 g, 1.99 mmol) was added followed by $NaHCO_3$ (0.47 g, 5.59 mmol) and Na_2SO_4 (0.93 g, 6.55 mmol). The mixture was heated at reflux for 20 h, then filtered, and the solvent was removed at 0.021 mbar/45 °C to afford pure **14** (mixture of diastereoisomers, *E*/*Z*=59:41) as a highly viscous yellow oil. Yield: 0.59 g (93%).

IR (NaCl): ν=1742 (vs, C=O), 1652 (s, C=N), 1601 (m), 1492 (m), 1448 (s), 1249 (vs, P=O), 1130 (s), 1107 (s), 1032 (vs, br, POC), 984 (m), 985 (s), 853 (s), 828 (s), 771 (m), 753 (m), 703 (s) cm^{-1}. ^1H NMR: Table 2. $^{13}C\{^1H\}$ NMR, (*Z*)-**14**: δ=18.15 ($C_{cp}CH_3$), 24.80 (d, *J*=1.8 Hz, $C_{cp}H_2$), 31.81 (d, *J*=1.8 Hz, $C_{cp}C$=N), 32.44 (d, *J*=186.3 Hz, PC_{cp}), 51.85 ($COOCH_3$), 52.70–53.02 ($P(OCH_3)_2$, both isomers), 61.40 (CH_2CO), 127.49 (d, *J*=2.2 Hz), 127.98 (br s), 128.82, 131.74 (br s), 132.09, 135.21 ($6C_{Ph}$), 170.62 (C=O), 172.02 (d, *J*=6.2 Hz, CH=N) ppm; (*E*)-**14**: δ=15.45 (d, *J*=4.8 Hz, $C_{cp}CH_3$), 24.05 (d, *J*=2.2 Hz, $C_{cp}H_2$), 30.63 (d, *J*=1.5 Hz, $C_{cp}C$=N), 32.55 (d, *J*=184.4 Hz, PC_{cp}), 51.84 ($COOCH_3$), 61.14 (CH_2CO), 127.37 (d, *J*=2.6 Hz), 128.50 (br s), 128.95, 129.74 (br s), 132.15 (br s), 135.49 ($6C_{Ph}$), 170.17 (C=O), 171.38 (d, *J*=2.6 Hz, CH=N) ppm. ^{31}P NMR: δ=27.27 (*E*), 28.39 (*Z*) ppm. MS (CI, 100 eV): *m*/*z* (%)=340 (100, [M+H]), 308 (6), 230 (17).

*3.4.3. (2S)-Methyl 2-(2′-dimethoxyphosphoryl-1′-methyl-2′-phenylcyclopropyl-1′-methylimino)propanoate (**18**).* The procedure was as given for **14** using a diastereomeric mixture of **6** (1.00 g, 3.73 mmol, *E*/*Z*=60:40, prepared with proline catalysis), (*S*)-alanine methylester hydrochloride (0.57 g, 4.10 mmol), $NaHCO_3$ (0.94 g, 11.19 mmol), and Na_2SO_4 (1.85 g, 13.06 mmol) in dry dichloromethane (20 mL). Pure **18** was formed as a mixture of four isomers in the molar ratio 30 (*E*):30 (*E*):21 (*Z*):19 (*Z*). Yield: 1.20 g (91%) of a highly viscous yellow oil.

IR (NaCl): ν=1743 (s, C=O), 1653 (s, C=N), 1601 (w), 1492 (m), 1448 (s), 1248 (s), 1204 (s, P=O), 1130 (m), 1107 (m), 1031 (s, br, POC), 985 (m), 958 (s), 853 (s), 827 (s), 771 (m), 752 (m), 703 (s) cm^{-1}. ^1H NMR, mixture of four diastereoisomers: δ=0.91/0.92 (2 s, $C_{cp}CH_3$, *Z*-cp), 0.95/1.17 (2 d, *J*=6.9 Hz, $NCHCH_3$, *E*-cp), 1.37/1.39 (2 d, *J*=6.6 Hz, $NCHCH_3$, *Z*-cp), 1.25–1.34 (m, $C_{cp}HH$), 1.50–1.55 (m, $C_{cp}HH$, *Z*-cp), 1.70 (s, $C_{cp}CH_3$, *E*-cp, two isomers), 1.77 (dd, *J*=11.6 Hz, $C_{cp}HH$, *E*-cp), 1.87–1.99 (m, $C_{cp}HH$, *Z*-cp and *E*-cp), 2.13 (dd, *J*=18.2, 5.0 Hz, 1H, $C_{cp}HH$, *Z*-cp), 3.46–3.68 ($COOCH_3$, $P(OCH_3)_2$, $NCHCH_3$ *E*-cp), 3.99–4.04 (m, 1.19H, $NCHCH_3$, *E*-cp), 6.47 (s, CH=N, *E*-cp), 6.69 (s, CH=N, *E*-cp), 7.08–7.40 (m, 20H, H_{Ph}), 7.99 (s, CH=N, *Z*-cp), 8.05 (s, CH=N, *Z*-cp) ppm. ^{31}P NMR: δ=27.57 (*E*), 27.78 (*E*), 28.70 (*Z*), 28.85 (*Z*) ppm. MS (CI, 100 eV): *m*/*z* (%)=354 (100, [M+1]), 322 (5), 294 (8), 244 (9).

*3.4.4. Methyl 2-(2′-dimethoxyphosphoryl-1′-methyl-2′-phenylcyclopropyl-1′-methylimino)-3-phenylpropanoate (**19**).* The procedure was as given for **13** starting from **6** (1.00 g, 3.73 mmol, *E*/*Z*=60:40), (*S*)-phenylalanine methylester (0.67 g, 3.77 mmol), and Na_2SO_4 (1.85 g, 13.06 mmol) in dry dichloromethane (20 mL). Imine **19** was obtained as a mixture of four isomers in the molar ratio 30 (*E*):30 (*E*):21 (*Z*):19 (*Z*). Yield: 1.00 g (94%) of a highly viscous yellow oil.

IR (NaCl): ν=1743 (s, C=O), 1648 (s, C=N), 1602 (m), 1493 (s), 1447 (s), 1405 (m), 1362 (m), 1318 (m), 1249–1147 (several strong bands), 1110 (s), 1024 (s, br, POC), 980 (m), 954 (s), 933 (m), 826 (s), 770 (s), 753 (s), 735 (s), 702 (s) cm^{-1}. ^1H NMR: δ=0.87 (s, $C_{cp}CH_3$, *Z*-cp), 1.66 and 1.68 (2 s, $C_{cp}CH_3$, *E*-cp), 1.37 (dd, *J*=4.8 Hz, 1H, $C_{cp}HH$), 1.44–1.49 (m, 2H, $C_{cp}H_2$), 1.68–1.72 (m, 1H, $C_{cp}HH$), 1.78–1.90 (m, 1H of $C_{cp}H_2$), 2.08 (dd, *J*=4.8 Hz, 1H of $C_{cp}H_2$), 2.66 (dd, *J*=13.5 and 8.5 Hz, 1H of CH_2Ph), 2.78 (dd, 1H, *J*=13.5 and 8.1 Hz, 1H of CH_2Ph), 2.89–3.08 (m, $3CH_2Ph$), 3.19–3.24 (m, 2H of CH_2Ph, $CHCH_2Ph$), 3.39–3.67 (all $COOCH_3$, all $PO(OCH_3)_2$, $CHCH_2Ph$ of *E*-cp), 4.03–4.06 and 4.09–4.12 (2×X-part of ABX system, $CHCH_2Ph$, *Z*-cp), 6.17 and 6.30 (2 s, 2CH=N, *E*-cp), 6.87–7.28 (m, all H_{Ph}), 7.61 and 7.92 (2 s, 2CH=N, *Z*-cp) ppm. ^{31}P NMR: δ=27.52 (*E*), 27.58 (*E*), 28.54 (*Z*), 28.62 (*Z*) ppm. MS (CI, 100 eV): *m*/*z* (%)=430 (100, [M+1]), 370 (3), 320 (11).

3.5. Reduction of cyclopropylaldimines

*3.5.1. Benzyl-(2-dimethoxyphosphoryl-1-methyl-2-phenylcyclpropylmethyl)amine (**15**).* In a 25 mL round-bottom flask flushed with argon were placed the diastereomeric mixture of **13** (1.00 g, 2.80 mmol, *E*/*Z*=60:40) in dry methanol (12 mL) and 0.60 g of 5% palladium on charcoal (0.03 g Pd, 0.28 mmol). The flask was flushed with hydrogen for 1.5 h with stirring at room temperature. After hydrogenation was complete, the catalyst was removed by filtration. The methanol was removed in vacuo to obtain the crude product, which was purified by Lobar column chromatography eluting with a mixture of ethyl acetate and cyclohexane (9:1) to afford **15** as a highly viscous yellow oil. Yield: 0.40 g (40%) of a diastereomeric mixture (*E*/*Z*=66:34), which was not separated.

IR (NaCl): ν=3320 (w, NH), 1601 (w), 1493 (m), 1447 (m), 1239 (s, P=O), 1183 (m), 1108 (m), 1066, 1031 (s, POC), 911 (m), 850 (m), 825 (m), 733 (s), 701 (s) cm^{-1}. ^1H NMR: Table 2. $^{13}C\{^1H\}$ NMR, (*Z*)-**15**: δ=21.18 (CH_3), 23.87 (d, *J*=4.0 Hz, $C_{cp}H_2$), 28.31 (d, *J*=1.8 Hz, $C_{cp}CH_2N$), 30.11 (d, *J*=184.8 Hz, PC_{cp}), 52.25 (d, *J*=6.7 Hz, $POCH_3$), 52.81 (d, *J*=7.3 Hz, $POCH_3$), 53.83 (d, *J*=6.2 Hz, $C_{cp}CH_2N$), 54.03 (CH_2Ph), 126.56, 127.73, 127.91, 128.09, 128.25 (d, *J*=1.5 Hz), 128.70, 129.74 (d, *J*=5.1 Hz), 132.16 (d, *J*=2.9 Hz), 136.39 (d, *J*=2.2 Hz), 140.31 (all C_{Ph}) ppm; (*E*)-**15**: δ=17.81 (d, *J*=4.8 Hz, CH_3), 22.90 (d, *J*=2.6 Hz, $C_{cp}H_2$), 27.41 (d, *J*=2.6 Hz, $C_{cp}CH_2N$), 30.12 (d, *J*=184.8 Hz, PC_{cp}), 52.34 (d, *J*=6.9 Hz, $POCH_3$), 52.50 (d, *J*=6.2 Hz, $POCH_3$), 53.69 (CH_2Ph), 55.78 (d, *J*=2.2 Hz, $C_{cp}CH_2N$), 126.56, 126.92 (d, *J*=2. 6 Hz), 127.67, 127.71, 128.03, 128.48, 129.60 (d, *J*=5.5 Hz), 131.01 (d, *J*=3.3 Hz), 136.30 (d, *J*=1.8 Hz), 140.01 (all C_{Ph}) ppm. ^{31}P NMR: δ=30.66 (*Z*), 30.67 (*E*) ppm. HRMS ((+)-ESI): *m*/*z*=360.1723 (calcd 360.1729 for $C_{20}H_{27}NO_3P$, [M+H]).

*3.5.2. Benzyl-(2-dimethoxyphosphoryl-1-methyl-2-phenylcyclopropylmethyl)amine-N-borane (**17**).* The diastereomeric mixture of **13** (3.21 g, 9.00 mmol, *E*/*Z*=60:40) was dissolved in THF (25 mL). The solution was cooled at 0 °C and $NaBH_4$ (0.51 g, 13.5 mmol) was added. The reaction mixture was stirred overnight. Aqueous HCl (2 M) was added dropwise in the cold until no effervescence was observed. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed at 15 mbar/20 °C, and the residue was subjected to Lobar column chromatography eluting with a 1:1 mixture of ethyl acetate and cyclohexane. Thereby, the originally formed mixture of four diastereomers of amine **17** (ratio 25:14:34:27 (*Z*-I/*Z*-II/*E*-I/*E*-II) according to ^{31}P NMR), could thereby be separated to give the pure *Z*-isomers and a mixture of the two *E*-isomers (total yield: 1.10 g, 30%).

Isomer (*Z*)-**17 I** was obtained as a highly viscous colorless oil. IR (NaCl): ν=3443 (s, br, NH), 2375 (s)/2321 (s)/2275 (m) (BH), 1601 (m), 1492 (m), 1455 (s), 1227 (s, P=O), 1177 (s), 1113 (m), 1030 (s, POC), 963 (m), 922 (m), 847 (m), 827 (m), 745 (m), 702 (s) cm^{-1}. ^1H NMR: Table 2. $^{13}C\{^1H\}$ NMR: δ=22.88 (d, *J*=1.0 Hz, $C_{cp}CH_3$), 25.56 (d, *J*=1.9 Hz, $C_{cp}CH_2N$), 26.50 (d, *J*=3.2 Hz, $C_{cp}H_2$), 32.19 (d, *J*=183.5 Hz, PC_{cp}), 53.12 (d, *J*=6.7 Hz, $POCH_3$), 53.19 (d, *J*=7.2 Hz, $POCH_3$), 59.60 (d, *J*=5.7 Hz, $C_{cp}CH_2N$), 60.69 (CH_2Ph), 127.46 (d, *J*=2.6 Hz), 128.04 (d, *J*=2.4 Hz), 128.39, 128.55 (d, *J*=1.4 Hz), 128.70, 129.75, 129.92 (d, *J*=5.0 Hz), 132.21 (d, *J*=2.8 Hz), 134.33, 135.45 (d, *J*=1.4 Hz) (all C_{Ph}) ppm. ^{31}P NMR: δ=29.86 ppm. ^{11}B NMR: δ=−15.1 ppm. MS (CI, 100 eV): *m*/*z* (%)=372 (100, [M−1]), 360 (19, M−BH_2).

Isomer (*Z*)-**17 II**: highly viscous colorless oil. ^1H NMR: Table 2. $^{13}C\{^1H\}$ NMR: δ=24.07 (d, *J*=0.9 Hz, $C_{cp}CH_3$), 24.88 (d, *J*=2.3 Hz, $C_{cp}H_2$), 25.13 (d, *J*=2.0 Hz, $C_{cp}CH_2$), 32.39 (d, *J*=183.3 Hz, PC_{cp}),

52.65 (d, J=7.4 Hz, POC), 53.44 (d, J=6.2 Hz, POC), 58.59 (d, J=5.9 Hz, $C_{cp}CH_2N$), 60.58 (CH_2Ph), 127.48 (d, J=2.5 Hz), 128.07, 128.32, 128.49, 128.63, 129.60 (d, J=4.6 Hz), 130.45, 131.61, 134.19, 135.45 (d, J=1.40 Hz) (all C_{Ph}) ppm. ^{31}P NMR: δ=30.57 ppm. ^{11}B NMR: δ=−15.40 ppm. MS (CI, 100 eV): m/z (%)=372 (100, [M−H]), 360 (19, M−BH_2).

A mixture of isomers (*E*)-**17 I** and (*E*)-**17 II** was obtained as a semisolid white compound. IR (NaCl): ν=3165 (w, br, NH), 2376 (m)/2321 (m)/2275 (w) (BH), 1492 (m), 1455 (m), 1229 (s, P=O), 1167 (m), 1069 (s), 1033 (vs, POC), 912 (s), 848 (m), 827 (m), 733 (s), 701 (s) cm^{-1}. ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR, (*E*)-**17 I**: δ=16.42 (d, J=5.5 Hz, $C_{cp}CH_3$), 23.76 (d, J=1.8 Hz, $C_{cp}CH_2N$), 25.70 (d, J=2.9 Hz, $C_{cp}H_2$), 29.28 (d, J=186.6 Hz, PC_{cp}), 52.64 (d, J=7.0 Hz, $POCH_3$), 52.57 (d, J=6.2 Hz, $POCH_3$), 60.28 (d, J=2.9 Hz, $C_{cp}CH_2N^+H$), 61.17 (CH_2Ph), 127.44 (d, J=2.2 Hz), 127.72 (d, J=2.2 Hz), 128.79, 128.85, 128.93 (d, J=1.5 Hz), 129.33, 129.77, 130.81 (d, J=2.6 Hz), 133.69, 135.06 (d, J=1.5 Hz) (all C_{Ph}) ppm; (*E*)-**17 II**: δ=17.29 (d, J=5.9 Hz, $C_{cp}CH_3$), 23.58 (d, J=2.9 Hz, $C_{cp}H_2$), 24.46 (d, J=1.5 Hz, $C_{cp}CH_2N$), 30.44 (d, J=186.6 Hz, PC_{cp}), 52.71 (d, J=4.5 Hz, POC), 52.76 (d, J=6.6 Hz, POC), 59.49 (CH_2Ph), 61.17 (d, J=2.2 Hz, $C_{cp}CH_2N$), 127.60 (d, J=2.2 Hz), 128.22 (d, J=2.6 Hz), 128.55, 128.65 (d, J=1.5 Hz), 128.68, 129.49 (d, J=5.5 Hz), 129.73, 130.97 (d, J=2.6 Hz), 134.13, 134.60 (d, J=1.1 Hz) (all C_{Ph}) ppm. ^{31}P NMR: δ=28.67 (isomer II), 29.20 (I) ppm. ^{11}B NMR: δ=−15.20 (isomer I), −15.10 (II) ppm. HRMS ((+)-ESI): m/z=396.1874 (calcd 396.1876 for $C_{20}H_{29}BNO_3PNa$, [M+Na]) for the mixture of four isomers. MS (CI, 100 eV): m/z (%)=372 (100, [M−1]), 360 (49, M−BH_2).

*3.5.3. Methyl 2-(2-dimethoxyphosphoryl-1-methyl-2-phenylcyclopropyl-1-methylamino)acetate (**16**).* The procedure as given for **15** was used. The crude product was purified by Lobar column chromatography eluting with a mixture of dichloromethane and methanol (9.5:0.5) to afford a diastereomeric mixture of **16** (*E*/*Z*=64:36) as a highly viscous, slightly yellow oil; yield: 0.41 g (82%). The diastereomers could not be separated by chromatography over alumina 90 (eluent: ethanol) or RP-18 (eluent: ethanol, acetonitrile, or chloroform). A partial separation was possible by preparative layer chromatography over silica gel (SIL G-200 UV_{254}, Macherey–Nagel, 2 mm, 20×20 cm; eluent: ethanol–petroleum ether–triethylamine (10:90:0.1)); from 18 mg of the mixture, a fraction with R_f=0.28 furnished 15 mg of the *E*/*Z* mixture and 25 mg of (*Z*)-**16** as an oil, which was not pure by ^{1}H NMR spectroscopy, however. Crystallization from CH_2Cl_2/*n*-pentane afforded very soft colorless crystals, mp 150 °C.

IR (NaCl): ν=3335 (w, br, NH), 1742 (s, C=O), 1601 (w), 1492 (m), 1447 (m), 1235 (s, P=O), 1182 (m), 1149 (w), 1066, 1032 (s, POC), 913 (s), 850 (m), 826 (m), 732 (s), 703 (m) cm^{-1}. ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR, (*Z*)-**16**: δ=20.58 ($C_{cp}CH_3$), 23.39 (d, J=2.9 Hz, $C_{cp}H_2$), 27.99 (d, J=1.8 Hz, $C_{cp}CH_2N$), 29.66 (d, J=185.2 Hz, PC_{cp}), 50.18 (CH_2CO), 51.10 ($COOCH_3$), 52.25 (d, J=6.9 Hz, $POCH_3$), 52.36 (d, J=6.9 Hz, $POCH_3$), 53.75 (d, J=5.9 Hz, $C_{cp}CH_2N$), 126.59 (d, J=2.6 Hz), 127.36 (d, J=2.6 Hz), 127.93 (d, J=1.5 Hz), 129.41, 131.84 (d, J=2.9 Hz), 136.21 (d, J=1.8 Hz) (all C_{Ph}), 172.30 (C=O) ppm; (*E*)-**16**: δ=17.34 (d, J=5.5 Hz, $C_{cp}CH_3$), 22.60 (d, J=2.6 Hz, $C_{cp}H_2$), 26.97 (d, J=1.8 Hz, $C_{cp}CH_2N$), 30.04 (d, J=185.2 Hz, PC_{cp}), 50.33 (CH_2CO), 51.03 ($COOCH_3$), 52.04 (d, J=6.9 Hz, $POCH_3$), 52.13 (d, J=6.9 Hz, $POCH_3$), 55.65 (d, J=2.2 Hz, $C_{cp}CH_2N$), 126.67 (d, J=2.6 Hz), 127.44 (d, J=2.6 Hz), 127.99 (d, J=1.5 Hz), 129.47, 130.85 (d, J=2.6 Hz), 136.20 (d, J=1.8 Hz) (all C_{Ph}), 172.08 (C=O) ppm. ^{31}P NMR: δ=30.31 (*E*), 30.57 (*Z*) ppm. MS (CI, 100 eV): m/z=342 (100, [M+1]), 310 (10), 269 (7), 253 (20, M), 159 (11), 129 (20). HRMS ((+)-ESI): m/z=342.1465 (calcd 342.1470 for $C_{16}H_{25}NO_5P$, [M+H]).

*3.5.4. (2S)-Methyl 2-(2′-dimethoxyphosphoryl-1′-methyl-2′-phenylcyclopropyl-1′-methylamino)propanoate (**20**).* The procedure as given for **15** was used. Starting from imine **18**, amine **20** was obtained as a mixture of four isomers. The crude product was purified by Lobar column chromatography eluting with ethyl acetate. Two major fractions were obtained, both as highly viscous colorless oils (combined yield: 0.40 g, 80%). The first fraction was a 1.75:1 mixture of the two *Z*-cyclopropanes *Z*-**20 I** and **II**; the second fraction was a mixture of *Z*-**20 I**, *Z*-**20 II**, *E*-**20 I**, and *E*-**20 II**.

Data for the mixture of four diastereomers: IR (NaCl): ν=3436 (m, br, NH), 1738 (vs, C=O), 1602 (m), 1493 (s), 1447 (s), 1237 (vs, br, P=O), 1111 (s), 1033 (vs, br, POC), 954 (m), 922 (m), 849 (m), 827 (s), 733 (vs), 702 (vs) cm^{-1}. HRMS ((+)-ESI): m/z=378.1441 (calcd 378.1446 for $C_{16}H_{26}NNaO_5P$, [M+Na]).

Data for *Z*-**20 I**: ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR: δ=18.70 ($CHCH_3$), 20.92 ($C_{cp}CH_3$), 23.71 ($C_{cp}H_2$), 28.52 (d, J=1.8 Hz, $C_{cp}CH_2N$), 30.11 (d, J=184.8 Hz, PC_{cp}), 51.57 ($COOCH_3$), 52.11–52.75 ($C_{cp}CH_2N$, $POCH_3$), 56.75 ($NCHCH_3$), 126.94, 127.71 (d, J=2.2 Hz), 128.27, 129.91 (d, J=5.1 Hz), 132.23, 136.64 (d, J=1.8 Hz) (all C_{Ph}), 175.95 (C=O) ppm. ^{31}P NMR: δ=30.36 ppm.

Data for *Z*-**20 II**: ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR: δ=18.81 ($CHCH_3$), 20.98 ($C_{cp}CH_3$), 23.74 ($C_{cp}H_2$), 28.33 (d, J=1.8 Hz, $C_{cp}CH_2N$), 30.09 (d, J=184.4 Hz, PC), 51.55 ($COOCH_3$), 52.64–52.79 ($C_{cp}CH_2N$, $POCH_3$), 56.90 ($NCHCH_3$), 126.97, 127.79 (d, J=2.6 Hz), 128.27, 129.76 (d, J=5.5 Hz), 132.25, 136.70 (d, J=1.8 Hz) (all C_{Ph}), 175.88 (C=O) ppm. ^{31}P NMR: δ=30.45 ppm.

Mixture of *Z*-**20 I**, *Z*-**20 II**, *E*-**20 I**, and *E*-**20 II**: ^{1}H NMR data for the *E*-isomers: Table 2. ^{31}P NMR: δ=30.60 (*E*-**20 I**), 30.47 (*E*-**20 II**) ppm.

*3.5.5. (2S)-Methyl 2-(2′-dimethoxyphosphoryl-1′-methyl-2′-phenylcyclopropyl-1′- methylamino)-3-phenylpropanoate (**21**).* The procedure as given for **15** was used. Starting from imine **19** (29:29:22:20 mixture), amine **21** was obtained as a mixture of four isomers in the molar ratio 30:30:21:19 (*E*-**21 I**/*E*-**21 II**/*Z*-**21 I**/*Z*-**21 II**). The crude product was purified by column chromatography over silica gel eluting with a mixture of ethyl acetate and cyclohexane (9:1). Two major fractions were obtained as highly viscous, colorless oils (combined yield: 0.42 g, 84%): (a) (*E*)-**21**, isomers I and II (1:0.85 ratio); (b) (*Z*)-cyclopropane *Z*-**21**, isomers I and II (1:0.85 ratio) (note that in both cases, the isomer ratio does not exactly reproduce the ratio before chromatography).

Data for the mixture of four diastereomers: IR (NaCl): ν=3335 (w, br, NH), 1738 (s, C=O), 1602 (w), 1493 (m), 1447/1446 (m), 1236 (s, br, P=O), 1111 (m), 1032 (s, br, POC), 912 (m), 849 (m), 827 (m), 732 (s) cm^{-1}. MS (CI, 100 eV): m/z (%)=432 (100, [M+1]), 400 (11, M), 372 (7, M), 340 (21), 253 (9). HRMS ((+)-ESI): m/z=432.1934 (calcd 432.1940 for $C_{23}H_{31}NO_5P$, [M+H]).

Data for the mixture of *E*-**21 I** and **II**: ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR, isomer I: δ=17.80 (d, J=5.1 Hz, $C_{cp}CH_3$), 22.60 (d, J=2.6 Hz, $C_{cp}H_2$), 27.59 (d, J=1.8 Hz, $C_{cp}CH_2N$), 30.56 (d, J=184.8 Hz, PC_{cp}), 39.41 (CH_2Ph), 51.15 ($COOCH_3$), 52.39 (d, J=7.0 Hz, $P(OCH_3)_2$), 54.03 (d, J=1.8 Hz, $C_{cp}CH_2N$), 63.05 (NCHCO), 126.40, 126.78 (d, J=2.6 Hz), 127.60 (d, J=2.6 Hz), 128.05, 128.94, 129.15, 129.89 (d, J=5.5 Hz), 131.25 (d, J=2.9 Hz), 136.35 (d, J=1.8 Hz), 137.16 (all C_{Ph}), 174.60 (C=O); isomer II: δ=17.59 (d, J=5.1 Hz, $C_{cp}CH_3$), 22.71 (d, J=2.6 Hz, $C_{cp}H_2$), 27.27 (d, J=2.2 Hz, $C_{cp}CH_2N$), 30.00 (d, J=185.2 Hz, PC_{cp}), 39.32 (CH_2Ph), 51.12 ($COOCH_3$), 52.33 (d, J=7.0 Hz, $P(OCH_3)_2$), 54.34 (d, J=1.8 Hz, $C_{cp}CH_2N$), 62.63 (NCHCO), 126.37, 126.86 (d, J=2.6 Hz), 127.79 (d, J=2.6 Hz), 128.08, 129.02, 129.06, 129.55 (d, J=5.5 Hz), 131.02 (d, J=2.9 Hz), 136.19 (d, J=1.8 Hz), 137.29 (all C_{Ph}), 174.28 (C=O) ppm. ^{31}P NMR: δ=30.19 (I), 30.30 (II) ppm.

Data for the mixture of *Z*-**21 I** and **II**: ^{1}H NMR: Table 2. ^{13}C{^{1}H} NMR, isomer I: δ=20.95 ($C_{cp}CH_3$), 23.56 (d, J=3.3 Hz, $C_{cp}H_2$), 28.50 (d, J=1.8 Hz, $C_{cp}CH_2N$), 30.18 (d, J=185.2 Hz, PC_{cp}), 39.54 (CH_2Ph), 51.51 ($COOCH_3$), 52.13 (d, J=5.9 Hz, $C_{cp}CH_2N$), 52.62–52.75 ($P(OCH_3)_2$, both isomers), 63.31 (NCHCO), 126.53, 127.00, 127.85 (d, J=2.6 Hz), 128.26, 128.31, 129.26, 129.80 (d, J=4.8 Hz), 132.31 (d, J=2.9 Hz), 136.78 (d, J=1.8 Hz), 137.29 (all C_{Ph}), 174.93 (C=O); isomer II: δ=20.97 ($C_{cp}CH_3$), 23.72 (d, J=3.3 Hz, $C_{cp}H_2$), 28.55 (d,

J=1.5 Hz, $C_{cp}CH_2N$), 29.98 (d, J=184.4 Hz, PC_{cp}), 39.77 (CH_2Ph), 51.45 ($COOCH_3$), 52.78 (d, J=2.9 Hz, $C_{cp}CH_2N$), 63.49 (NCHCO), 126.44, 127.02, 127.77 (d, J=3.3 Hz), 128.18, 128.28, 129.35, 129.94 (d, J=5.5 Hz), 132.25 (d, J=2.9 Hz), 136.71 (d, J=1.5 Hz), 137.84 (all C_{Ph}), 174.52 (C=O) ppm. ^{31}P NMR: δ=30.54 (I), 30.52 (II) ppm.

Acknowledgements

A. El-G. thanks the government of the Republic of Egypt for a fellowship. We thank Stefan Buck for his help with chromatographic separations.

References and notes

1. Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2001**, *103*, 1625–1647.
2. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
3. Selected recent publications: (a) Liu, F.; Park, J.-E.; Lee, K. S.; Burke, T. R., Jr. *Tetrahedron* **2009**, *65*, 9673–9679; (b) Han, L.; Hiratake, J.; Kamiyama, A.; Sakata, K. *Biochemistry* **2007**, *46*, 1432–1447; (c) Foss, F. W., Jr.; Snyder, A. H.; Davis, M. D.; Rouse, M.; Okusa, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem.* **2007**, *15*, 663–677; (d) Lopez, S.; Turle-Lorenzo, N.; Acher, F.; De Leonibus, E.; Mele, A.; Amalric, M. *J. Neurosci.* **2007**, *27*, 6701–6711; (e) Reyes-Rangel, G.; Marañón, V.; Avila-Ortiz, C. G.; Anaya de Parrodi, C.; Quintero, L.; Juaristi, E. *Tetrahedron* **2006**, *62*, 8404–8409; (f) Hudtloff, C.; Thomsen, C. In *Metabotropic Glutamate Receptors and Brain Function*; Moroni, F., Nicoletti, F., Pellegrini-Giampietro, D. E., Eds.; Portland Ltd.: 1998; pp 281–291; (g) Sanchez-Prieto, J.; Herrero, I.; Sistiaga, A.; Vazquez, E. In *Metabotropic Glutamate Receptors and Brain Function*; Moroni, F., Nicoletti, F., Pellegrini-Giampietro, D. E., Eds.; Portland Ltd.: 1998; pp 243–250.
4. Couthon, H.; Gourvès, J.-P.; Guervenou, J.; Corbel, B.; Sturtz, G. *Synth. Commun.* **1999**, *29*, 4251–4260.
5. (a) Sturtz, G.; Couthon, H.; Fabulet, O.; Mian, M.; Rosini, S. *Eur. J. Med. Chem.* **1993**, *28*, 899–903; (b) Hosain, F.; Spencer, R. P.; Couthon, H. M.; Sturtz, G. L. *J. Nucl. Med.* **1996**, *37*, 105–107.
6. Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J.-C. *Org. Lett.* **2000**, *2*, 453–455.
7. Devreux, V.; Wiesner, J.; Goeman, J. L.; Van der Eycken, J.; Jomaa, H.; Van Calenbergh, S. *J. Med. Chem.* **2006**, *49*, 2656–2660.
8. Marinozzi, M.; Serpi, M.; Amori, L.; Gavilan Diaz, M.; Costantino, G.; Meyer, U.; Flor, P. J.; Gasparini, F.; Heckendorn, R.; Kuhn, R.; Giorgi, G.; Brunsgaard Hermit, M.; Thomsen, C.; Pellicciari, R. *Bioorg. Med. Chem.* **2007**, *15*, 3161–3170.
9. Krysiak, J.; Midura, W. H.; Wieczorek, W.; Sieron, L.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1486–1493.
10. Dappen, M. S.; Pellicciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161–168.
11. (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1975**, *87*, 259–268; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 222–231; (b) Maas, G.; Regitz, M. *Chem. Ber.* **1978**, *111*, 1733–1752; (c) Maas, G. *Chem. Ber.* **1979**, *112*, 3241–3272; (d) Maas, G. *Phosphorus and Sulfur* **1983**, *14*, 143–150.
12. (a) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123–8129; (b) Hanson, P. R.; Sprott, K. T.; Wrobleski, A. D. *Tetrahedron Lett.* **1999**, *40*, 1455–1458; (c) Simonneaux, G.; De Montigny, F.; Paul-Roth, C.; Gulea, M.; Masson, S. *Tetrahedron Lett.* **2002**, *43*, 3685–3687.
13. For example, epoxide formation has been observed in the rhodium(II)-catalyzed reaction of aryldiazoacetates with α,β-unsaturated aldehydes: Davies, H. M. L.; DeMeese, J. *Tetrahedron Lett.* **2001**, *42*, 6803–6805.
14. Selected examples: (a) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059–4068; (b) Hamaguchi, M.; Nakaishi, M.; Nagai, T.; Tamura, H. *J. Org. Chem.* **2003**, *68*, 9711–9722; (c) García Ruano, J. L.; Alonso de Diego, S.; Martín, M. R.; Torrente, E.; Martín Castro, A. M. *Org. Lett.* **2004**, *6*, 4945–4948; (d) García Ruano, J. L.; Peromingo, M. T.; Martín, M. R.; Tito, A. *Org. Lett.* **2006**, *8*, 3295–3298; (e) García Ruano, J. L.; Alonso, M.; Cruz, D.; Fraile, A.; Martin, M. R.; Peromingo, M. T.; Tito, A.; Yuste, F. *Tetrahedron* **2008**, *64*, 10546–10551; (f) Cruz Cruz, D.; Yuste, F.; Martín, M. R.; Tito, A.; García Ruano, J. L. *J. Org. Chem.* **2009**, *74*, 3820–3826.
15. Reviews: Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79–87; Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759–1772; Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470; Vicario, J. L.; Badía, D.; Carillo, L. *Synthesis* **2007**, 2065–2092.
16. Selected examples: Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, 4838–4840; Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241; Rios, R.; Sundén, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028–1032; Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 7867–7879; Uria, Z.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, 701–713.
17. Cycloaddition reactions with nitrones: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875; Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923–926; Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782–2791; Azomethine imines: Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818–1822; Azomethine: Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170 ylides.
18. See, for example: (a) Clarke, T. C.; Wendling, L. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 2740–2750; (b) McGreer, D. E.; Chiu, N. W. K.; Vinje, M. G.; Wong, K. C. K. *Can. J. Chem.* **1965**, *43*, 1405–1414; (c) McGreer, D. E.; Masters, I. M. E.; Liu, M. T. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1791–1794.
19. In this context, it is interesting to note that the cycloaddition of *tert*-butyl phenyldiazoacetate with α-isopropylacrolein under very mild conditions (BF_3-catalysis, CH_2Cl_2, −78 °C) gave the expected 3,3,5,5-tetrasubstituted 1-pyrazoline also with low diastereoselectivity (58.5:41.5). Unfortunately, the authors did not report the (uncatalyzed) thermal cyclopropane formation of this pyrazoline mixture; see supporting information in Ref. 20.
20. Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143–5145.
21. Thiem, J.; Meyer, B. *Org. Magn. Reson.* **1978**, *11*, 50–51.
22. Maas, G.; Hoge, R. *Liebigs Ann. Chem.* **1980**, 1028–1045.
23. A one-step aminobenzylation of a γ-oxophosphonate [$(EtO)_2(O)P–(CH_2)_2–CHO$], using benzylamine and NaBH3CN, has been described: Fabre, G.; Collignon, N.; Savignac, P. *Can. J. Chem.* **1981**, *59*, 2864–2869.
24. The two-step one-pot conversion of the aldehyde function of a 2-formylcyclopropylphosphonate into an *N*-substituted α-aminonitrile was a step in the synthesis of **4a**, see Ref. 8.
25. Scherer, H.; Hartmann, A.; Regitz, M.; Tunggal, B. D.; Günther, H. *Chem. Ber.* **1972**, *105*, 3357–3381.