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Enantioselective synthesis of phosphinyl peptidomimetics via an asymmetric Michael reaction of phosphinic acids with acrylate derivatives

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Abstract

Asymmetric Michael reaction of phosphinic or aminophosphinic acids with acrylate derivatives afforded phosphinyl dipeptidomimetics in excellent yields (>90%). Chiral induction of substituents at the α-position of acrylate derivatives of Evans oxazolidinone type auxiliaries was obtained in moderate to excellent diastereomeric and enantiomeric excesses (50–98%). Pure diastereomers and enantiomers of phosphinyl dipeptidomimetics **16–19** were also successfully separated by HPLC. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Phosphinic acid; Acrylate; Asymmetric Michael reaction; Chiral auxiliary; Phosphinyl peptidomimetics

1. Introduction

Peptidomimetic drug design has been a very important research area in medicinal chemistry because of the importance of many natural peptides as hormones, neurotransmitters, growth factors, cytokines, enzyme inhibitors, neuromodulators, and modulators of ion channels and many other biological functions. Work continues in the field to develop diverse non-peptidic scaffolds and amide isosteres to increase metabolic stability, to restrict the conformational properties of short peptides, and to provide three-dimensional mimics of peptide motifs such as β-turns and α-helices [1,2]. Several studies have demonstrated that the use of phosphinic acid peptide isosteres can be a very effective approach for the development of highly potent and selective inhibitors of various Zn metalloproteases [3,4]. These unnatural peptide analogs contain the metabolically stable phosphinic moiety $\Psi[P(O)OHCH_2]$, which mimics the transition state tetrahedral geometry of a scissile peptide bond during enzymatic hydrolysis [5]. Unnatural $\Psi[P(O)OHCH_2]$ peptide analogs also provide the peptidomimetic chemist additional metabolically stable isosteres/scaffolds to scan conformational requirements within receptor ligand pharmacophores. Phosphinic acid isosteres of dipeptide building blocks are therefore likely to find growing utility in medicinal chemistry.

Inspection of the literature revealed that the classical approach to prepare phosphinic $\Psi[P(O)OHCH_2]$ peptides relies on the synthesis of phosphinyl pseudodipeptidic units, which are typically obtained by Michael addition of phosphinic acids with acrylate analogues [6,7]. In the presence of hexamethyldisilizane (HMDS) [7], TMSCl [8], BSA [9] or NaOMe [10], Michael addition of racemic 1-aminophosphinic acids with 2-substituted acrylates gives mixtures of four stereoisomers, due to the presence of two asymmetric carbons as shown in Fig. 1. Also, complete separation by HPLC proved difficult due to similar retention times, and two pairs of diastereomers were usually obtained [9].

Often, optically pure diastereomers are needed both for the determination of absolute configuration and for studying the relationships between stereochemistry and bioactivity. Therefore, the availability and ease of making four individual isomers of the phosphinic acid bearing pseudodipeptidic unit have become crucial to future developments in this research area. In this paper,

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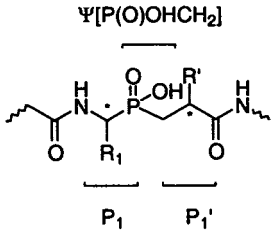


Fig. 1. General structure of phosphinyl peptidomimetic analogs.

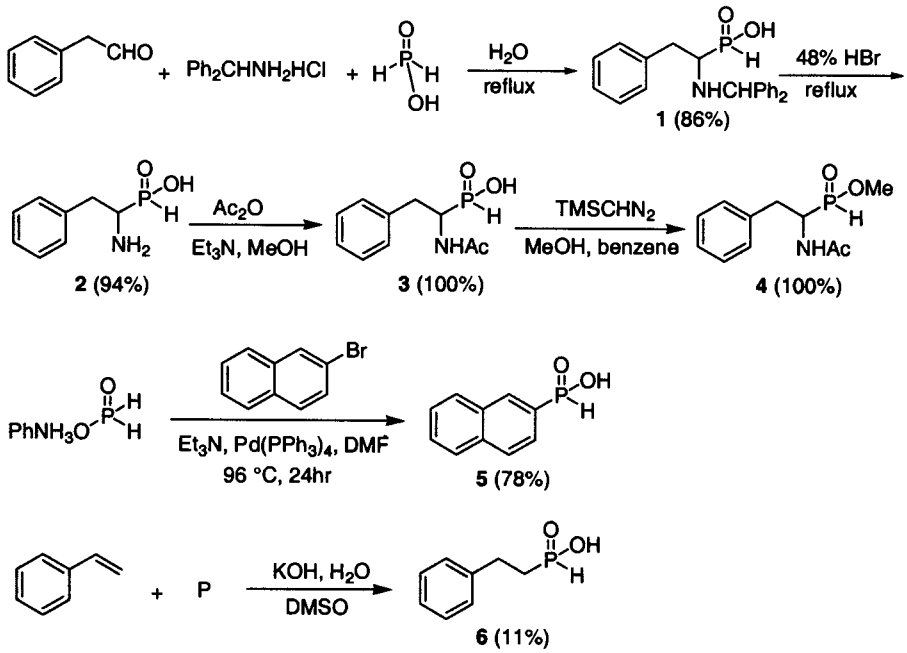
we describe the first phosphinic acid-involved asymmetric Michael addition reaction with excellent chiral induction at the α-position (P_1') of acrylate derivatives of Evans oxazolidinone type auxiliaries. We also report the isolation of optically pure diastereomers or enantiomers prepared via a Michael addition reaction by utilizing these auxiliaries.

2. Results and discussion

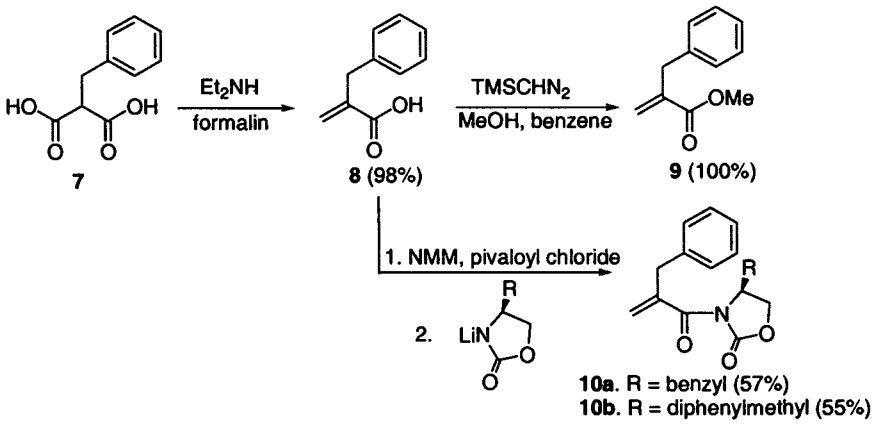
In this study, phosphinic acids, (1-(*N*-Ac-amino)-2-phenylethyl)phosphonous acid (**3**), (2-naphthalenyl)-phosphonous acid (**5**), (2-phenylethyl)phosphonous acid (**6**), hypophosphorous acid were chosen for the nucleophilic Michael addition reaction. Hypophosphorous acid (100%) was prepared from the commercially available 50% aqueous solution according to the method of Fitch [11]. As shown in Scheme 1, 1-amino-2-phenylethylphosphonous acid (**2**) was prepared in racemic form as previously described [12]. Simple acetylation of **2** with acetic anhydride and triethylamine in methanol gave racemic (1-(*N*-Ac-amino)-2-phenylethyl)phosphonous acid (**3**). Functionalized monoarylphosphinic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates. (2-Naphthalenyl)phosphonous acid (**5**) was obtained by slight modification of Montchamp's method [13]. We have obtained (2-naphthalenyl)-phosphonous acid in 78% yield by stirring the reaction mixture at 96 °C in DMF for 24 h. (2-Phenylethyl)-phosphonous acid (**6**) was prepared by the reaction of red phosphorus with styrene in basic aqueous solution [14].

The preparation of 2-substituted acrylate derivatives was carried out as summarized in Scheme 2. The diacid **7** was converted to α-benzylacrylate acid (**8**) by a Mannich reaction accompanied by in situ decarboxylation [15,16]. Acrylic acid **8** was methylated to its ester **9** with trimethylsilyl diazomethane [17]. (*S*)-4-Benzyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10a**) and (*S*)-4-diphenylmethyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10b**) were prepared by coupling the pivaloyl anhydride of acid **8** with the lithium salt of Evans type auxiliaries (57% for R = benzyl and 55% for R = diphenylmethyl). A slightly higher yield was obtained than that originally reported 49% for a similar reaction [18–20], probably due to our higher dilution conditions and/or alternate preparative HPLC conditions described in the Section 4.

In order to study the opportunity for chiral induction, it was first necessary to find mild conditions for a potential asymmetric Michael addition reaction. As summarized in Table 1, several conditions were exam-

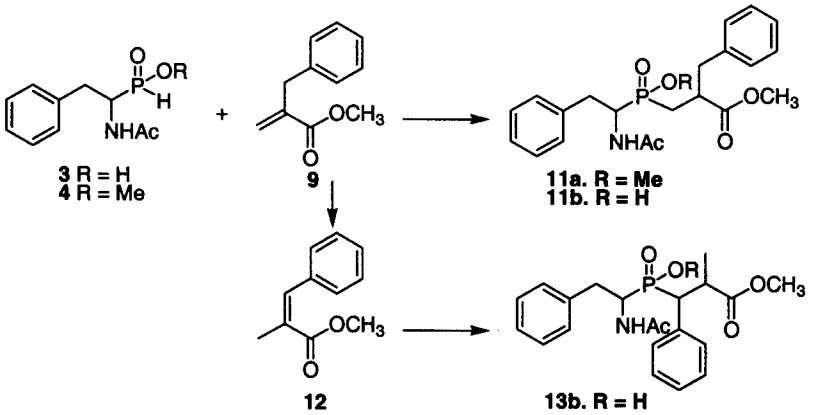


Scheme 1.



Scheme 2.

Table 1
Optimization of Michael addition reaction



Entry	Phosphinic acid	Conditions	Product	Yield (%)
1	**4**	NaOMe, r.t., overnight	**11a**	82
2	**4**	NaH, −40 °C, 3 h	**11a**	22
3	**4**	LDA, −78 °C, 3 h	**11a**	15
4	**3**	TMSCl, *i*PrNEt$_2$, 0 °C-r.t., 24 h	**11b**	94
5	**3**	HMDS, 100–110 °C, 3 h	**11b**	96
6	**3**	HMDS, >115 °C, 6 h	**13b**	67

ined in the addition of **3** or its methyl ester **4**–**9**. A number of bases were utilized for this purpose such as LDA, NaH, and NaOMe, to catalyze the Michael reaction at low temperature. This allows low temperature protonation, which is typically required in asymmetric synthesis. However, some yields were very low (15% for LDA; 22% for NaH). Sodium methoxide led to higher yields (82%), but protection of the phosphinylhydroxy group was required and poor diastereoselectivity was observed in preliminary experiments. HMDS has been widely used at elevated temperature (110 °C) to catalyze these reactions and gave an excellent yield (greater than 90%). But not surprisingly, 110 °C was also an unacceptable temperature for asymmetric induction. Under these conditions the unwanted acrylate double bond rearranged product **12** was observed. Also, to confirm the desired Michael regiochemistry achieved from **3** and **9** to yield **11**, we prepared acrylate **12** from **9** to allow the synthesis of **13b**.

After further analysis to optimize conditions, we were pleased to discover that reaction of (1-(*N*-Ac-amino)-2-phenylethyl)phosphonous acid (**3**) with TMSCl at low temperature led to a mild and versatile Michael addition to **9** that proceeded with excellent yields. Moreover, there was no need for prior protection of the phosphinylhydroxy moiety function. TMSCl was therefore used for the following studies of the asymmetric Michael addition reaction. As shown in Table 2, these conditions did in fact allow asymmetric induction via the Michael addition reaction in very high yield. Thus,

the phosphinic acid **3** was treated with TMSCl in the presence of *N*,*N*-diisopropylethylamine at room temperature for 3 h. Michael addition to **10a** was then accomplished at room temperature over 24 h followed by an ethanol quench at −10 °C to yield phosphinyl dipeptidomimetic (**16a**) (96%). We were also pleased to note that a 3:1 ratio of two diastereomers was produced. We now believe the chiral carbon at the P1′ side chain position of the phosphinyl dipeptide structure **16a** was formed preferentially in the *R* configuration and we have assigned it and related analogs as such. This stereochemical proposal is supported by the evidence presented at the end of this manuscript.

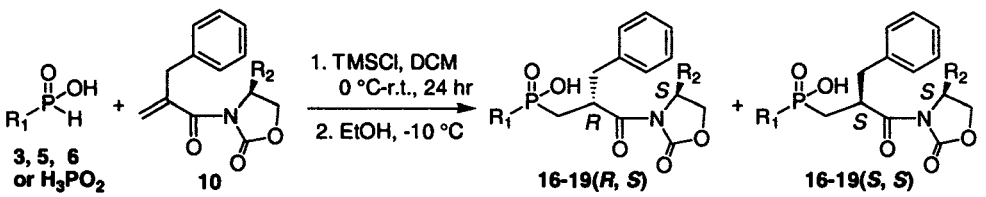
This asymmetric Michael addition reaction was thus further studied using four phosphinic acid nucleophiles **3**, **5**, **6** and hypophosphorous acid, and two auxiliary derivatives **10a** and **10b**. As shown in Table 2, most importantly, even higher asymmetric induction was achieved via usage of the diphenylmethyl auxiliary on comparison of products **16a**, **17a**, **18a**, **19a** to **16b**, **17b**, **18b**, **19b**, respectively, presumably because of the increased steric bulk directing the protonation. Note that although these results reflect products **16a** and **16b** utilizing a racemic mixture of **3**, the same ratio of asymmetric induction was obtained upon utilizing the Cbz protected form of **3** in the pure *R* configuration. Also, similar asymmetric induction was observed without a P1 stereocenter in phosphinic acids **5** and **6**.

Because of the complexity of this stereochemical analysis, we also sought crystallographic confirmation of our isomeric assignments. To readily prepare sufficient quantities of each isomer for this purpose, the HMDS procedure was used to prepare intermediates **16a**(*S*, *S*), **16a**(*R*, *S*), **17a**(*S*, *S*), **17a**(*R*, *S*), **18a**(*S*, *S*), and **18a**(*R*, *S*). Each was separated by HPLC as optically pure diastereomers or epimers in the case of **16a**. Again, the lack of asymmetric induction was observed in all cases. To determine the relative configuration of each pair of isomers and to prepare intermediates for future elongation of phosphinyl pseudodipeptides to polypeptide analogs **20**, **21**, and **22** were synthesized by hydrolysis of the resulting purified **16a**, **17a**, and **18a** with lithium hydroxide as shown in Table 3.

The isolation of purified stereoisomers allowed us to generate crystallographic evidence for the absolute configuration proposed in Tables 2 and 3. X-ray crystal analysis of compound **17a**(***R***, ***S***), which is the major product in the asymmetric Michael reaction with the TMSCl method, supports this stereochemical prediction. This data shows that in the case of the formation of **17a**(***R***, ***S***) the benzyl group on the oxazolidinone also creates enough steric bulk on one face of the double bond to favor the protonation at the opposite face of the double bond. X-ray crystal analysis and related results will be reported later. Since the diphenylmethyl oxazolidinone enhances formation of **17b**(***R***, ***S***), we propose that the *R* isomer is the preferred major isomer formed in all cases of asymmetric induction reported here.

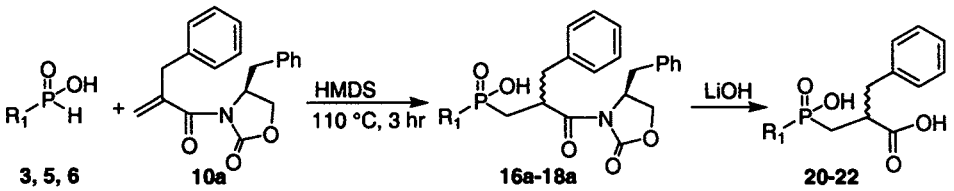
In order to rationalize the diastereoselectivity observed, we propose this Michael reaction proceeds via a stepwise process outlined in Scheme 3. The phosphorus(III) intermediate **14** is formed initially after addition of TMSCl to the cooled phosphinic acid **3** in the presence of diisopropylethylamine. Upon addition of an acrylate species, the trivalent phosphorus nucleophile (**14**) attacks the β-carbon of **10**, forming the TMS enol ether **15** as an intermediate. After 24 h, absolute ethanol was added to quench the reaction, resulting in asymmetric protonation of the TMS enol ether **15** to

Table 2
Asymmetric Michael addition reactions using different phosphinic acids and auxiliaries



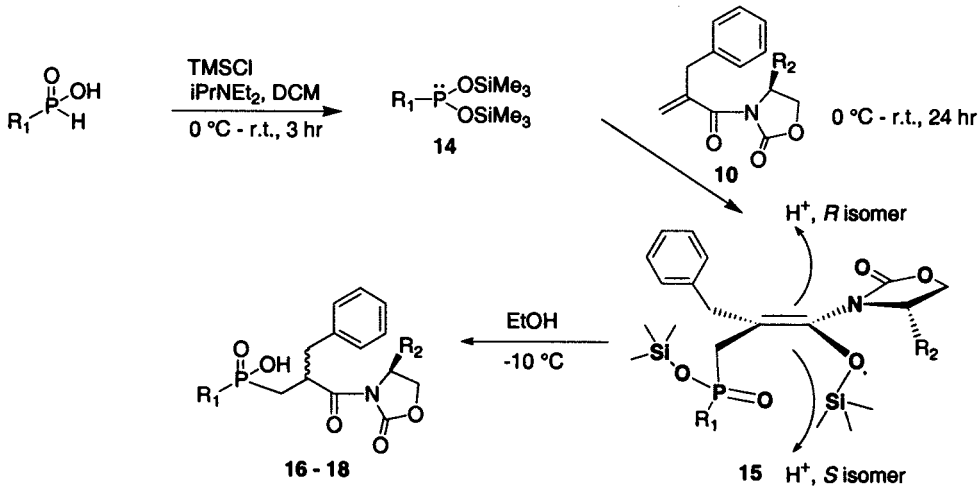
Entry	Phosphinic acid	Acrylate, R_2	Product	Yield (%)	(*R*, *S*)/(*S*, *S*)
1	**3**	$PhCH_2$	**16a**	94	3/1
2	**3**	Ph_2CH	**16b**	90	86/1
3	**5**	$PhCH_2$	**17a**	78	5/1
4	**5**	Ph_2CH	**17b**	73	55/1
5	**6**	$PhCH_2$	**18a**	91	12/1
6	**6**	Ph_2CH	**18b**	90	54/1
7	H_3PO_2	$PhCH_2$	**19a**	84	9/1
8	H_3PO_2	Ph_2CH	**19b**	78	25/1

Table 3
Diastereomers and enantiomers of phosphinyl dipeptides



Entry	Phosphinic acid	Yield (%)	*S*/*R*	$[\alpha]_D^{20}$, MeOH	
1	**3**	96	1/1	**16a**(*S*, *S*): +16.4° [a] **16a**(*R*, *S*): −14.6° [a]	**20*S***: +13.2° [a] **20*R***: −13.4° [a]
2	**5**	80	1.2/1	**17a**(*S*, *S*): +51.2° **17a**(*R*, *S*): −51.8°	**21*S***: +18.1° **21*R***: −18.0°
3	**6**	92	1/1	**18a**(*S*, *S*): +75.6° **18a**(*R*, *S*): −54.5°	**22*S***: +7.2° **22*R***: −7.4°

[a] An epimeric mixture at the P1 stereocenter exists.



Scheme 3.

Table 4
AM1 energies of intermediates **15** and products **16a** and **17b**

Product	Intermediate **15**	Energy (kcal mol^{-1})	Product isomer (P1')	Energy (kcal mol^{-1})
16b (P1 *R* epimer)	*Z*	−278.1	*S*	−180.0
	E	−275.4	*R*	−171.8
16b (P1 *S* epimer)	*Z*	−278.7	*S*	−182.3
	E	−280.5	*R*	−177.8
17b	*Z*	−217.4	*S*	−125.0
	E	−219.2	*R*	−115.8

form a chiral center at the α-position of the amide group in structure **16**. The effect of temperature on *R*/*S* ratio was also studied. In the case of **10a**, a 3:1 ratio was obtained upon addition of cold absolute ethanol at −10 °C. However, quenching the reaction mixture at −40 and −78 °C, respectively led to no better stereoselectivity, but the chemical yields were lower.

In order to examine factors contributing to the high selectivity in the formation of the *R* isomers (**16**–**18**), we have calculated semiempirical AM1 energies [21] of the *Z* and *E* isomers of the potential enol ethers **15** as well as the energies of the ***R***, ***S*** isomers of **16b** (*R* and *S* epimers at P1) and **17b** (Table 4) where the factors inducing asymmetry are clearly enhanced by the

diphenylmethyl oxazolidinone. High stereoselection favoring the *R* isomer is likely to result from protonation of the less hindered side in the *trans* olefin as depicted in **15** and consequently, we propose that the *E* olefin (with respect to the phosphinate and oxazolidinone) is the intermediate in this Michael addition. In case of the *Z* olefin, the protonation would have to occur from the more hindered face to produce the *R* isomer. Interestingly, if the *Z* olefin was formed in this reaction, its protonation would lead to the *S* isomer, since formation of the latter product would be driven by both thermodynamic and kinetic factors. As shown in Table 4, the ground state energies of the *E* and *Z* isomers are similar and do not indicate a substantial preference for the formation of the *trans* olefin. Therefore, we hypothesize that the preferred formation of **16** (*R* and *S* epimers) and **17b** results from the *E* isomer of the intermediate **15**, which is likely to be produced from a cyclic intermediate such as a phosphorane or some other silyl transfer intermediate leading to the amide and phosphinic acid oxygen atoms residing on the same face. Formation of 5-member cyclic phosphorane rings and their opening to enol ethers were documented by Evans et al. [22] in the conjugate additions of trivalent phosphorus esters to α,β-unsaturated aldehydes and ketones.

3. Conclusion

In summary, the enantioselective Michael addition of phosphinic or aminophosphinic acids to acrylate derivatives of a chiral auxiliary offers an efficient entry into a variety of phosphinic dipeptidomimetics. Aided by Evans oxazolidinone type auxiliaries, the chirality at the α-position of acrylate derivatives was stereoselectively controlled during the process of hydrolysis and protonation of the resulting TMS enol ether. Diastereomeric and enantiomeric excesses of 50–98% have been achieved through this process. Pure isomers can be isolated after separation by HPLC and used as building blocks in the synthesis of peptidomimetics.

4. Experimental

4.1. General

All reactions were carried out under Ar atmosphere. Glassware was assembled hot from the drying oven. Solvents and reagents were used as purchased from Aldrich Chemical Co., unless otherwise stated. Reactions were monitored by TLC, MS, or LC–MS. Analytical HPLC was used to determine the purity of products operated on Polaris C18-A 3 μ column (4.6 mm × 25 cm) eluted at 1 ml min^{-1} flow rate, using a linear gradient of water containing 0.1% H_3PO_4 (from 80 to 0%) and MeCN (from 20 to 100%) over 25 min, with UV detection at 214 nm. Preparative HPLC separations were performed on a Polaris C18-A 10 μ column (50 mm × 25 cm) operated at room temperature (r.t.) and eluted at 60 ml min^{-1} flow rate, using a linear gradient of water containing 0.1% TFA (from 95 to 0%) and MeCN (from 5 to 100%) over 60 min, with UV detection at 214 nm. ^{1}H-, ^{13}C- and ^{31}P-NMR were obtained using Varian 300 and referenced to CD_3OD, $CDCl_3$, or D_2O. The yields reported in this paper are isolated yields.

4.2. Preparation of phosphinic acids

4.2.1. (1-(N-Ac-amino)-2-phenylethyl)phosphonous acid (3)

(1-Diphenylmethylamino-2-phenylethyl)phosphonous acid (HCl salt form) (**1**). To a refluxing solution of diphenylmethylamine hydrochloride (43.9 g, 0.2 mol) and 50% aq. H_3PO_2 (21 ml, 0.2 mol) in H_2O (100 ml) was added a solution of 90% phenylacetaldehyde (38 ml, 0.3 mol) in H_2O (45 ml) with vigorous stirring. White precipitation appeared when the aldehyde was added, and refluxing was continued for 2 h. The mixture was cooled with an ice bath and gave a granule of solid. It was ground with C_3H_6O in a mortar, washed with cold C_3H_6O and dried under vacuum to give pure product **1** (66.6 g, 86%) as white powder. MS (ESI): m/z 352.4 [M + 1].

4.2.1.1. (1-Amino-2-phenylethyl)phosphonous acid (2). A solution of (1-diphenylmethylamino-2-phenylethyl)-phosphonous acid (**1**) (HCl salt form, 14.09 g, 36.4 mmol) in 48% aq. HBr (100 ml) of was heated at 100 °C for 2 h until two distinct phases separated. The mixture was allowed to cool to r.t., the volatile materials were evaporated under reduced pressure, and the oily residue was partitioned between water and ether. The aq. layer was washed several times with ether to remove diphenylmethyl bromide, and water was evaporated again under reduced pressure. The oily residue of the aminophosphonous acid hydrobromide was dissolved in EtOH (250 ml) and propylene oxide was added dropwise to neutralize the hydrobromide until precipitation started. The mixture was allowed to stand at r.t. overnight to complete the precipitation. The solid was collected by filtration, washed with cold EtOH and ether, and dried under vacuum to afford aminophosphonous acid **2** (6.3 g, 94%). MS (ESI): m/z 186.3 [M + 1]; m.p. 210–211 °C; ^{1}H-NMR (CD_3OD): δ 7.35 (m, 5H, Ph), 7.09 (d, $^{1}J = 531$ Hz, 1H, H–P), 3.21–3.39 (m, 1H, CH), 2.81–2.92 (m, 2H, CH_2Ph). ^{13}C-NMR (CD_3OD): 136.0, 129.2, 129.0, 127.3, 52.6 (d, $^{1}J = 90$ Hz); ^{31}P-NMR (121.27 MHz, CD_3OD): 17.15 (d, $^{1}J =$ 531 Hz).

*4.2.1.2. (1-(N-Ac-amino)-2-phenylethyl)phosphonous acid (**3**).* To an ice-water chilled solution of aminophosphonous acid **2** (200 mg, 1.09 mmol) and Et_3N (0.91 ml, 6.5 mmol) in MeOH (8 ml) was added Ac_2O (0.31 ml, 3.29 mmol) dropwise. The mixture was stirred for 1 h at r.t. The excess of Et_3N, Ac_2O and solvent were removed under high vacuum to give **3** as a colorless oil (247.0 mg, 100%). MS (ESI): m/z 228.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.18 (m, 5H, Ph), 6.94 (d, $^1J = 523$ Hz, 1H, H–P), 3.34 (m, 1H, CH), 2.69–2.81 (m, 2H, CH_2Ph), 2.01 (s, 3H, CH_3); ^{13}C-NMR δ (CD_3OD): δ 175.4, 139.0, 138.8, 129.0, 128.1, 126.1, 52.2 (d, $^1J = 100$ Hz), 32.8, 21.4; ^{31}P-NMR (CD_3OD): 27.40 (d, $^1J = 507$ Hz).

*4.2.1.3. Methyl ester of (1-(N-Ac-amino)-2-phenylethyl)phosphonous acid (**4**).* To a stirred solution of **3** (300.0 mg, 1.32 mmol) in MeOH (2 ml) and C_6H_6 (7 ml) was added trimethylsilyldiazomethane (2 M solution in hexanes, 0.73 ml, 1.45 mmol) at r.t. The mixture was stirred for 2 h at r.t. and concentrated to give the corresponding methyl ester **4** (318.0 mg, 1.32 mmol, 100%). ^{1}H-NMR (CD_3OD): δ 7.32 (m, 5H, Ph), 7.01 (d, $^1J = 557$ Hz, 1H, H–P), 3.85 (d, 3H, CH_3, $^3J = 12$ Hz), 3.35 (m, 1H, CH), 2.86–2.94 (m, 2H, CH_2Ph), 2.02 (s, 3H, CH_3); ^{31}P-NMR (CD_3OD): 30.69 (d, $^1J =$ 557 Hz).

*4.2.2. (2-Naphthalenyl)phosphonous acid (**5**) [13,23]*

4.2.2.1. Anilinium hypophosphite. Aniline (9.8 g, 105.0 mmol) was added dropwise to an aq. solution of H_3PO_2 (50 wt.%, 13.9 g, 10.9 ml) at 0 °C. The light brown solution rapidly turned into a thick slurry. It was transferred into a Buchner funnel, washed with chilled C_3H_6O and ether to give light yellow needle crystals. The filtrate was concentrated under reduced pressure, and a second crop of the product was obtained. They were combined, washed with ether and dried under high vacuum to provide anilinium hypophosphite (15.8 g, 99.2 mmol, 95%): m.p. 113.5–114.0 °C; ^{1}H-NMR (D_2O) 8.10–8.45 (br s, 3H), 7.12 (d, $^2J_{HP} = 520$ Hz, 2H), 7.0–7.4 (m, 5H); ^{31}P-NMR (D_2O) 3.7 (t, $^2J_{PH} =$ 520 Hz).

*4.2.2.2. (2-Naphthalenyl)phosphonous acid (**5**).* T solution of 2-bromonaphthalene (1.656 g, 8.0 mmol), anilinium hypophosphite (1.592 g, 10 mmol), Et_3N (3.4 ml, 24 mmol), and tetrakis(triphenylphosphine) (184 mg, 0.16 mmol) in DMF was heated at 90–96 °C for 24 h. The reaction mixture was concentrated under reduced pressure, diluted in water, washed with CH_2Cl_2. The aq. layer was acidified to pH < 1 with 1 N $KHSO_4$ (saturated with NaCl) and extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a yellow solid. It was dissolved in saturated $NaHCO_3$ aq. solution, washed with CH_2Cl_2 three times. The aq. layer was acidified to pH < 1 with 2 N HCl and extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **5** as a light yellow solid (1.198 g, 78%). MS (ESI): m/z 193.1 [M + 1]; ^{1}H-NMR (CD_3OD): δ 8.39 (d, $^3J = 16$ Hz, 1H), 8.04–8.08 (m, 2H), 7.98 (d, $^3J = 8$ Hz, 1H), 7.80–7.84 (d, $^3J = 8$ Hz, 1H), 7.69 (d, $^1J = 563$ Hz, 1H, H–P), 7.62–7.70 (m, 2H); ^{13}C-NMR (CD_3OD): 135.0, 133.3 (d, $J = 12$ Hz), 133.2, 128.7, 127.5 (d, $^2J = 19$ Hz), 127.1, 126.0, 125.9 (d, $^1J = 339$ Hz) 124.8 (d, $^2J = 15$ Hz); ^{31}P-NMR (CD_3OD): 21.91 (m + m, $^1J = 563$ Hz).

*4.2.3. (2-Phenylethyl)phosphonous acid (**6**)*

A mixture of red phosphorus (6.2 g, 0.2 mol), KOH (20 g), water (10 ml), and Me_2SO (100 ml) was heated to 53–55 °C. Styrene (4.3 ml) was added dropwise to the above solution. The reaction mixture was stirred at 60–65 °C for 3 h, cooled, diluted with water, and extracted with CH_2Cl_2. The aq. phase was acidified to pH < 1 and extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give colorless oil **6** (3.62 g, 11%). MS (ESI): m/z 171.2 [M + 1]; ^{1}H-NMR (CD_3Cl): δ 7.06 (m, 5H, Ph), 6.92 (d, $^1J = 535$ Hz, 1H, H–P), 2.70 (m, 2H) 1.82 (m, 2H); ^{13}C-NMR (CD_3Cl): 140.6, 140.4, 128.5, 128.0, 126.3, 31.5 (d, $^1J = 91$ Hz), 27.0; ^{31}P-NMR (CD_3Cl): 29.46 (m + m, $^1J = 535$ Hz).

4.3. Preparation of acrylate analogues

*4.3.1. 2-Benzyl acrylic acid (**8**)*

To a stirred solution of benzylmalonic acid (**7**) (10.0 g, 51.5 mmol) and 37% formalin (21.8 ml, 268.7 mmol) was added Et_2NH (5.3 ml, 51.5 mmol) at r.t. The solution was stirred at r.t. for 3 h and then was refluxed for additional 2 h. The reaction mixture was cooled to r.t., diluted with $CHCl_3$, and extracted with saturated aq. $NaHCO_3$. The basic aq. layer was acidified with 2 N HCl to pH < 1 and was extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **8** as a white solid (8.193 g, 98%). MS (ESI): m/z 161.3 [M − 1]; ^{1}H-NMR (CD_3Cl): δ 7.20–7.37 (m, 5H, Ph), 6.42 (br s, 1H, HC=), 5.62 (br s, 1H, HC=), 3.67 (br s, 2H, CH_2); ^{13}C-NMR (CD_3Cl): 172.5 (C=O), 139.8 (=C), 138.7, 129.3, 129.0, 128.7, 126.7 (H_2C=), 37.8.

*4.3.2. Methyl 2-benzyl acrylate (**9**)*

To a stirred solution of 2-benzyl acrylic acid (**8**) (1.0 g, 6.17 mmol) in MeOH (12 ml) and C_6H_6 (42 ml) was added trimethylsilyldiazomethane (2 N solution in hexanes, 4.0 ml, 8.02 mmol) at r.t. The mixtures was stirred for 30 min at r.t. and concentrated to give the corre-

sponding methyl ester **9** (1.086 g, 6.17 mmol, 100%). MS (ESI): m/z 177.3 [M + 1]; ^{1}H-NMR (CD_3Cl): δ 7.23–7.34 (m, 5H, Ph), 6.27 (s, 1H, HC=), 5.50 (s, 1H, HC=), 3.78 (s, 3H), 3.67 (br s, 2H, CH_2).

4.3.3. (S)-4-Benzyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10a**)

In an 100 ml round-bottom flask, pivaloyl chloride (1.5 ml, 12.3 mmol) was added to a solution of 2-benzyl acrylic acid (**8**) (2.0 g, 12.3 mmol) and *N*-methylmorpholine (1.4 ml, 12.3 mmol) in anhydrous THF (20 ml) at −78 °C under Ar. In another 100 ml round-bottom flask, *n*-BuLi, (1.6 M in hexanes, 6.4 ml, 10.2 mmol) was added to a solution of (*S*)-4-benzyl-2-oxazolidinone (1.8 g, 10.2 mmol) in anhydrous THF (20 mL) at −78 °C under Ar. Both of them were stirred for 1 h at −78 °C. The suspension of acryloyl mixed anhydride in the former flask was transferred via a cannula at −78 °C to the latter flask. The resulting mixture was stirred first at −78 °C for 2 h and then at r.t. for 2 h. The mixture was diluted in saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give a white solid. It was further purified on preparative HPLC to provide **10a** (1.87 g, 5.81 mmol, 57%) as white crystals. MS (ESI): m/z 322.3 [M + 1]; ^{1}H-NMR (CD_3Cl): δ 7.15–7.38 (m, 10H, 2Ph), 5.61 (s, 1H, HC=), 5.41 (br s, 1H, HC=), 4.62 (m, 1H, NCH); 4.14 (m, 2H, OCH_2); 3.81 (s, 2H, $=CCH_2Ph$); 2.56–3.24 (dd + dd, $^2J = 180$ Hz, $^3J = 13$ Hz, 2H, $PhCH_2$); ^{13}C-NMR (CD_3Cl): 170.5 (C=O), 153.2, 143.8, 137.6, 135.1, 129.6, 129.2, 128.8, 127.6, 127.0, 122.0, 66.8, 55.5, 39.3, 37.7.

4.3.4. (S)-4-Diphenylmethyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10b**)

Compound **10b** was synthesized by the same method as used for **10a** on 10.2 mmol scale. Compound **10b** (2.24 g, 5.63 mmol, 55%) was obtained as white crystals. MS (ESI): m/z 398.3 [M + 1]; ^{1}H-NMR (CD_3Cl): δ 7.18–7.38 (m, 15H, 3Ph), 5.33 (s, 1H, HC=), 5.20 (br s, 1H, HC=), 5.40 (m, 1H, NCHP); 4.56 (dd, $^2J = 111$ Hz, $^3J = 6$ Hz 2H, OCH_2); 3.66 (d, $^3J = 16$ Hz, 1H, $CHPh_2$); 3.51 (s, 2H, $PhCH_2$); ^{13}C-NMR (CD_3Cl): 170.3 (C=O), 153.0, 143.1, 139.7, 138.5, 137.6, 129.8, 129.5, 129.3, 129.0, 128.7, 128.1, 127.5, 127.3, 126.9, 121.6, 65.7, 56.6, 52.1, 39.0.

4.4. Study of optimal reagents and conditions for Michael addition reaction

4.4.1. NaOMe

Sodium methoxide (25 wt.% solution in MeOH, 0.15 ml, 0.27 mmol) was added dropwise to a solution of **4** (65.3 mg, 0.27 mmol) in MeOH (2 ml) at 0 °C. The mixture was stirred at r.t. until gas evolution ceased, and then cooled down to 0 °C. Methyl 2-benzyl acrylate (**9**) (61.8 mg, 0.3 mmol) in MeOH (1 ml) was then added slowly. The mixture was stirred at r.t. overnight, and then it was partitioned between water and CH_2Cl_2. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **11a** as a white solid (92.5 mg, 22.2 mmol, 82%).

4.4.2. NaH

The reaction was performed as in Section 4.4.1 utilizing NaH as coupling reagent. Yield 22%.

4.4.3. LDA

The reaction was performed as in Section 4.4.1 utilizing LDA as coupling reagent. Yield 15%.

4.4.4. TMSCl

To an ice-cold solution of (1-(*N*-Ac-amino)-2-phenylethyl)phosphonous acid (**3**) (123 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (4 ml) were added *N*,*N*-diisopropylethylamine (0.42 ml, 2.43 mmol) and chlorotrimethylsilane (0.31 ml, 2.43 mmol) under an Ar atmosphere. The mixture was stirred for 3 h at r.t. The mixture was then cooled to 0 °C, and methyl 2-benzyl acrylate (**9**) (105.6 mg, 0.60 mmol) was added dropwise. The solution was stirred at r.t. for 24 h. The mixture was again cooled to 0 °C and absolute EtOH (0.44 ml) was added to quench the reaction. After 30 min, the solvent was removed and the residue was subjected to separation on preparative HPLC. The final product **11b** (227.3 mg, 0.51 mmol, 94%) was obtained as white solid.

4.4.5. HMDS

A mixture of (1-(*N*-Ac-amino)-2-phenylethyl)-phosphonous acid (**3**) (246.0 mg, 1.08 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (0.92 ml, 5.40 mmol) was heated at 110 °C for 1 h under Ar, then methyl 2-benzyl acrylate (**9**) (211.2 mg, 1.2 mmol) was added dropwise. The resulting mixture was stirred at 105–110 °C for additional 3 h and cooled to 70 °C. Ethanol (2 ml) was added and the mixture was cooled to r.t. slowly. The solvent was removed under vacuum, the residue was dissolved in MeOH (5 ml) and purified on preparative HPLC. The final product **11b** (419.6 mg, 1.04 mmol, 96%) was obtained as a white solid. MS (ESI): m/z 404.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.16–7.30 (m, 10H, 10Ph), 4.52 (m, 1H, PCHN), 3.60 (ss, 3H, OCH_3), 3.15–3.26 (m, 1H, CHCO), 2.73–3.15 (m, 4H, $2PhCH_2$), 1.80–2.30 (m, 2H, PCH_2CCO), 1.79 (ss, 3H, CH_3); ^{13}C-NMR (CD_3OD): 175.4 (O=C–O), 171.8 (CH_3CO), 138.3, 137.6, 129.1, 129.0, 128.4, 128.3, 126.7, 126.6, 51.5, 50.3 (d, $^1J = 104$ Hz, PCN), 41.5, 39.5, 32.9, 28.2 (d, $^1J = 90$ Hz, PCCCO), 21.2; ^{31}P-NMR (CD_3OD): 52.8, 52.4.

The reaction mixture (on a scale of 0.84 mmol) was heated at above 115 °C for 6–8 h. The rearrangement product **13b** (146.3 mg, 0.36 mmol, 67%) was separated. MS (ESI): m/z 404.3 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.16–7.30 (m, 10H, 2Ph), 4.52 (m, 1H, PCHN), 3.60 (ss, 3H, OCH_3), 3.15–3.26 (m, 1H, CHCO), 2.73–3.15 (m, 4H, $2PhCH_2$), 1.80–2.30 (m, 2H, PCH_2CO), 1.79 (ss, 3H, CH_3); ^{13}C-NMR (CD_3OD): 175.6 (O=C–O), 171.8 (CH_3CO), 138.1, 137.6, 129.0, 128.9, 128.4, 128.3, 128.2, 126.6, 126.5, 57.2, 51.2, 50.3 (d, $^1J = 104$ Hz, PCN), 41.5, 39.8, 32.9, 28.3 (d, $^1J = 90$ Hz, PCCCO), 21.1, 17.2; ^{31}P-NMR (CD_3OD): 52.7, 52.3.

4.5. Studies of asymmetric Michael addition reactions with (S)-(−)-4-benzyl-2-oxazolidinone or (S)-(−)-4-diphenylmethyl-2-oxazolidinone

4.5.1. General procedure

To an ice-cold solution of (1-(*N*-Ac-amino)-2-phenylethyl)phosphonous acid (**3**), (2-naphthalenyl)phosphonous acid (**5**), (2-phenylethyl)phosphonous acid (**6**), or H_3PO_2 (0.081 mmol) in anhydrous CH_2Cl_2 (1 ml) were added *N*,*N*-diisopropylethylamine (63 μl, 0.36 mmol) and chlorotrimethylsilane (46 μl, 2.43 mmol) under an Ar atmosphere. The mixture was stirred for 3 h at r.t. Then, the mixture was cooled to 0 °C, and (*S*)-4-benzyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10a**) or (*S*)-4-diphenylmethyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10b**) (0.097 mmol) was added dropwise. The solution was allowed to warm up slowly and stirred at r.t. for 24 h. The mixture was again cooled to 0 °C and absolute EtOH (66 μl) was used to quench the reaction. After 30 min, the product was isolated and the ratio of two isomers was determined with LC–MS and analytical HPLC.

4.5.2. Racemization of *11b*

The reaction mixture of Section 4.4.4 was not subjected to separation after removal of solvent. Instead, it was heated at 105–110 °C with three equivalents of 1,1,1,3,3,3-hexamethyldisilazane for 3 h, and then cooled to r.t. The product and the ratio of two isomers were determined with LC–MS and analytical HPLC.

4.6. Synthesis of diastereomerically or enantiomerically pure phosphinyl dipeptidomimetics

4.6.1. General coupling procedure

A mixture of phosphinic acid **3**, **5** or **6** (0.63 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (3.2 mmol) was heated at 110 °C for 1 h under Ar, then (*S*)-4-benzyl-3-(2-benzyl-prop-2-enoyl)-1,3-oxazolidin-2-one (**10a**) (0.76 mmol) was added dropwise. The resulting mixture was stirred at 105–110 °C for additional 3 h and cooled to 70 °C. Absolute EtOH (1.5 ml) was added and the mixture was cooled to r.t. slowly. The solvent was removed under vacuum, the residue was dissolved in MeOH (4 ml) and purified on preparative HPLC. Two diastereomers were separated as twin peaks and collected, respectively.

16a(***S***, ***S***): MS (ESI): m/z 549.1 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.20–7.38 (m, 15H, 3Ph), 4.54 (m, 1H, NCH), 4.08 (m, 2H, OCH_2); 4.00 (m, 1H, CHCO), 3.33 (m, 2H, NCH_2Ph); 2.70–2.90 (m, 4H, $2PhCH_2$), 2.04 (s, 3H, CH_3), 1.90–2.00 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 175.2 (O=C–N), 172.0 (CH_3–C=O), 153.9 (N–COO), 138.4, 136.2, 129.5, 129.3, 129.2, 129.0, 128.7, 128.4, 128.3, 126.9, 126.7, 126.5, 66.2, 56.0, 50.8 (d, $^1J = 106$ Hz, NCP), 39.4, 37.2, 33.1, 28.4 (d, $^1J =$ 100 Hz, PCC), 21.3; ^{31}P-NMR (CD_3OD): 53.1, 52.1; Analytical HPLC $t_R = 13.56$ min.

16a(***R***, ***S***): MS (ESI): m/z 549.3 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.11–7.36 (m, 15H, 3Ph), 4.58 (m, 1H, NCH), 4.20 (m, 2H, OCH_2); 3.68 (m, 1H, CHCO), 3.18 (m, 2H, NCH_2Ph); 2.60–2.85 (m, 4H, $2PhCH_2$), 2.02 (s, 3H, CH_3), 1.80–2.00 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 175.4 (O=C–N), 172.0 (CH_3–C=O), 154.1 (N–COO), 138.2, 135.7, 129.6, 129.5, 129.0, 128.9, 128.7, 128.5, 128.4, 127.0, 126.8, 126.5, 66.5, 55.5, 50.8 (d, $^1J = 106$ Hz, NCP), 39.2, 37.4, 33.0, 28.2 (d, $^1J =$ 100 Hz, PCC), 21.2; ^{31}P-NMR (CD_3OD): 52.6, 52.2; Analytical HPLC $t_R = 14.24$ min.

17a(***S***, ***S***): MS (ESI): m/z 514.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.00–8.26 (m, 17H, NaPh + 2Ph), 4.56 (m, 1H, NCH), 4.18 (m, 1H, CHCO), 3.65 (m, 2H, OCH_2); 2.60–3.00 (m, 4H, $2PhCH_2$), 1.90–2.10 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 174.6 (O=C–N), 153.1 (N–COO), 137.5, 135.1, 133.6, 130.0, 129.5, 129.3, 129.0, 128.5, 128.3, 127.9, 126.9, 126.5, 66.0, 55.8, 41.1, 38.9, 37.2, 32.7 (d, $^1J = 100$ Hz, PCC), 21.2; ^{31}P-NMR (CD_3OD): 41.7; Analytical HPLC $t_R = 16.82$ min.

17a(***R***, ***S***): MS (ESI): m/z 514.2 [M + 1]; ^{1}H-NMR (CD_3Cl): δ 6.90–8.23 (m, 17H, NaPh + 2Ph), 4.48 (m, 1H, NCH), 4.06 (m, 1H, CHCO), 3.93 (m, 2H, OCH_2); 2.50–3.00 (m, 4H, $2PhCH_2$), 2.04 (m, 2H, PCH_2); ^{13}C-NMR (CD_3Cl): 174.2 (O=C–N), 153.6 (N–COO), 137.8, 135.5, 133.4, 129.4, 128.9, 128.6, 128.5, 128.3, 128.1, 127.7, 127.0, 126.7, 126.5, 126.4, 66.0, 55.2, 39.9, 39.1, 37.1, 30.6 (d, $^1J = 100$ Hz, PCC), 21.2; ^{31}P-NMR (CD_3Cl): 40.4; Analytical HPLC $t_R = 17.30$ min.

18a(***S***, ***S***): MS (ESI): m/z 492.3 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.19–7.36 (m, 15H, 3Ph), 4.54 (m, 1H, NCH), 4.09 (m, 2H, OCH_2); 3.88 (m, 1H, CHCO), 2.98–3.30 (m, 2H, Ph CH_2CHN); 2.70–2.85 (m, 2H, $PhCH_2$), 2.44 (m, 2H, $PCCH_2$), 2.09 (m, 2H, PCH_2C) 1.83 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 174.9 (O=C–N), 154.0 (N–COO), 138.2, 136.0, 129.5, 129.2, 128.6, 128.5, 128.4, 128.0, 127.0, 126.8, 126.2, 66.1, 55.9, 40.5, 39.3, 37.1, 30.8 (d, $^1J = 101$ Hz, PCCCO), 30.2, 28.5 (d, $^1J = 101$ Hz, PCCC), 21.2; ^{31}P-NMR (CD_3OD): 52.7; Analytical HPLC $t_R = 16.60$ min.

18a(*R*, *S*): MS (ESI): m/z 492.3 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.11–7.50 (m, 15H, 3Ph), 4.75 (m, 1H, NCH), 4.30 (m, 1H, CHCO), 4.18 (m, 2H, OCH_2), 2.95–3.20 (m, 2H, $PhCH_2$), 2.62–2.82 (m, 2H, $PCCH_2$), 2.36 (m, 2H, $PCCH_2$), 1.97 (m, 2H, PCH_2C) 1.79 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 175.2 (O=C–N), 154.4 (N–COO), 138.6, 135.8, 129.5, 129.2, 128.6, 128.5, 128.0, 127.0, 126.8, 126.2, 66.4, 55.4, 40.5, 39.1, 37.3, 30.8 (d, $^1J = 101$ Hz, PCCCO), 30.2, 28.1 (d, $^1J = 101$ Hz, PCCC), 21.2; ^{31}P-NMR (CD_3OD): 52.4; Analytical HPLC $t_R = 17.09$ min.

4.6.2. General hydrolysis procedure

Compounds **16**, **17**, or **18** (0.23 mmol) was dissolved in anhydrous THF (3 ml) and the solution was cooled to 0 °C. LiOH (0.69 mmol) in water (1 ml) was added. The mixture was stirred at r.t. for 2 h, acidified with 3 N HCl to pH 1–3, and extracted with EtOAc. The combined organic layers were concentrated, and the residue was subjected to separation on HPLC.

20*S*: MS (ESI): m/z 390.1 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.19–7.34 (m, 10H, 10Ph), 4.48 (m, 1H, PCHN), 3.20–3.26 (m, 1H, CHCO), 2.73–3.15 (m, 4H, $2PhCH_2$), 1.80–2.20 (m, 2H, PCH_2CCO), 1.79 (ss, 3H, CH_3); ^{13}C-NMR (CD_3OD): 176.5 (O=C–O), 171.7 (CH_3CO), 138.6, 137.6, 129.2, 128.9, 128.3, 128.2, 127.8, 126.9, 126.5, 50.4 (d, $^1J = 104$ Hz, PCN), 41.0, 39.0, 33.0, 27.6 (d, $^1J = 90$ Hz, PCCCO), 21.1; ^{31}P-NMR (CD_3OD): 49.1, 48.9; Analytical HPLC $t_R =$ 11.87 min. Anal. Calc. for $C_{20}H_{24}NO_5P{\cdot}CH_3COOH$: C, 52.48; H, 4.97; N, 2.78. Found: C, 52.75; H, 5.23; N, 2.97%.

20*R*: MS (ESI): m/z 390.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.15–7.38 (m, 10H, 10Ph), 4.48 (m, 1H, PCHN), 3.20–3.26 (m, 1H, CHCO), 2.74–3.15 (m, 4H, $2PhCH_2$), 1.84–2.26 (m, 2H, PCH_2CCO), 1.79 (ss, 3H, CH_3); ^{13}C-NMR (CD_3OD): 176.4 (O=C–O), 171.5 (CH_3CO), 138.6, 137.6, 129.1, 129.0, 128.4, 128.2, 127.8, 126.6, 126.5, 50.4 (d, $^1J = 104$ Hz, PCN), 41.4, 39.6, 33.0, 28.0 (d, $^1J = 90$ Hz, PCCCO), 21.1; ^{31}P-NMR (CD_3OD): 49.2, 48.9; Analytical HPLC $t_R =$ 11.93 min. Anal. Calc. for $C_{20}H_{24}NO_5P{\cdot}CH_3COOH$: C, 52.48; H, 4.97; N, 2.78. Found: C, 52.94; H, 5.06; N, 3.14%.

21*S*: MS (ESI): m/z 355.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.00–8.40 (m, 12H, Naph + Ph), 3.02 (m, 1H, CHCO), 2.90 (m, 2H, $PhCH_2$), 2.04–2.54 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 175.1 (O=C–O), 138.3, 135.6, 133.6, 129.0, 128.9, 128.3, 127.8, 126.9, 126.5, 41.7, 39.4, 31.7 (d, $^1J = 104$ Hz, PCC); ^{31}P-NMR (CD_3OD): 40.6; Analytical HPLC $t_R = 13.73$ min. Anal. Calc. for $C_{20}H_{19}O_4P{\cdot}2H_2O$: C, 61.53; H, 5.89. Found: C, 61.41; H, 6.09%.

21*R*: MS (ESI): m/z 355.2 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.00–8.40 (m, 12H, Naph + Ph), 2.89 (m, 1H, CHCO), 2.68 (m, 2H, $PhCH_2$), 2.04–2.60 (m, 2H, PCH_2); ^{13}C-NMR (CD_3OD): 174.8 (O=C–O), 138.3, 135.6, 132.8, 129.3, 129.0, 128.9, 128.6, 128.5, 128.3, 127.8, 127.0, 126.5, 126.2, 42.6, 40.0, 31.8 (d, $^1J = 104$ Hz, PCC); ^{31}P-NMR (CD_3OD): 40.8; Analytical HPLC $t_R = 13.72$ min. Anal. Calc. for $C_{20}H_{19}O_4P{\cdot}0.3H_2O$: C, 66.78; H, 5.45. Found: C, 66.68; H, 5.49%.

22*S*: MS (ESI): m/z 333.1 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.20–7.35 (m, 10H, 2Ph), 3.04 (m, 1H, CHCO), 2.70–2.88 (m, 2H, $PhCH_2$), 2.12–2.45 (m, 2H, $PCCH_2Ph$), 1.96–2.04 (m, 2H, PCH_2CCO), 1.80 (m, 2H, PCH_2CPh); ^{13}C-NMR (CD_3OD): 176.5 (O=C–O), 141.5, 141.3, 138.5, 129.1, 128.5, 128.4, 128.0, 126.6, 126.2, 41.7, 39.6, 39.4, 31.7 (d, $^1J = 90$ Hz, PCCCO), 29.8 (d, $^1J = 91$ Hz, PCCPh), 27.7; ^{31}P-NMR (CD_3OD): 52.6; Analytical HPLC $t_R = 14.09$ min. Anal. Calc. for $C_{18}H_{21}O_4P{\cdot}0.4H_2O$: C, 63.68; H, 6.42. Found: C, 63.62; H, 6.31%.

22*R*: MS (ESI): m/z 333.1 [M + 1]; ^{1}H-NMR (CD_3OD): δ 7.20–7.35 (m, 10H, 2Ph), 3.08 (m, 1H, CHCO), 2.70–2.90 (m, 2H, $PhCH_2$), 2.12–2.28 (m, 2H, $PCCH_2Ph$), 1.95–2.06 (m, 2H, PCH_2CCO), 1.81 (m, 2H, PCH_2CPh); ^{13}C-NMR (CD_3OD): 176.4 (O=C–O), 141.5, 141.3, 138.5, 129.1, 128.5, 128.4, 128.0, 126.6, 126.2, 41.7, 39.7, 39.6, 31.3 (d, $^1J = 90$ Hz, PCCCO), 29.8 (d, $^1J = 91$ Hz, PCCPh), 27.7; ^{31}P-NMR (CD_3OD): 52.7; Analytical HPLC $t_R = 14.07$ min. Anal. Calc. for $C_{18}H_{21}O_4P{\cdot}0.4H_2O$: C, 63.68; H, 6.42. Found: C, 63.54; H, 6.25%.

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