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Temporary Protection of *H*-Phosphinic Acids as a Synthetic Strategy

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H-Phosphinates obtained through various methodologies are protected directly by the reaction with triethyl orthoacetate. The resulting products can be manipulated easily, and various synthetic reactions are presented. For example, application to the synthesis of aspartate transcarbamoylase (ATCase) or kynureninase inhibitors are illustrated. Other reactions, such as Sharpless' asymmetric dihydroxylation, or Grubbs' olefin cross-metathesis are also demonstrated.
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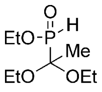
Introduction

Gallagher, and soon afterwards chemists at Ciba-Geigy (formerly) have introduced and developed an ingenious family of reagents in which one P–H bond of hypophosphorous acid (HPA, H_3PO_2, **1**) is masked temporarily and then re-introduced in a later step.[1] This allows selective reactions and solves the problem of disubstitution of the two reactive P–H bonds in HPA. We have been referring to these reagents as "Ciba-Geigy reagents" [ethyl 1,1-(diethoxyethyl)- and 1,1-(diethoxymethyl)-*H*-phosphinates, $RC(OEt)_2P(O)(OEt)H$, R = Me, H; **2** and **3**, respectively], in keeping with their historical origins. Reagents **2** and **3** have permitted the synthesis of many phosphinic acid derivatives through alkylation, and they have been used rather extensively.[2] Reagent **2** is often superior to reagent **3** because cleavage of the acetal functionality takes place under milder conditions and without cleavage of the P(O)OEt ester group.[1d]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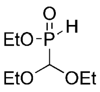
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Over the past ten years, we have developed several reactions for the synthesis of *H*-phosphinates, directly from hypophosphorous precursors (HPA, anilinium and sodium hypophosphites, alkyl phosphinates, etc.).[3] Many of these reactions provide an environmentally benign access to *H*-phosphinates, because halogenated compounds and/or stoichiometric strong bases are avoided, the reactions proceed with low loadings of transition-metal catalysts or with a radical initiator, and either no by-product is created (addition/hydrophosphinylation) or water is formed (condensation/cross-coupling). As a result, many *H*-phosphinates are now accessible directly, through routes unavailable to the Ciba-Geigy reagents. However, *H*-phosphinates are often not compatible with many reactions (oxidation/reduction, etc.) that would modify the carbon chain, so a temporary protection scheme is sometimes necessary. We recently reported one solution to this problem, based on borane complexes.[4] Because our methodologies provide compounds which cannot be made easily (or efficiently) from reagents **2** or **3**, we decided to investigate a protection strategy based on acetals. Perhaps surprisingly, few reports have described the reaction of *H*-phosphinates with orthoesters. There is only one reference that describes the reaction of a single *H*-phosphinic acid with triethyl orthoformate,[5] and none with triethyl orthoacetate (Table 1).

Table 1. Literature references to access protected phosphinates.[a]

	H_3PO_2	R_2PCl	RPO_2H_2	$RP(O)(OR^1)H$
$(EtO)_3CH$	[1]	[7]	[5]	[1a,1b,8]
$(EtO)_3CMe$	[1]	[7]	this work	[1g,9]
$H_2C=C(OEt)_2$	[6]	–	–	[10]
$TIPSCl/BH_3$	[4]	–	[4]	[4]

[a] See references.

During the synthesis of an aspartate transcarbamoylase (ATCase) inhibitor, we recently were confronted with the need to protect cinnamyl-*H*-phosphinic acid before an ozonolysis step, and we successfully employed triethyl orthoacetate to prepare **4** in excellent yield [Equation (1)].[11] We realized that this strategy would be synthetically useful, and this prompted the present study on the direct synthesis of various ethyl (1,1-diethoxyethyl)phosphinates from *H*-phosphinic acids, and some of their reactivity.

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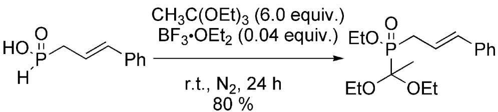

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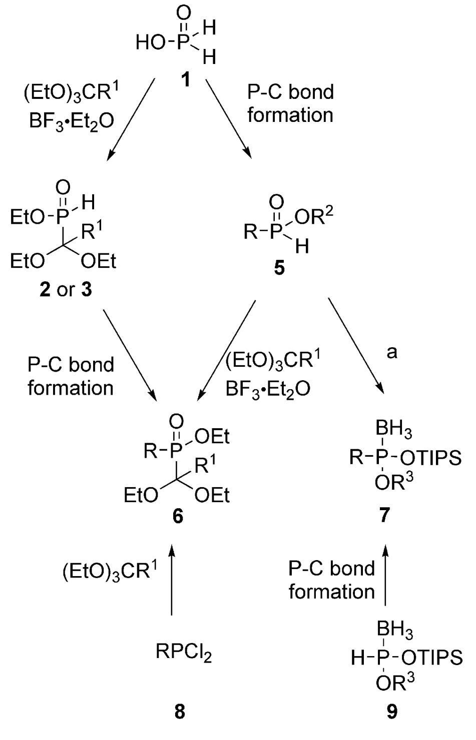
(1)

Herein, we report on the reaction of *H*-phosphinic acids with triethyl orthoacetate, as well as some subsequent transformations not previously exploited in the literature. The synthetic transformations illustrated include oxidations (ozonolysis, epoxidation, Sharpless' asymmetric dihydroxylation), reductions (hydrogenation, hydroboration), Buchwald–Hartwig amination, and olefin cross-metathesis. All these reactions are not compatible with free P–H bonds, at least in our hands.

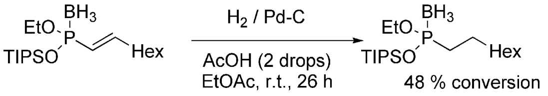
Results and Discussion

The advantages of our strategy (Scheme 1), over the use of the Ciba-Geigy reagents, stems from the much wider availability of *H*-phosphinates **5** using our methodologies, as well as the more practical nature of using triethyl orthoacetate on *H*-phosphinates **5** instead of HPA **1**, or the simpler purification of the products **5** as opposed to purifying **2** and **3**. Thus, although the two strategies are only differing in the order of the steps, the limited transformations available from **2** (or **3**) to compounds **6** are narrowing the scope of these reagents. For example, **2** and **3** can be alkylated using a strong base and an electrophile, they can be silylated and alkylated, and some cross-coupling chemistry has been reported (with high loadings of palladium catalyst).



Scheme 1. Strategies for the synthesis of protected phosphinates. R^1 = H, Me; R^2 = H, Et; R^3 = TIPS, Et. [a] (i) TIPSCl/Et_3N (1.5/1.6 equiv.), CH_3CN, 0 °C to room temp., 14 h; (ii) BH_3·Me_2S (2.0 equiv.), CH_3CN, room temp., 5 h.

Even our protecting strategy based on phosphonite–borane complexes **7** obtained either from **5** or **9** (Scheme 1),[4] is not competitive because, for example, the simple hydrogenation of an alkene is sluggish [Equation (2)], and if the same reaction is conducted in methanol, decomplexation of the borane takes place exclusively.



(2)

The protection of dichlorophosphanes **8** (Scheme 1 and Table 1) has been used, especially with $ClCH_2PCl_2$, but the lack of availability of these compounds is a significant limitation (in fact, **8** can be made from **5**, R^2 = H).

1. Synthesis of Phosphinate Acetals 6 from *H*-Phosphinates 5

Because the reaction of *H*-phosphinic acids with triethyl orthoacetate has not been described previously,[12] we decided to investigate its scope. Table 2 shows the results of this study. All the substrates are readily available through various methodologies we have developed. Isolated yields of protected acetals range from moderate to good (41–80%) for a wide range of functionalized substrates.

As described for other phosphinylidene-containing compounds, BF_3·Et_2O in a sub-stoichiometric amount was satisfactory in general (Method A, Table 1). In some cases, a small amount of ytterbium triflate also gave good results, especially in hydroxy-containing substrates. In this case, some acetate is directly obtained as a mixture with the alcohol, so acetylation was conducted on the crude reaction mixture. With alcohol-containing substrates, partial esterification was observed, and acetylation was conducted to drive the reaction to completion (Method E). With BF_3·Et_2O, a full equivalent was used for alcohols (Method D).

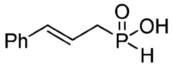
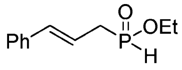
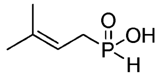
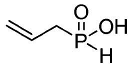
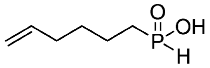
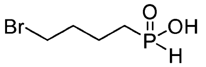
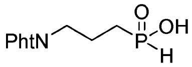
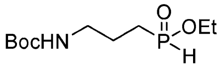
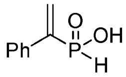
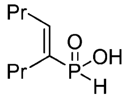
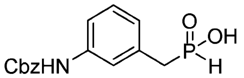
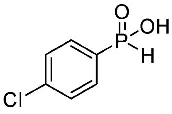
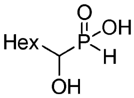
Triethyl orthoformate is less satisfactory (Method B), but only useful in cases where the *H*-phosphinic acid intermediate is ultimately desired because selective deprotection is problematic.[2] Attempts at using the literature condition (*p*TosOH),[5] or BF_3·Et_2O, did not give good results.

2. Synthetic Applications with Compounds 6

Several reactions were tried on protected ethyl *H*-phosphinates **6** (Schemes 2 and 3).

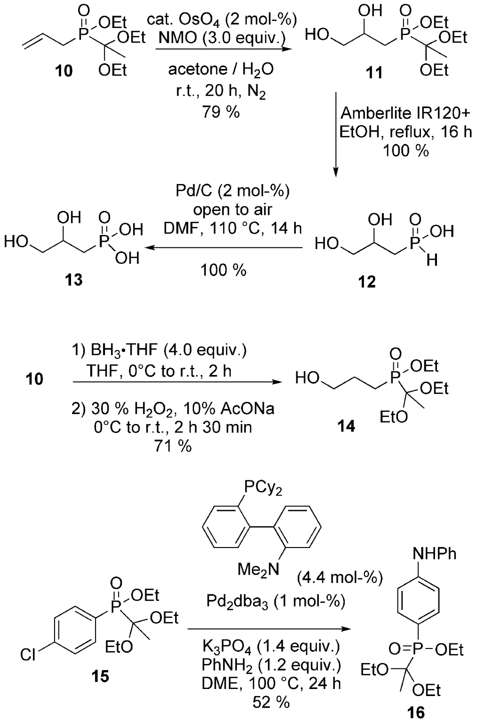
Dihydroxylation of allyl-*H*-phosphinate **10** (Scheme 2) proceeds in good yield to afford diol **11**. Compound **11** can be used to prepare phospholipid analogs, and this will be investigated in future work. Hydrolysis of **11** afforded *H*-phosphinate **12** in quantitative yield. Diol **12** was also oxidized using our catalytic process[3h] to afford phosphonic

Table 2. Protection of *H*-phosphinates.

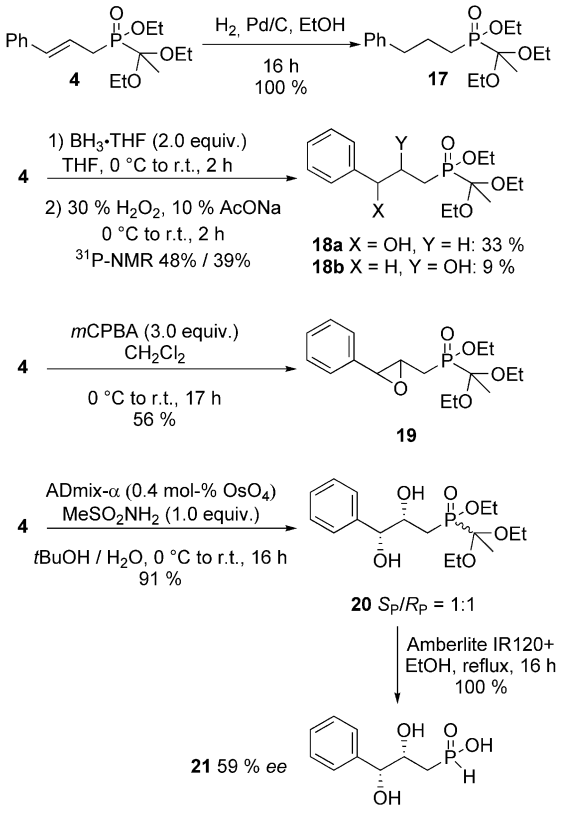
Entry	Phosphinate	Conditions[a]	Yield (%)[b]
1		A	80
		B	60
		C	37[c]
2		A	67
		B	20[c]
3		A	64
4		A	50
5		A	53
6		A	50
7		A	55
8		A	41
9		A	74
10		A	69
11		A	60
12		A	76
13		D	58[d]
		E	74[d]

[a] Method A: $BF_3{\cdot}Et_2O$ (0.2 or 0.5 equiv.), $CH_3C(OEt)_3$ (6.0 equiv.), room temp., N_2, 16–24 h; Method B: $HC(OEt)_3$ (60 equiv.), reflux, N_2, 24 h; Method C: $Yb(OTf)_3$ (3 mol-%), $CH_3C(OEt)_3$ (6.0 equiv.), THF (0.4 M), room temp., N_2, 22 h; Method D: $BF_3{\cdot}Et_2O$ (1.0 equiv.), $CH_3C(OEt)_3$ (6.0 equiv.), room temp., N_2, 4 h then at 0 °C, pyridine (10.0 equiv.) and Ac_2O (5.0 equiv.), room temp., N_2, 4 h; Method E: $Yb(OTf)_3$ (3 mol-%), $CH_3C(OEt)_3$ (6.0 equiv.), room temp., N_2, 3 h then at 0 °C, pyridine (10.0 equiv.) and Ac_2O (5.0 equiv.), room temp., N_2, 4 h. [b] Isolated yields (unless otherwise noted). [c] NMR yield. [d] Acetate.

acid **13**. Hydroboration/oxidation of **10** proceeded uneventfully to afford alcohol **14** in 71% yield. Another important reaction (Scheme 2) is the palladium-catalyzed cross-coupling of chloride **15**. Buchwald–Hartwig amination took place in moderate yield to afford aniline derivative **16**. Because *H*-phosphinates can undergo oxidation or cross-coupling, protection of the P–H functionality is necessary to perform these reactions.



Scheme 2. Dihydroxylation, hydroboration, and Buchwald–Hartwig amination.



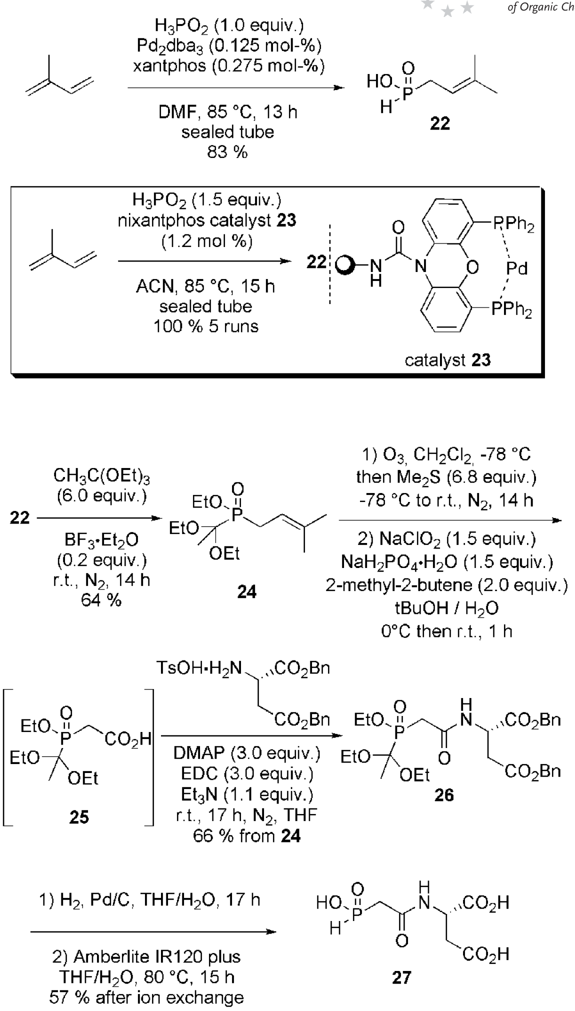
Scheme 3. Reactions of compound **4**.

A series of reactions was performed on ethyl cinnamyl-1,1-(diethoxy)ethylphosphinate (**4**) (Scheme 3). Unlike the sluggish hydrogenation of borane complexes [Equation (2)], hydrogenation of **4** under standard conditions takes place in quantitative yield to produce **17**. The presence of a phosphinylidene functionality P(O)H seems to be incompatible with hydrogenation as we have never been able to conduct the heterogeneous hydrogenation of *H*-phosphinic acids or esters, most likely because of complexation to Pd and poisoning of the catalyst. Hydroboration of **4** gave a mixture of regioisomers **18** (97% NMR yield) in low yield after chromatographic separation of each isomer (**18a** and **18b**). On the other hand, epoxidation gave racemic **19** in moderate yield. Finally, Sharpless' asymmetric dihydroxylation[13] gave the corresponding diol **20** in good yield. Interestingly, no kinetic resolution was observed in the formation of **20**. As in Scheme 2, acidic hydrolysis delivered the diol **21** in quantitative yield and 59% *ee*. The absolute configuration was assigned based on the Sharpless–Corey models.[14] Enantiomeric excess determination was based on the formation of a diastereomeric salt with quinine and ^{31}P NMR analysis.

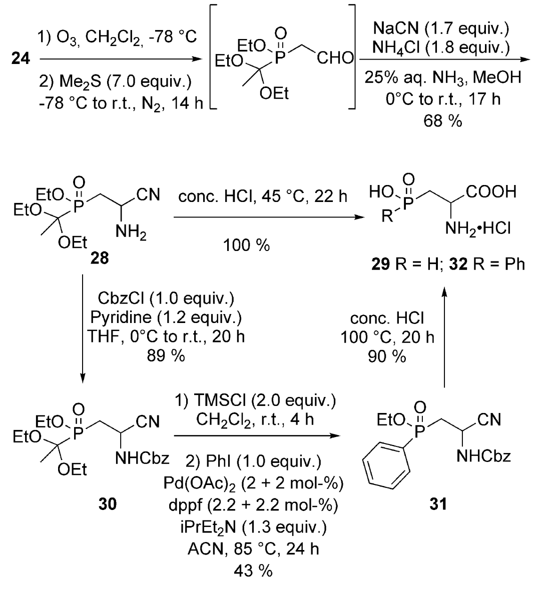
Another illustration of our strategy is an improved synthesis of a potent ATCase inhibitor (K_i = 0.42 μM, **27**, Scheme 4).[11] Initially, we used the temporary protection strategy with cinnamyl-*H*-phosphinic acid [Equation (1)], but because no purification was conducted, the benzoic acid side product required an adjustment in stoichiometry for the amidation step. Instead, we realized that isoprenylation would give volatile acetone after ozonolysis/reduction and so the reaction product would be cleaner and the subsequent yield higher. We have previously described the hydrophosphinylation of isoprene,[3n] and low catalyst loading can be employed. In spite of this, selection of our reusable polystyrene-supported catalyst[3l] for the hydrophosphinylation of isoprene was superior, resulting in a quantitative yield of product **22** after 5 runs of nixantphos-polymer **23** recycling (Scheme 4).

Isoprenyl-*H*-phosphinic acid (**22**) was protected according to method A (Table 1, Entry 3) to produce **24**. The synthesis of **22** and subsequently **24** is much more efficient and environmentally friendly than the alternative alkylation of **2** with isoprenyl halides (either through deprotonation or silylation of **2**) would be (Scheme 1). Ozonolysis and oxidation of **24** with sodium chlorite[15] gave the corresponding carboxylic acid **25**, which was used without intermediate isolation. Deprotection of the resulting amide **26** through hydrogenolysis of the benzyl groups, and acid hydrolysis of the acetal provided inhibitor **27** in good yield after ion-exchange chromatography.

Another application of building block **24**, this time through an ozonolysis/Strecker sequence is shown in Scheme 5. Compound **28** could be hydrolyzed to the phosphinyl analog **29** of aspartic acid,[16] or it could be *N*-protected to **30**, *P*-deprotected selectively, then cross-coupled to an aryl halide to form **32**[17] after deprotection of intermediate **31**.[18] This strategy could be applied to the combinatorial synthesis of other kynureninase inhibitors **32** by selecting other aryl halides for coupling.



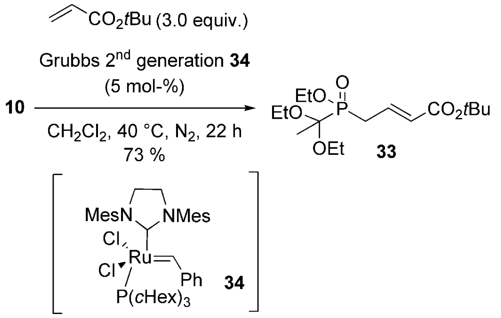
Scheme 4. Improved synthesis of ATCase inhibitor **27**.



Scheme 5. Syntheses of phosphinylaspartate analog **29** and kynureninase inhibitor **32**.

Kynureninase inhibitors have potential for the blockage of quinolinic acid biosynthesis. Quinolinic acid has been implicated in various neurological disorders, such as epilepsy, Huntington's disease, and AIDS-related dementia.[17] Thus, our method offers a flexible entry to prepare various analogs of **33** which could have useful biological activities.

The last example of a reaction on protected phosphinic acid **10** is shown in Equation (3). Olefin metathesis of phosphorus-containing compounds,[19] as well as cross-metathesis of phosphonates[20] are known, but no example related to the cross-metathesis of phosphinic acids has ever been reported. Phosphinylidene-containing compounds are not reactive partners in this reaction, but temporary protection clearly solves this problem. Cross-metathesis of **10** using the "second generation Grubbs' catalyst" **34** afforded acrylate **33** in good yield.



(3)

Conclusions

The temporary protection of *H*-phosphinic acids has not been described previously. In spite of 20 years of successful use of the Ciba-Geigy reagents, a more efficient approach to useful synthetic intermediates has been developed. This manuscript describes the synthesis of various temporarily protected *H*-phosphinic acids for the synthesis of more complex intermediates. Because numerous *H*-phosphinic acids are now readily available using various environmentally benign methodologies we have developed, the present strategy offers an attractive alternative to others previously described in the literature. For certain *H*-phosphinic acids that can be difficult to purify, this method also allows purification and esterification, so the purified ethyl *H*-phosphinate ester can be obtained easily after treatment with TMSCl/$CHCl_3$. Even if P-diastereoselective reactions were not observed and kinetic resolution could not be accomplished for the preparation of P-chiral compounds, the present approach should be useful to phosphorus chemists in general. From dihydroxylation to cross-coupling to cross-metathesis, the temporary protection of *H*-phosphinic acids as the corresponding acetals offers a new and efficient approach toward functional intermediates. Because deprotection of the 1,1-(diethoxy)ethyl group can deliver *H*-phosphinate esters or acids, a wide range of intermediates is accessible. Future work from our laboratory will investigate the synthesis of phospholipid analogs and additional asymmetric reactions on protected phosphinates **6**, as well as Tsuji–Trost-type allylation reactions on unsaturated acetates.

Experimental Section

General Procedure for the Protection of *H*-Phosphinates: (Table 2, Method A). To *H*-phosphinic acid or *H*-phosphinic acid ethyl ester (5.0 mmol, 1.0 equiv.) were added triethyl orthoacetate (5.5 mL, 30.0 mmol, 6.0 equiv.) and boron trifluoride–diethyl ether (0.13 or 0.31 mL, 1.0 or 2.5 mmol, 0.2 or 0.5 equiv.) at room temp. The reaction mixture was vigorously stirred for 16–24 h under N_2 at room temp. to afford a yellow solution. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 0.5 M aqueous $NaHCO_3$ (1 × 15 mL) then brine (2 × 15 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The resulting oil was purified by chromatography over silica to afford the clean product.

Ethyl (1,1-Diethoxyethyl)cinnamylphosphinate (4): [Equation (1), Table 2, Entries 1a and 2a]. Method A, 0.2 equiv. $BF_3 \cdot OEt_2$, 24 h, using cinnamyl-*H*-phosphinic acid.[21] Chromatography over silica gel (hexanes/ethyl acetate, 6:4, v/v) afforded **4** as a light yellow oil (1.3 g, 80% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.38 (m, 5 H, $CH_{arom.}$), 6.53 (dd, $^3J_{H,H}$ = 16.0, $^4J_{HCCCP}$ = 4.0 Hz, 1 H, -CH=), 6.19–6.31 (m, 1 H, -CH=), 4.15–4.28 (m, 2 H, -CH_2-O), 3.60–3.83 (m, 4 H, -CH_2-O), 2.71–2.92 (m, 2 H, -CH_2-P), 1.54 (d, $^3J_{HCCP}$ = 11.0 Hz, 3 H, CH_3-C-P), 1.31 (t, J = 7.0 Hz, 3 H, CH_3-), 1.22 (t, J = 7.0 Hz, 3 H, CH_3-), 1.21 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-) ppm. ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 137.3, 134.8 (d, J_{PCCC} = 12.0 Hz), 128.8 (2 C), 127.7, 126.4 (d, J_{PCCCCC} = 1.5 Hz, 2 C), 119.1 (d, J_{PCC} = 10.5 Hz), 101.5 (d, J_{PC} = 139.0 Hz), 62.1 (d, J_{POC} = 7.0 Hz), 58.5 (d, J_{PCOC} = 5.0 Hz), 57.0 (d, J_{PCOC} = 7.0 Hz), 31.7 (d, J_{PC} = 82.5 Hz), 20.8 (d, J_{PCC} = 12.0 Hz), 17.0 (d, J_{POCC} = 5.0 Hz), 15.7, 15.5 ppm. ^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 45.96 (s) ppm. HR-MS (EI$^+$): calcd. for $C_{15}H_{22}O_3P$, [M – OEt]$^+$ 281.1307; found 281.1302.

Ethyl (1,1-Diethoxyethyl)[4-(phenylamino)phenyl]phosphinate (16): (Scheme 2) In a sealed tube, K_3PO_4 (0.297 g, 1.4 mmol, 1.4 equiv.), Pd_2dba_3 (0.0092 g, 0.01 mmol, 4.0 mol-%) and 2-(dicyclohexylphosphanyl)-2′-(dimethylamino)biphenyl (0.017 g, 0.044 mmol, 4.4 mol-%) were added to the ester **15** (0.32 g, 1.0 mmol) in DME (2.0 mL) at room temp. After 24 h at 100 °C, the reaction mixture was cooled and filtered through Celite®. The solution was concentrated in vacuo and the resulting oil was purified by chromatography over silica gel (hexanes/ethyl acetate, 4:6, v/v) to afford the amine **16** as a colorless oil (0.197 g, 52%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (dd, $^3J_{H,H}$ = 10.5, $^3J_{H,H}$ = 8.5 Hz, 2 H, $CH_{arom.}$), 7.30–7.36 (m, 2 H, $CH_{arom.}$), 7.18 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, $CH_{arom.}$), 7.02–7.08 (m, 3 H, $CH_{arom.}$), 4.02–4.26 (m, 2 H, -CH_2-O), 3.56–3.80 (m, 4 H, -CH_2-O), 1.45 (d, $^3J_{HCCP}$ = 12.0 Hz, 3 H, CH_3-C-P), 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-), 1.19 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-), 1.18 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-) ppm. ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 148.1 (d, J_{PCCCC} = 2.5 Hz), 141.4, 134.7 (d, J_{PCC} = 10.5 Hz, 2 C), 129.5 (2 C), 122.8, 120.5 (2 C), 118.1 (d, J_{PC} = 128.5 Hz), 114.9 (d, J_{PCCC} = 13.0 Hz, 2 C), 101.6 (d, J_{PC} = 153.5 Hz), 61.4 (d, J_{POC} = 7.0 Hz), 58.4 (d, J_{PCOC} = 5.5 Hz), 58.0 (d, J_{PCOC} = 7.0 Hz), 20.5 (d, J_{PCC} = 13.0 Hz), 16.9 (d, J_{POCC} = 5.5 Hz), 15.8, 15.6 ppm. ^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 36.74

(s) ppm. HR-MS (EI$^+$): calcd. for $C_{20}H_{28}NO_4P$, [M]$^+$ 377.1756; found 377.1754.

Isoprenyl-*H*-Phosphinic Acid 22. Synthesis with the Polymer Catalyst:[3n] (Scheme 4, Table 2, phosphinate, Entry 3). In a sealed tube, isoprene (0.5 mL, 5.0 mmol, 1.0 equiv.) was added to concentrated H_3PO_2 (0.495 g, 7.5 mmol, 1.5 equiv.) in acetonitrile (10.0 mL, 0.5 M), followed by Pd_2dba_3 (0.023 g, 0.025 mmol, 0.5 mol-%) and nixantphos-polystyrene catalyst **23**[3l] (0.06 mmol, 1.2 mol-%). After the tube was sealed, the reaction was heated at 85 °C for 12–16 h. After cooling, the reaction was filtered and the polymer recovered and used directly in another run. The combined filtrate from 5 reaction runs was concentrated in vacuo. The resulting crude was diluted with ethyl acetate (75 mL) and washed with brine (3 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to afford **22** as a light yellow oil (3.34 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.91 (br. s, 1 H, OH), 6.94 (d, $^1J_{HP}$ = 550 Hz, 1 H, H-P), 5.13 (m, 1 H, -CH=), 2.57 (dd, $^2J_{HCP}$ = 19.0, $^3J_{H,H}$ = 8.0 Hz, 2 H, $-CH_2$-P), 1.77 (d, $^4J_{H,H}$ = 4.0 Hz, 3 H, CH_3-C=), 1.66 (d, $^4J_{H,H}$ = 4.0 Hz, 3 H, CH_3-C=) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 138.4 (d, J_{PCCC} = 14 Hz), 110.6 (d, J_{PCC} = 9 Hz), 30.1 (d, J_{PC} = 92 Hz), 25.8 (d, J_{PCCCC} = 3 Hz), 18.2 (d, J_{PCCCC} = 3 Hz) ppm. ^{31}P NMR ($CDCl_3$, 121.47 MHz): δ = 35.86 (dm, J_{PH} = 550 Hz) ppm. HR-MS (EI$^+$): calcd. for $C_5H_{11}O_2P$, [M]$^+$ 134.0497; found 134.0494.

Ethyl (1,1-Diethoxyethyl)(3-methylbut-2-enyl)phosphinate (24): (Scheme 4, Table 2, Entry 3). Method A, 0.2 equiv. $BF_3{\cdot}OEt_2$, 24 h. Chromatography over silica gel (hexanes/ethyl acetate, 7:3, v/v) afforded **24** as a light yellow oil (0.89 g, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.22–5.29 (m, 1 H, -CH=), 4.12–4.26 (m, 2 H, $-CH_2$-O), 3.62–3.83 (m, 4 H, $-CH_2$-O), 2.59 (dd, $^2J_{HCP}$ = 15.5, $^3J_{H,H}$ = 8.0 Hz, 2 H, $-CH_2$-P), 1.77 (d, $^4J_{H,H}$ = 4.0 Hz, 3 H, CH_3-C=), 1.67 (d, $^4J_{H,H}$ = 4.0 Hz, 3 H, CH_3-C=), 1.51 (d, $^3J_{HCCP}$ = 11.0 Hz, 3 H, CH_3-C-P), 1.30 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3-), 1.22 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3-) ppm. ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 136.5 (d, J_{PCCC} = 12.0 Hz), 112.6 (d, J_{PCC} = 9.5 Hz), 101.4 (d, J_{PC} = 137.0 Hz), 61.7 (d, J_{POC} = 7.0 Hz), 58.2 (d, J_{PCOC} = 4.5 Hz), 57.7 (d, J_{PCOC} = 7.0 Hz), 26.2 (d, J_{PC} = 84.5 Hz), 25.9 (d, J_{PCCCC} = 2.5 Hz), 20.6 (d, J_{PCC} = 12.0 Hz), 18.1 (d, J_{PCCCC} = 2.0 Hz), 16.7 (d, J_{POCC} = 5.5 Hz), 15.3, 15.6 ppm. ^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 47.30 (s) ppm. HRMS (CI, NH_3): calcd. for $C_{13}H_{28}O_4P$, [M + H]$^+$ 279.1725; found 279.1727.

Phosphinate 26: (Scheme 4): After saturation of a solution of the ester **24** (1.37 g, 4.93 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 M, 26.0 mL) at –78 °C with ozone, Me_2S (2.5 mL, 33.5 mmol, 6.8 equiv.) was added under N_2 at –78 °C. The reaction mixture was warmed up to room temp. overnight, then the solution was concentrated in vacuo. The resulting oil was dissolved in a mixture *t*BuOH/H_2O (2:1, v/v, 20 mL) and treated successively with 2-methylbutene (0.5 M in THF, 9.8 mL, 9.8 mmol, 2.0 equiv.), $NaH_2PO_4{\cdot}H_2O$ (1.0 g, 7.4 mmol, 1.5 equiv.) and $NaClO_2$ (0.67 g, 3.4 mmol, 1.5 equiv.) at 0 °C. After 3 h at room temp., the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 10% aqueous tartaric acid (2 × 15 mL). The aqueous layer was reextracted with ethyl acetate (1 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to afford compound **25** which was used without further purification.

L-Aspartic acid dibenzyl ester *p*-toluenesulfonate (2.38 g, 4.9 mmol, 1.0 equiv.), Et_3N (0.76 mL, 5.4 mmol, 1.1 equiv.), EDC·HCl (2.8 g, 14.7 mmol, 3.0 equiv.) and DMAP (2.38 g, 4.9 mmol, 3.0 equiv.) was added to a solution of the compound **25** (4.93 mmol, 1.0 equiv.) in distilled THF (0.2 M, 26 mL). After 16 h at room temp. under N_2, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 0.5 M aqueous HCl (1 × 10 mL) and brine (2 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The resulting oil was purified by chromatography over silica gel (hexanes/ethyl acetate, 6:4, v/v to ethyl acetate 100%) to afford amide **26** as a lightly yellow oil (1.81 g, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 & 7.75 (2d, $^3J_{H,H}$ = 8.0 Hz, 1 H, NH), 7.29–7.37 (m, 10 H, $CH_{arom.}$), 5.10 & 5.09 (2d, $^2J_{H,H}$ = 12.0 Hz, 4 H, *Bn* $-CH_2$-), 4.90–4.98 (m, 1 H, -CH-N), 4.13–4.5 (m, 2 H, $-CH_2$-O), 3.59–3.81 (m, 4 H, $-CH_2$-O), 2.74–3.08 (m, 4 H, $-CH_2$- & $-CH_2$-P), 1.49 (d, $^3J_{HCCP}$ = 12.0 Hz, 3 H, CH_3-C-P), 1.17–1.37 (m, 9 H) ppm. ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 170.3, 170.1, 164.6 (2d, J_{PCC} = 8.5 Hz), 135.4, 135.2, 128.5 (2 C), 128.4 (2 C), 128.3, 101.0 (d, J_{PC} = 150.5 Hz), 67.4, 66.8, 62.6 (2d, J_{POC} = 8.0 Hz), 58.5 (2d, J_{PCOC} = 5.0 Hz), 57.9 (2d, J_{PCOC} = 8.0 Hz), 49.1 (d, J_{PCCNC} = 10.5 Hz), 36.4 (d, J_{PCCNCC} = 6.0 Hz), 34.6 & 34.5 (2d, J_{PC} = 72.0 Hz), 20.0 (d, J_{PCC} = 13.0 Hz), 16.5 (2d, J_{POCC} = 4.5 Hz), 15.3, 15.6 ppm. ^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 42.77 & 42.70 (2s) ppm. HRMS (CI, NH_3): calcd. for $C_{28}H_{38}NO_9P$, ([M + H]$^+$) 564.2362; found 564.2355.

***H*-Phosphinic Acid 27:** (Scheme 4) To a solution of amide **26** (1.0 g, 1.78 mmol) in a mixture THF/H_2O (2:1, v/v, 5.1 mL) was added Pd/C (0.24 g, 10 wt.-%). The reaction was placed in a hydrogenator at 50 psi H_2 and room temp. After 17 h, the reaction mixture was filtered through Celite® and concentrated in vacuo. The resulting oil was dissolved in water (30 mL) and washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was concentrated then dissolved in a mixture THF/H_2O (2:1, v/v, 12 mL) and treated with washed Amberlite IR-120 plus (0.83 g). The suspension was heated at 80 °C for 15 h under N_2. After filtration, the reaction mixture was concentrated in vacuo. The resulting oil was dissolved in water, neutralized at pH 7.0 and purified by ion exchange over AG-1 X8 anion exchange resin (70 mL) which had been equilibrated with 100 mM $Et_3NH^+HCO_3^-$ (pH 7.3). The column was washed with water (60 mL) then eluted with a linear gradient (200 mL + 200 mL, 100–500 mM) of $Et_3NH^+HCO_3^-$ (pH 7.3). Fractions containing phosphorus compounds were identified by using the Pi assay developed by Ames[22] and concentrated. The resulting white residue was dissolved in water, the solution passed through a Dowex H$^+$ column, neutralized to pH 7 and then concentrated to afford *H*-phosphinic acid **27** as a light yellow oil (0.243 g, 57% yield). ^{1}H NMR (300 MHz, D_2O): δ = 6.95 (d, $^1J_{HP}$ = 540.0 Hz, 1 H, H-P), 4.22 (dd, $^3J_{H,H}$ = 9.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, -CH-N), 2.47–2.58 (m, 3 H, $-CH_2$-P, $-CH_2$-), 2.35 (dd, $^2J_{H,H}$ = 16.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, $-CH_2$-) ppm. ^{13}C NMR (75.45 MHz, D_2O): δ = 179.0, 178.8, 168.9, 53.6, 41.5 (d, J_{PC} = 78.5 Hz), 39.8 ppm. ^{31}P NMR (121.47 MHz, D_2O): δ = 20.76 (dt, J_{PH} = 539.5, J_{PCH} = 17.0 Hz) ppm. HRMS (ESI$^+$): calcd. for $C_6H_{10}O_7NP$, ([M + Na]$^+$) 262.0093; found 262.0096.

Ethyl (1,1-Diethoxyethyl)(2-amino-2-cyanoethyl)phosphinate (28): (Scheme 5) After saturation of a solution of the ester **24** (0.834 g, 3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 M, 15.0 mL) at –78 °C with ozone, Me_2S (1.5 mL, 20.4 mmol, 6.8 equiv.) was added under N_2 at –78 °C. The reaction mixture was warmed up to room temp. overnight then the solution was concentrated in vacuo. The resulting oil was dissolved in methanol (0.8 M, 4.0 mL) then added dropwise to a solution of sodium cyanide (0.25 g, 5.1 mmol, 1.7 equiv.), ammonium chloride (0.284 g, 5.4 mmol, 1.8 equiv.) in 25% aqueous ammonium hydroxide (1.0 M, 4.5 mL) at 0 °C. The reaction mixture was kept at 0 °C for 1 h then at room temp. for 17 h. The reaction mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine (2 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to afford amine **28** as a colorless oil (0.566 g, 68%). 2 diastereoisomers 54/46. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.19–4.35 (m, 2 H & 1 H, -CH$_2$-O & -CH-N), 3.63–3.84 (m, 4 H, -CH$_2$-O), 1.94–2.49 (m, 2 H & 2 H, -CH$_2$-P & NH$_2$), 1.53 (2d, $^{3}J_{\text{HCCP}}$ = 11.5 Hz, 3 H, CH$_3$-C-P), 1.37 (t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-), 1.24 & 1.23 (2t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 6 H, CH$_3$-) ppm. ^{13}C NMR (75.45 MHz, CDCl$_3$): δ = 121.4 (d, J_{PCCC} = 14.0 Hz), 121.3 (d, J_{PCCC} = 12.0 Hz), 101.3 (d, J_{PC} = 147.0 Hz), 101.2 (d, J_{PC} = 146.0 Hz), 62.6 (d, J_{POC} = 6.5 Hz), 62.4 (d, J_{POC} = 7.0 Hz), 58.8 (2d, J_{PCOC} = 5.5 Hz), 58.2 (d, J_{PCOC} = 7.0 Hz), 58.1 (d, J_{PCOC} = 8.0 Hz), 38.9 (d, J_{PCC} = 4.0 Hz), 38.5 (d, J_{PCC} = 3.5 Hz), 32.1 & 31.7 (2d, J_{PC} = 83.0 Hz), 20.1 (d, J_{PCC} = 14.0 Hz), 19.9 (d, J_{PCC} = 12.5 Hz), 16.8 (d, J_{POCC} = 5.5 Hz), 15.7, 15.5 & 15.4 ppm. ^{31}P NMR (11.47 MHz, CDCl$_3$): δ = 44.87 (s, 54%), 44.68 (s, 46%) ppm.

Ethyl (2-Benzyloxycarbonylamino-2-cyanoethyl)(1,1-diethoxyethyl)-phosphinate (30): (Scheme 5) To amine **28** (1.2 g, 4.3 mmol) in THF (0.2 M, 22.0 mL) was added pyridine (0.42 mL, 5.18 mmol, 1.2 equiv.) followed by benzyl chloroformate (0.61 mL, 4.13 mmol, 1.0 equiv.) at 0 °C under N$_2$. After 3 h at room temp., the reaction mixture was diluted with ethyl acetate (75 mL) and washed with brine (3 × 20 mL). The organic layer was dried with MgSO$_4$ and concentrated in vacuo. The resulting oil was purified by chromatography over silica gel (hexanes/ethyl acetate, 7:3, v/v) to afford protected amine **30** as a colorless oil (1.58 g, 89%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.35 (s, 5 H, CH$_{\text{arom.}}$), 6.83 (d, $^{3}J_{\text{H,H}}$ = 8.0 Hz, 0.54 H, NH), 6.49 (d, $^{3}J_{\text{H,H}}$ = 6.5 Hz, 0.46 H, NH), 5.14 (s, 2 H, *Cbz* -CH$_2$-), 4.90–5.10 (m, 1 H, -CH-N), 4.08–4.35 (m, 2 H, -CH$_2$-O), 3.55–3.82 (m, 4 H, -CH$_2$-O), 2.23–2.52 (m, 2 H, -CH$_2$-P), 1.51 & 1.48 (2d, $^{3}J_{\text{HCCP}}$ = 11.5 Hz, 3 H, CH$_3$-C-P), 1.34 & 1.30 (2t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-), 1.17–1.23 (m, 6 H, CH$_3$-) ppm. ^{13}C NMR (75.45 MHz, CDCl$_3$): δ = 155.2, 135.7, 128.5 (2 C), 128.3, 128.2 (2 C), 118.0 & 117.8 (2d, J_{PCCC} = 10.0 Hz), 100.9 (d, J_{PC} = 148.5 Hz) & 100.8 (d, J_{PC} = 148.0 Hz), 67.5, 62.7 & 62.6 (2d, J_{POC} = 7.0 Hz), 58.8 & 58.7 (2d, J_{PCOC} = 5.5 Hz), 58.2 & 58.1 (2d, J_{PCOC} = 7.5 Hz), 38.0 (d, J_{PCC} = 4.0 Hz), 28.9 & 27.9 (2d, J_{PC} = 82.0 Hz), 19.6 & 19.5 (2d, J_{PCC} = 12.0 Hz), 16.5 (2d, J_{POCC} = 5.5 Hz), 15.4, 15.2 & 15.1 ppm. ^{31}P NMR (11.47 MHz, CDCl$_3$): δ = 45.75 (s, 54%), 43.82 (s, 46%) ppm. HRMS (CI, NH$_3$): calcd. for $C_{19}H_{30}N_2O_6P$, [M + H]$^+$ 413.1842; found 413.1839.

Ethyl (2-Benzyloxycarbonylamino-2-cyanoethyl)phenylphosphinate (31): (Scheme 5) Chlorotrimethylsilane (0.25 mL, 2.0 mmol, 2.0 equiv.) was added to the acetal **30** (0.412 g, 1.0 mmol) in chloroform (0.1 M, 10.0 mL) at room temp. under N$_2$. After 4 h, the reaction mixture was diluted with chloroform (50 mL) and washed with 0.5 M aqueous NaHCO$_3$ (1 × 20 mL) and brine (2 × 20 mL). The organic layer was dried with MgSO$_4$ and concentrated in vacuo to afford the *H*-phosphinic ethyl ester as a colorless oil, which was used without further purification. To the *H*-phosphinic ethyl ester in acetonitrile (0.1 M, 10.0 mL) was added diisopropylethylamine (0.23 mL, 1.3 mmol, 1.3 equiv.), iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.) followed by Pd(OAc)$_2$ (0.0045 mg, 0.02 mmol, 2.0 mol-%) and dppf (0.0122 mg, 0.022 mmol, 2.2 mol-%). After 2 h at reflux under N$_2$, the reaction mixture was cooled and another portion of Pd(OAc)$_2$ (0.0045 mg, 0.02 mmol, 2.0 mol-%) and dppf (0.0122 mg, 0.022 mmol, 2.2 mol-%) was added. After a total of 16 h at reflux under N$_2$, the reaction mixture was cooled and concentrated in vacuo. The resulting oil was dissolved with ethyl acetate (50 mL) and washed with brine (3 × 20 mL). The organic layer was dried with MgSO$_4$ and concentrated in vacuo. The resulting oil was purified by chromatography over silica gel (hexanes/ethyl acetate, 1:1, v/v) to afford the phosphinic acid ethyl ester **31** as a colorless oil (0.16 g, 43%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.72–7.82 (m, 2 H, CH$_{\text{arom.}}$), 7.57–7.64 (m, 1 H, CH$_{\text{arom.}}$), 7.50–7.52 (m, 2 H, CH$_{\text{arom.}}$); 7.32–7.36 (m, 5 H, CH$_{\text{arom.}}$), 6.84 (d, $^{3}J_{\text{H,H}}$ = 6.5 Hz, 0.5 H, NH), 6.71 (d, $^{3}J_{\text{H,H}}$ = 6.5 Hz, 0.5 H, NH), 4.85–5.13 (m, 3 H, *Cbz* -CH$_2$- & -CH-N), 3.83–4.19 (m, 2 H, -CH$_2$-O), 2.22–2.66 (m, 2 H, -CH$_2$-P), 1.32 & 1.29 (2d, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-) ppm. ^{13}C NMR (75.45 MHz, CDCl$_3$): δ = 155.4 & 155.3, 136.0 & 135.9, 133.5 (2d, J_{PCCCC} = 6.5 Hz), 132.0 & 131.7 (2d, J_{PCC} = 10.5 Hz, 2 C), 129.5 (d, J_{PC} = 128.5 Hz), 129.3 & 129.2 (2d, J_{PCCC} = 13.0 Hz, 2 C), 128.8 (2 C), 128.6, 128.5 (2 C), 117.8 (d, J_{PCCC} = 12.0 Hz), 117.6 (d, J_{PCCC} = 14.0 Hz), 67.7 (d, J_{POC} = 7.0 Hz), 62.0 & 61.8 (d, J_{PCC} = 5.5 Hz), 38.3 & 38.2, 32.6 (d, J_{PC} = 99.0 Hz) & 32.4 (d, J_{PC} = 100.0 Hz), 16.6 (d, J_{POCC} = 6.0 Hz) ppm. ^{31}P NMR (11.47 MHz, CDCl$_3$): δ = 40.55 (s, 50%), 39.79 (s, 50%) ppm. HRMS (EI$^+$): calcd. for $C_{19}H_{21}N_2O_4P$, [M]$^+$ 372.1239; found 372.1241.

2-Amino-3-(hydroxyphenylphosphinoyl)propionic Acid Hydrochloride (32):[17] (Scheme 5). A solution of phosphinate **31** (0.072 g, 0.19 mmol) in concentrated aqueous HCl (5.0 mL) was refluxed under nitrogen. After 20 h, the reaction mixture was cooled and concentrated. The resulting oil was dissolved with water (30 mL) and washed with dichloromethane (3 × 10 mL). The aqueous layer was concentrated to afford phosphinic acid **32** (0.046 mg, 90%). ^{1}H NMR (300 MHz, D$_2$O): δ = 7.56–7.63 (m, 2 H, CH$_{\text{arom.}}$), 7.34–7.48 (m, 3 H, CH$_{\text{arom.}}$), 3.98 (ddd, $^{3}J_{\text{HCCP}}$ = 15.0 Hz, 1 H, -CH-N), 2.36 (ddd, $^{2}J_{\text{HCP}}$ = 14.0, $^{2}J_{\text{H,H}}$ = 13.5, $^{3}J_{\text{H,H}}$ = 5.0 Hz, 1 H, -CH$_2$-P), 2.13 (ddd, $^{2}J_{\text{HCP}}$ = 14.0, $^{2}J_{\text{H,H}}$ = 13.5, $^{3}J_{\text{H,H}}$ = 8.5 Hz, 1 H, -CH$_2$-P) ppm. ^{13}C NMR (75.45 MHz, D$_2$O): δ = 171.1 (d, J_{PCCC} = 11.0 Hz), 133.4 (d, J_{PC} = 131.0 Hz),132.3 (d, J_{PCCCC} = 2.5 Hz), 131.0 (d, J_{PCC} = 10.0 Hz, 2 C), 128.9 (d, J_{PCCC} = 12.5 Hz, 2 C), 49.0, 30.7 (d, J_{PC} = 92.0 Hz) ppm. ^{31}P NMR (121.47 MHz, CDCl$_3$): δ = 31.09 (s) ppm.

Phosphinate 33: See Equation (3); *tert*-butyl acrylate (0.44 mL, 3.0 mmol, 3.0 equiv.) and 2nd generation Grubbs catalyst **34** (0.042 g, 0.05 mmol, 5 mol-%) was added to alkene **10** (0.25 g, 1.0 mmol) in dichloromethane (0.02 M, 20.0 mL) at room temp. After 22 h, at reflux under N$_2$, the reaction mixture was cooled. Charcoal (2 g) was added and the suspension was filtered through Celite®. The solution was concentrated in vacuo. The resulting oil was purified by chromatography over silica gel (hexanes/ethyl acetate, 6:4, v/v) to afford ester **33** as a colorless oil (0.257 g, 73%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.80–6.92 (m, 1 H, -CH=), 5.85–5.92 (m, 1 H, -CH=), 4.10–4.32 (m, 2 H, -CH$_2$-O), 3.60–3.81 (m, 4 H, -CH$_2$-O), 2.67–2.87 (m, 2 H, -CH$_2$-P), 1.53 (d, $^{3}J_{\text{HCCP}}$ = 12.0 Hz, 3 H, CH$_3$-C-P), 1.49 [s, 9 H, C(CH$_3$)$_3$], 1.34 (t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-), 1.23 (t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-), 1.22 (t, $^{3}J_{\text{H,H}}$ = 7.0 Hz, 3 H, CH$_3$-) ppm. ^{13}C NMR (75.45 MHz, CDCl$_3$): δ = 165.2, 136.6 (d, J_{PCC} = 9.0 Hz), 127.6 (d, J_{PCCC} = 11.0 Hz), 101.5 (d, J_{PC} = 143.0 Hz), 80.6, 62.2 (d, J_{POC} = 7.0 Hz), 58.5 (d, J_{PCOC} = 4.5 Hz), 58.0 (d, J_{PCOC} = 7.0 Hz), 31.1 (d, J_{PC} = 80.0 Hz), 28.3, 20.5 (d, J_{PCC} = 12.5 Hz), 16.8 (d, J_{POCC} = 5.0 Hz), 15.7, 15.4 ppm. ^{31}P NMR (121.47 MHz, CDCl$_3$): δ = 44.57 (s) ppm. HRMS (CI, NH$_3$): calcd. for $C_{16}H_{32}O_6P$, [M + H]$^+$ 351.1937; found 351.1941.

Supporting Information (see also the footnote on the first page of this article): General chemistry (1 page), procedures and spectroscopic data, ^{1}H, ^{13}C and ^{31}P NMR spectra.

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