Direct Monoalkylation of Alkyl Phosphinates to Access H-Phosphinic Acid Esters

Isabelle Abrunhosa-Thomas, Patrice Ribière, Alicia C. Adcock, Jean-Luc Montchamp*

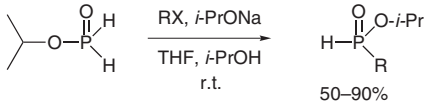
Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, TX 76129, USA
Fax +1(817)2575851; E-mail: j.montchamp@tcu.edu

Received 1 July 2005

Abstract: Simple alkyl phosphinates prepared by the silicate esterification method can be alkylated under Barbier-like conditions with butyl lithium at –78 °C followed by warming to room temperature. The method is limited to the more reactive electrophile such as allylic bromides and alkyl iodides. With these electrophiles good yields of H-phosphinic acid esters are generally obtained in a straightforward manner.

Key words: phosphorus, H-phosphinic acid, phosphinates, alkylation, hypophosphite

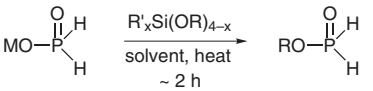
In principle, the direct alkylation of alkyl phosphinates [$ROP(O)H_2$] under basic conditions would be an efficient approach towards variously substituted H-phosphinic acid esters [R′P(O)(OR)H]. However, this approach was not considered viable until Gallagher reported the alkylation of isopropyl phosphinate using alkyl halides and sodium isopropoxide (Equation 1).[1] Previously, only conjugate addition using a catalytic amount of base was demonstrated.[2] The reason for the failed alkylation was proposed to be the result of the rapid decomposition of the anion derived from unhindered esters (R = Me, Et) of hypophosphorous acid.[3] Gallagher prepared isopropyl phosphinate using the Nifant'ev esterification method,[4] and successful alkylation was attributed to the more hindered nature of the ester which slowed down decomposition.[1] Unfortunately, this method has apparently not found widespread use, in spite of the importance of H-phosphinic acid esters as intermediates for the preparation of various organophosphorus compounds. Instead the alkylation of alkyl phosphinate equivalents [$(EtO)_2CHP(O)(OEt)H$, and $(EtO)_2CMeP(O)(OEt)H$, 'Ciba-Geigy reagents'] has been employed commonly even if it involves a protection–deprotection sequence.[5]



RX = CH_3I, CH_2=$CHCH_2Br$, BnBr, n-$C_5H_{11}I$, $Br(CH_2)_4Br$

Equation 1

A few years ago, we reported a novel and high yielding method to prepare alkyl phosphinates using alkoxysilanes or silicates (Equation 2).[6] It was found that the alkyl phosphinates are more robust than when prepared with the other methods.[6] We therefore set out to investigate the alkylation of these phosphinates under basic conditions, and the results are presented herein.



M = H, $PhNH_3$, NH_4
R = Me, Et, Bu, Allyl, Ph, etc.

Equation 2

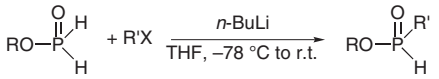
Alkyl phosphinates were prepared by our silicate method[6] (Equation 2) and used in situ, since isolation of alkyl phosphinates is not possible due to the sensitivity of these esters. We previously showed that alkyl phosphinate solutions can be used conveniently for a wide range of reactions.[6,7]

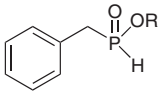
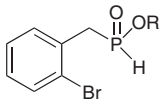
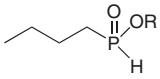
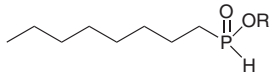
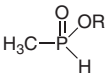
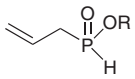
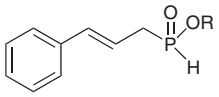
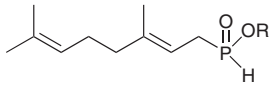
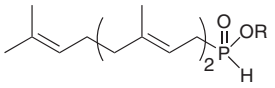
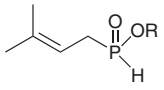
The alkylation of ethyl phosphinate with benzyl bromide was selected as the model reaction. Because butyl lithium is employed, we further settled on THF as the solvent. After some experimentation, it was found that Barbier-like conditions in which the base is added to a mixture of the nucleophile (alkyl phosphinate) and electrophile (alkyl halide) in nearly stoichiometric ratios, is more satisfactory and also experimentally simpler. Table 1 shows the results with various alkyl halides and phosphinates. Under these conditions, ethyl H-benzylphosphinate was obtained in 71% isolated yield (Table 1, entry 1). The alkylation of butyl and isopropyl phosphinates proceeded similarly (entries 2 and 3). Benzyl phosphinate was also benzylated successfully (entry 4) but in lower yield due to the higher hydrolytic lability of the product during chromatographic purification over silica gel.[8] There was no significant difference between the preparation of the alkyl phosphinate from H_3PO_2 or from anilinium hypophosphite.

Reactive electrophiles generally give good yields, but less reactive halides are problematic (Table 1). 2-Bromobenzyl bromide reacted uneventfully (entry 5). Butyl iodide still delivered an acceptable yield (entries 6 and 7), except with benzyl phosphinate (entry 8). As expected, octyl iodide reacted similarly (entry 9), but the bromide was unsatisfactory (entry 10). Although this fact represents a

SYNTHESIS 2006, No. 2, pp 0325–0331
Advanced online publication: 21.12.2005
DOI: 10.1055/s-2005-924768; Art ID: M04305SS

Table 1 Butyl Lithium Promoted Alkylation of Alkyl Phosphinates under Barbier-like Conditions

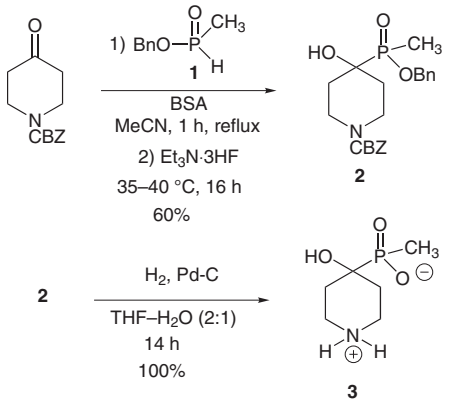


Entry	R	Electrophile	Product	Isolated yield (%)
1	Et	Benzyl bromide		71
2	Bu			70
3	*i*-Pr			65
4	Bn			45
5	Bu	2-Bromobenzyl bromide		76
6	Et	Butyl iodide		22
7	Bu			51
8	Bn			0
9	Bu	Octyl iodide		35
10	Bu	Octyl bromide		8
11	Bu	MeI		82
12	Bn			76
13	Bu	Allyl bromide		71
14	Bn			39
15	Bu	Cinnamyl chloride		0
16	Bu	Cinnamyl bromide		60
17	Bu	Geranyl bromide		62
18	Bu	Farnesyl bromide		80
19	Bu	4-Bromo-2-methyl-2-butene		81

significant limitation, alkyl H-phosphinates can be obtained from the corresponding alkenes using methodology we have developed.[9]

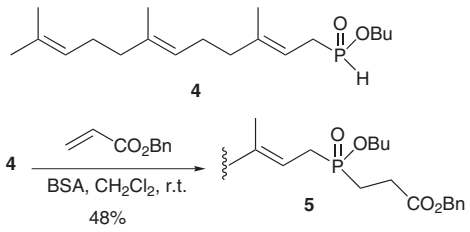
For benzylic substrates, we have also reported a palladium-catalyzed cross-coupling approach.[10] Another approach[11] involves the reaction of the Grignard reagent with $ClP(OR)_2$ but it suffers from obvious limitations, and provides butyl benzyl-H-phosphinate in 58% yield[11c] (compared to 70% in entry 2). Unfortunately, there is still no general approach to prepare alkyl H-phosphinates from alkyl halides. In our hands, even the Gallagher method[1] (Equation 1) which reportedly works with a bromoalkane is unsatisfactory, and this prompted the present study.

Methylation is readily accomplished with MeI. Both butyl and benzyl methyl-H-phosphinate esters are obtained in good yields (entries 11 and 12, respectively). For comparison, the Grignard method affords butyl methyl-H-phosphinate in 55% yield.[11c] Methyl-H-phosphinate esters are also available from the reaction of an alcohol with commercially available dichloromethylphosphine (CH_3PCl_2),[12] but the latter reagent is expensive and hazardous. The methylation of benzyl phosphinate produces the novel and synthetically useful intermediate **1** which we are currently employing in a variety of synthetic applications. Scheme 1 shows an example, in connection with a project aiming at the preparation of GABA analogues. *N*,*O*-Bis(trimethylsilyl)acetamide (BSA)-promoted addition of reagent **1** to CBZ-protected piperidone, followed by cleavage of the resulting silyl ether,[13] produced intermediate **2**. Hydrogenolysis then cleanly delivered the pure GABA analogue **3** as the zwitterion, without the need for tedious ion-exchange chromatography. Analogue **3** showed no activity on the $GABA_B$ receptor.[14] Reagent **1** can be prepared routinely in multigram quantities.



Scheme 1 Synthesis of a GABA analogue using reagent **1**

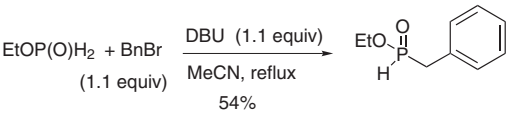
The present method is particularly useful to access allylic H-phosphinates from the corresponding bromides. Allylic H-phosphinates have previously been obtained by the Regan–Boyd allylation of $(TMSO)_2PH$,[15] but the reaction is inconvenient and often produces bis-allylated products which are difficult to separate.[16] Esterification of the H-phosphinic acid product is also required. We have shown previously that similar products can be accessed via nickel-catalyzed cross-coupling but over-reduction can also be observed.[10] Gallagher has reported a single example using allyl bromide and isopropyl phosphinate (65% yield).[1] In comparison, our present method is advantageous because it is experimentally simple, does not require the preparation and manipulation of isopropyl phosphinate (Dean–Stark, benzene removal, and solvent exchange), can be conducted on small or large scales, and it can produce various esters (entries 13 and 14). Cinnamyl, geranyl, farnesyl, and prenyl bromides all reacted in high yield (entries 16–19). Farnesyl H-phosphinate **4** is a useful intermediate as related compounds have been prepared previously through multistep synthesis.[17] For example (Scheme 2), conjugate addition with benzyl acrylate afforded compound **5**, which is similar to an intermediate used in the synthesis of an inhibitor of Ras farnesyl protein transferase.[17a] Through known methods,[18] **4** is also a precursor to the corresponding phosphonochloridate which was employed in the preparation of a farnesyl pyrophosphate analogue.[17b]



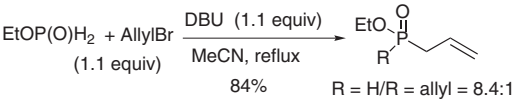
Scheme 2

As mentioned above, the method is still limited to reactive electrophiles. Alkyl bromides are not sufficiently reactive, and even simple alkyl iodides only afford moderate yields. Other electrophiles that were tested but failed to give any significant amounts of products include: styrene oxide, cyclohexene oxide, ethyl iodomethylacetate, methylene iodide, *N*-bromomethylphthalimide, and octyl chloride. As suggested previously,[3] failed alkylations can be attributed to the decomposition of the anionic intermediate which then takes place more rapidly than the intermolecular reaction with the electrophile.

During these studies, the reaction of ethyl phosphinate with benzyl bromide was investigated with other bases. Somewhat surprisingly, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in acetonitrile actually promoted alkylation in moderate yield (Equation 3). Analysis of the reaction mixture obtained by mixing ethyl phosphinate with DBU by ^{31}P NMR showed a peak at $\delta = 160$ ppm (dm, $J_{P-H} = 204$ Hz). This signal could correspond to the P(III) form of ethyl phosphinate hydrogen-bonded to DBU [(EtO)P(H)OH.DBU] or to a tight ion-pair, instead of the fully deprotonated phosphinate anion.[19] Allyl bromide and methyl iodide also reacted similarly, however other electrophiles only gave traces of products irrespective of the conditions (solvent, stoichiometry, temperature). With allyl bromide, a small amount of disubstitution was observed, but the product mixture could be obtained after a simple extractive workup (Equation 4).



Equation 3



Equation 4

In conclusion, we have investigated the alkylation of alkyl phosphinates with various electrophiles. The butyl lithium method is straightforward and is compatible with the formation of various esters of H-phosphinic acids. However, good yields are only obtained with the more reactive electrophiles such as methyl iodide and allylic bromides. With allylic bromides this approach is currently the best available to produce the corresponding allylic H-phosphinate esters. Benzyl methyl-H-phosphinate (reagent **1**) was also prepared for the first time and employed for the synthesis of a GABA analogue. While a wide range of H-phosphinic acid derivatives is now becoming available through various P–C bond-forming methodologies,[20] the reaction of phosphinates with unactivated alkyl halides remains a significant and largely unresolved challenge.

All reactions were conducted in dry glassware under N_2. Organic solutions of products were dried over $MgSO_4$, and filtered. Aqueous hypophosphorous acid (50 wt.%), and BuLi (1.6 M in hexanes) were obtained from Aldrich and used as received. Concentrated hypophosphorous acid was obtaining by concentrating the 50 wt.%

aqueous solution in vacuo on a rotary evaporator, at r.t. for 20–30 min before reaction. Anilinium hypophosphite was prepared as previously described by us.[21] When anhyd solvents were used, they were prepared as follows: THF was distilled under N_2 from Na–benzophenone ketyl, and used immediately; anhyd MeCN was freshly distilled from CaH_2. ^1H NMR spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts for ^1H NMR spectra are reported (in ppm) relative to internal TMS (δ = 0.00 ppm) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in ppm) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 121 MHz on a Varian Mercury-300, spectrometer and/or at 36 MHz on an Anasazi EFT-90 spectrometer, and chemical shifts are reported (in ppm) relative to external 85% phosphoric acid (δ = 0.0 ppm). Radial chromatography was carried out with a Harrison Associates Chromatotron using 1, 2, or 4 mm layers of silica gel 60 PF_{254} containing gypsum (E. Merck). Silica gel (200–300 mesh, Natland International Corporation) was used for flash chromatography. EtOAc–hexanes mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by immersion in anisaldehyde stain (by volume: 93% EtOH, 3.5% H_2SO_4, 1% HOAc, and 2.5% anisaldehyde) followed by heating. Mass spectrometry was provided by the Mass Spectrometry Facility of the University of South Carolina.

Formation of AlkOP(O)H_2; Typical Procedure

This synthesis was conducted as described in the literature.[6] A solution (or suspension) of the hypophosphorous compound (5 mmol), alkoxysilane [3.33 mmol for $(RO)_4Si$, or 7.5 mmol for $(RO)_2SiMe_2$] in solvent (10 mL) was refluxed for 2 h under N_2. After cooling to r.t., the reaction mixture was used for the alkylation reaction, or stored under N_2 as a stock solution.

Alkylation; Typical Procedure (Table 1)

To a solution of alkyl phosphinate (1.5 equiv, 1.5 mmol) and alkyl halide (1 equiv, 1 mmol) in anhyd THF was added BuLi (1.6 M in hexane, 1.2 equiv, 1.2 mmol), at –78 °C under N_2. After the addition of BuLi, the temperature of the solution was slowly allowed to reach r.t. (1.5 h). Once at r.t., the reaction mixture was quenched by a solution of $NaHSO_4$ (20% in water), and extracted with EtOAc (2 ×). The organic layer was washed with brine, dried over anhyd $MgSO_4$ and concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel.

Benzyl Methyl-H-phosphinate (1) (Table 1, Entry 12; Scheme 1)

To a mixture of benzyl hypophosphite [prepared from $(BnO)_4Si$] in anhyd THF (0.6 M, 117 mL, 1.8 equiv, 70 mmol) and iodomethane (2.4 mL, 1 equiv, 38.9 mmol), was added BuLi (*c* = 1.6 M in hexane, 1.2 equiv, 46.7 mmol, 29.2 mL) dropwise at –78 °C, under N_2. Once the addition was complete, the reaction mixture was allowed to warm slowly to r.t. over 2 h. The mixture was quenched with 20% aq $NaHSO_4$ (60 mL) and extracted with EtOAc (2 ×). The combined organic phases were washed with brine, then dried over $MgSO_4$ and concentrated under vacuum. The crude oil obtained was purified by chromatography over silica gel (MeOH–EtOAc, 5:95) to produce the expected compound (5.0 g, 76%) as a yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, J_{HP} = 3, 15 Hz, 3 H), 5.02, 5.10 (ABX system, J_{AB} = 11.7 Hz, $^2J_{AX}$ = 10.5 Hz, $^2J_{BX}$ = 8.5 Hz, 2 H), 7.26 (d, J_{HP} = 542 Hz, 1 H), 7.12–7.46 (m, 5 H).

^{13}C {^1H} NMR (75.45 MHz, $CDCl_3$): δ = 15.4 (d, J_{PC} = 95 Hz), 67.8 (d, J_{POC} = 6 Hz), 128.4, 128.9, 129.0, 135.8 (d, J_{PCC} = 6 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 35.2 (dm, J_{PH} = 542 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_8H_{11}O_2P$: 170.0497; found: 170.0491.

Benzyl (*N*-Benzyloxycarbonyl-4-piperidinyl)methylphosphinate 2 (Scheme 1)

To a mixture of benzyl methyl-H-phosphinate (0.198 g, 1.3 equiv, 1.2 mmol) and *N*-benzyloxycarbonylpiperid-4-one (0.23 g, 1 equiv, 0.89 mmol), in anhyd MeCN (3 mL) was added BSA (0.246 mL, 1 equiv, 0.89 mmol) dropwise at r.t. The reaction mixture was refluxed for 1.5 h, then cooled to r.t. Et_3N–3 HF (0.064 mL, 0.4 equiv, 0.4 mmol) was added dropwise and the reaction mixture was warmed at 35–40 °C for 18 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ (5 mL), then washed with aq HCl (0.1 M, 5 mL), and extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with brine, then dried over $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by chromatography over silica gel (hexanes–EtOAc, 60:40) to produce the expected compound (0.22 g, 60%) as a viscous yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, J_{HP} = 13.2 Hz, 3 H), 1.52–1.87 (m, 4 H), 3.12–3.38 (m, 2 H), 3.95–4.19 (m, 2 H), 5.06–5.12 (m, 4 H), 7.30–7.41 (m, 10 H).

^{13}C {^1H} NMR (22.63 MHz, $CDCl_3$): δ = 9.04 (d, J_{PC} = 86 Hz), 29.7, 31.0, 38.0, 38.5, 66.7 (d, J_{POC} = 6.3 Hz), 66.8, 69.5 (d, J_{PC} = 116 Hz), 127.5, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 136.7, 155.1.

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 56.04 (81%), 54.81 (19%).

HRMS (EI$^+$): *m*/*z* calcd for $C_{21}H_{26}O_5PN$: 404.1627; found: 404.1639.

(4-Hydroxypiperidin-4-yl)methylphosphinic Acid (3) (Scheme 1)

To a dry flask under N_2 containing Pd/C (10%, 110 mg) was added 1.5 mL of a mixture of solvent H_2O–THF (1:2), following by a solution of the benzyl (*N*-benzyloxycarbonyl-4-piperidin-yl)methylphosphinate (0.197 g) in 3.5 mL of the same mixture of solvent H_2O–THF. Then reaction was shaken in a Parr apparatus, at r.t. under H_2 pressure (52 psi) for 15 h. The mixture was filtered through celite and the aqueous layer was concentrated under vacuum to give a white solid (85 mg, 100%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, J_{HP} = 13.2 Hz, 3 H), 1.60–2.13 (m, 4 H), 3.22–3.37 (m, 4 H).

^{13}C {^1H} NMR (22.63 MHz, $CDCl_3$): δ = 9.81 (d, J_{PC} = 92 Hz), 26.9 (d, J_{PCCC} = 5.2 Hz), 38.6 (d, J_{PCC} = 8.8 Hz), 67.7 (d, J_{PC} = 116 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 43.48.

HRMS (EI$^+$): *m*/*z* calcd for $C_6H_{14}O_3PN$: 180.0789; found: 180.0782.

Ethyl Benzyl-H-phosphinate[22] (Equation 3)

To a mixture of benzyl bromide (0.94 g, 1.1 equiv, 5.5 mmol) and a solution of EtOP(O)H_2 (10 mL, 0.5 M in MeCN, 1 equiv, 5 mmol) in a dry flask under N_2, was added DBU (0.84 g, 1.1 equiv, 5.5 mmol) at r.t. A water bath was used to prevent any increase in the temperature. After 1 h, the mixture was quenched with a 10% $NaHSO_4$ solution (5 mL) and extracted with EtOAc. The combined organic phases were washed with brine, then dried over $MgSO_4$. Concentration afforded the crude compound, which was purified by silica gel chromatography (hexanes → EtOAc) to produce the expected compound (0.50 g, 54%) as a clear oil. Yield: 71%; RN: [114425-49-9].

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7 Hz, 3 H), 3.20 (dd, J_{HP} = 18 Hz, *J* = 2 Hz, 2 H), 3.95–4.20 (m, 2 H), 7.05 (dt, J_{HP} = 544 Hz, *J* = 2 Hz, 1 H), 7.20–7.40 (m, 5 H).

^{13}C {^1H} NMR (75.45 MHz, $CDCl_3$): δ = 16.2 (d, J_{POCC} = 6 Hz), 37.0 (d, J_{PC} = 89 Hz), 62.7 (d, J_{POC} = 7 Hz), 127.2 (d, J_{PCCCCC} = 4 Hz), 128.9 (d, J_{PCCCC} = 3 Hz), 129.7 (d, J_{PCCC} = 6 Hz), 129.8 (d, J_{PCC} = 7 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.52 (dm, J_{PH} = 544 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_9H_{13}O_2P$: 184.0653; found: 184.0654.

Ethyl Allyl-H-phosphinate[5e,23] (Equation 4, Alternate Workup Procedure)

To a mixture of allyl bromide (0.40 g, 1.1 equiv, 3.3 mmol) and a solution of $EtOP(O)H_2$ (6 mL, 0.5 M in MeCN, 1 equiv, 3 mmol), was added DBU (0.49 g, 1.1 equiv, 3.3 mmol) at r.t., under N_2. A water bath was used to prevent any increase in the temperature. After 1 h, the mixture was washed with hexanes (3 ×), then quenched with a 10% aq $NaHSO_4$ solution (5 mL) and extracted with EtOAc. The combined organic phases were washed with brine, and dried over $MgSO_4$. Concentration afforded cleanly a mixture of the mono-alkylation and bis-alkylation products as a clear oil (0.35 g, 84%, 8.4:1 ratio).

Mono-Alkylation Product

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7 Hz, 3 H), 2.67 (dd, *J* = 8, 19 Hz, 2 H), 4.1–4.5 (m, 2 H), 5.3–5.4 (m, 2 H), 5.65–5.85 (m, 1 H), 7.02 (dt, J_{HP} = 543 Hz, *J* = 2 Hz, 1 H).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.26 (dm, J_{PH} = 543 Hz, 89%, mono-alkylation product), 50.42 (11%, bis-alkylation product[16a]).

Butyl Benzyl-H-phosphinate[10,11c] (Table 1, Entry 2)

Yield: 70%; RN: [115049-29-1].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 1.30 (sext, *J* = 7.3 Hz, 2 H), 1.57–1.67 (m, 2 H), 3.19 (dd, J_{HP} = 18.6 Hz, *J* = 2 Hz, 2 H), 3.94, 4.08 (tdd, J_{HP} = 6.4 Hz, *J* = 8.5, 10 Hz, 2 H), 7.03 (dt, J_{HP} = 544 Hz, *J* = 1.8 Hz, 1 H), 7.21–7.37 (m, 5 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 18.9, 32.6, 37.2 (d, J_{PC} = 89 Hz), 66.9 (d, J_{POC} = 7.5 Hz), 127.4 (d, J_{PCCCCC} = 3.8 Hz), 129.1 (d, J_{PCCCC} = 3.2 Hz), 130.0 (d, J_{PCCC} = 6.6 Hz), 130.1 (d, J_{PCC} = 7.2 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 38.01 (dm, J_{PH} = 544 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{11}H_{17}O_2P$: 212.0966; found: 212.0966.

Isopropyl Benzyl-H-phosphinate[1] (Table 1, Entry 3)

Yield: 65%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24, 1.33 (2 × d, *J* = 6.2 Hz, 6 H), 3.20 (dd, J_{HP} = 17.9 Hz, *J* = 1.8 Hz, 2 H), 4.55–4.63 (m, 1 H), 7.06 (dt, J_{HP} = 541 Hz, *J* = 2 Hz, 1 H), 7.23–7.33 (m, 5 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 23.5, 24.4 (2 × d, J_{POCC} = 4.3 Hz), 37.5 (d, J_{PC} = 89 Hz), 71.9 (d, J_{POC} = 6 Hz), 127.4 (d, J_{PCCCCC} = 4.4 Hz), 129.0 (d, J_{PCCCC} = 3.2 Hz), 130.0 (d, J_{PCCC} = 6.3 Hz), 130.1 (d, J_{PCC} = 7.2 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 35.10 (dm, J_{PH} = 541 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{10}H_{15}O_2P$: 198.0816; found: 198.0810.

Benzyl Benzyl-H-phosphinate (Table 1, Entry 4)

Yield: 45%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.24 (dd, J_{HP} = 19 Hz, *J* = 1.5 Hz, 2 H), 5.01, 5.12 (ABX system, J_{AB} = 11.8 Hz, J_{AX} = 10.2 Hz, J_{BX} = 8.5 Hz, 2 H), 7.09 (dt, J_{HP} = 548 Hz, *J* = 1.5 Hz, 1 H), 7.21–7.39 (m, 10 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 37.2 (d, J_{PC} = 88 Hz), 68.1 (d, J_{POC} = 6.6 Hz), 127.2, 127.6 (d, J_{PCCCCC} = 3.8 Hz), 128.2, 128.8, 128.9, 129.2 (d, J_{PCCCC} = 3.2 Hz), 130.0 (d, J_{PCCC} = 6.6 Hz), 130.1 (d, J_{PCC} = 7.2 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.73 (dm, J_{PH} = 548 Hz).

Butyl (2-Bromobenzyl)-H-phosphinate (Table 1, Entry 5)

Yield: 76%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 1.30 (sext, *J* = 7.3 Hz, 2 H), 1.58–1.67 (m, 2 H), 3.33–3.52 (m, 2 H), 3.90, 4.16 (m, 2 H), 7.14 (m, 1 H), 7.15 (d, J_{HP} = 552 Hz, 1 H), 7.26–7.34 (m, 2 H), 7.57 (d, *J* = 8.2 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 18.9, 32.5 (d, J_{POCC} = 6.0 Hz), 37.4 (d, J_{PC} = 89 Hz), 66.8 (d, J_{POC} = 7.5 Hz), 124.9 (d, J_{PCCC} = 7.5 Hz), 128.1 (d, J_{PCCCC} = 3.8 Hz), 129.2 (d, J_{PCCCCC} = 3.7 Hz), 130.8 (d, J_{PCC} = 7.8 Hz), 132.1 (d, J_{PCCC} = 5.7 Hz), 133.2 (d, J_{PCCCC} = 3.4 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 34.6 (dm, J_{PH} = 552 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{11}H_{16}O_2BrP$: 291.0150; found: 291.0153.

Ethyl Butyl-H-phosphinate[11c,22,24] (Table 1, Entry 6)

Yield: 22%; RN: [21661-52-9].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7 Hz, 3 H), 1.37 (t, *J* = 7 Hz, 3 H), 1.38–1.66, 1.73–1.83 (m, 6 H), 4.04–4.24 (m, 2 H), 7.08 (d, J_{HP} = 526 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 16.5 (d, J_{POCC} = 6 Hz), 22.9 (d, J_{PCC} = 3.2 Hz, CH_2), 23.8 (d, J_{POC} = 16 Hz), 28.6 (d, J_{PC} = 94 Hz), 32.2, 32.6 (d, J_{PCC} = 6 Hz), 62.5 (d, J_{POC} = 6.9 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 40.26 (dm, J_{PH} = 526 Hz).

Butyl Butyl-H-phosphinate (Table 1, Entry 7)

Yield: 51%; RN: [21661-55-2].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–0.97 (m, 6 H), 1.26–1.83 (m, 10 H), 3.93–4.17 (m, 2 H), 7.08 (d, J_{HP} = 529 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 18.99, 22.9 (d, J_{PCC} = 3.2 Hz), 23.8 (d, J_{POC} = 16 Hz), 28.6 (d, J_{PC} = 93 Hz), 32.6 (d, J_{PCC} = 6 Hz), 66.4 (d, J_{POC} = 7 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 40.95 (dm, J_{PH} = 529 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_8H_{19}O_2P$: 179.1201; found: 179.1201.

Butyl Octyl-H-phosphinate[9] (Table 1, Entry 9)

Yield: 35%; ref.[9a]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.7 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 1.20–1.82 (m, 18 H), 3.98, 4.11 (tdd, J_{HP} = 6.5 Hz, *J* = 8.5, 10 Hz, 2 H), 7.03 (dt, J_{HP} = 526 Hz, *J* = 1.7 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.4, 13.9, 18.6, 20.5, 20.6, 22.4, 28.6 (d, J_{PC} = 93 Hz), 30.6 (d, J_{POC} = 16 Hz), 32.2, 32.6 (d, J_{PCC} = 6 Hz), 65.9 (d, J_{POC} = 7 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 40.78 (dm, J_{PH} = 526 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{12}H_{27}O_2P$: 235.1827; found: 235.1829.

Butyl Methyl-H-phosphinate[12d,e] (Table 1, Entry 11)

Yield: 82%; RN: [6172-80-1].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3 H), 1.44 (sext, *J* = 7.4 Hz, 2 H), 1.63 (dd, J_{HP} = 16 Hz, *J* = 1.8 Hz, 3 H), 1.69–1.75 (m, 2 H), 3.94–4.22 (m, 2 H), 7.48 (d, J_{HP} = 547 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 15.2 (d, J_{PC} = 94 Hz), 18.9, 32.6 (d, J_{PCC} = 6.7 Hz), 66.9 (d, J_{POC} = 7.5 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 40.13 (dm, J_{PH} = 547 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_5H_{13}O_2P$: 137.0731; found: 137.0726.

Butyl Allyl-H-phosphinate[25] (Table 1, Entry 13)

Yield: 71%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3 H), 1.42 (sext, *J* = 7.6 Hz, 2 H), 1.64–1.74 (m, 2 H), 2.66 (ddd, J_{HP} = 19 Hz, *J* = 1.7, 7.5 Hz, 2 H), 4.03, 4.13 (tdd, J_{HP} = 6.7 Hz, *J* = 8.5, 9.5 Hz,

2 H), 5.25–5.82 (m, 2 H), 5.68–5.82 (m, 1 H), 7.00 (td, J_{HP} = 543 Hz, J = 2 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 18.9, 32.6 (d, J_{POCC} = 5.8 Hz), 35.0 (d, J_{PC} = 90.4 Hz), 66.5 (d, J_{POC} = 7.5 Hz), 121.5 (d, J_{PCCC} = 13.8 Hz), 125.9 (d, J_{PCC} = 9.2 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.69 (dm, J_{PH} = 543 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_7H_{15}O_2P$: 163.0888; found: 163.0883.

Benzyl Allyl-H-phosphinate (Table 1, Entry 14)
Yield: 39%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (dd, J_{HP} = 18 Hz, J = 7.3 Hz, 2 H), 5.03, 5.15 (ABX system, J_{AB} = 11.7 Hz, J_{AX} = 9.4 Hz, J_{BX} = 10.3 Hz, 2 H), 5.20–5.33 (m, 1 H), 5.65–5.81 (m, 2 H), 7.04 (dtd, J_{HP} = 549 Hz, J = 0.9, 2.3 Hz, 1 H), 7.34–7.51 (m, 5 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 34.9 (d, J_{PC} = 90 Hz), 67.9 (d, J_{POC} = 6.6 Hz), 121.8 (d, J_{PCCC} = 13.8 Hz), 125.6 (d, J_{PCC} = 9.5 Hz), 128.3, 128.9, 129.0, 135.8 (d, J_{POCC} = 5.5 Hz).

^{31}P NMR (121.47, $CDCl_3$): δ = 37.54 (dm, J_{PH} = 549 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{10}H_{13}O_2P$: 196.0653; found: 196.0654.

Butyl Cinnamyl-H-phosphinate (Table 1, Entry 16)
Yield: 60%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.6 Hz, 3 H), 1.42 (sext, J = 7.6 Hz, 2 H), 1.65–1.74 (m, 2 H), 2.66 (dd, J = 7.6 Hz, J_{HP} = 19 Hz, 2 H), 4.03, 4.13 (tdd, J_{HP} = 6.5 Hz, J = 8.5, 10.2 Hz, 2 H), 6.03–6.16 (m, 1 H), 6.54 (dd, J = 5.9, 15.8 Hz, 1 H), 7.04 (td, J_{HP} = 543 Hz, J = 1.7 Hz, 1 H), 7.27–7.37 (m, 5 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 19.0, 32.6 (d, J_{POCC} = 5.7 Hz), 34.3 (d, J_{PC} = 90.4 Hz), 66.6 (d, J_{POC} = 7.5 Hz), 116.9 (d, J_{PCC} = 10.1 Hz), 126.5 (d, J_{PCCCC} = 2.3 Hz), 128.1, 128.8, 136.1 (d, J_{PCCCC} = 4.3 Hz), 136.6 (d, J_{PCCC} = 14.4 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.28 (dm, J_{PH} = 543 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{13}H_{19}O_2P$: 238.1123; found: 238.1122.

Butyl Geranyl-H-phosphinate (Table 1, Entry 17)
Yield: 62%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3 H), 1.51 (sext, J = 7.3 Hz, 2 H), 1.60 (s, 3 H), 1.63–1.75 (m, 9 H), 2.08 (s, 3 H), 2.55–2.66 (m, 2 H), 3.98, 4.10 (tdd, J_{HP} = 6.7 Hz, J = 8.5, 10.0 Hz, 2 H), 5.04–5.15 (m, 2 H), 7.04 (ddd, J_{HP} = 537 Hz, J = 2.6 Hz, J = 1.5 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 16.7 (d, J_{PCCCC} = 3.2 Hz), 17.9, 19.0, 25.9, 26.6 (d, J_{PCCCCC} = 3.7 Hz), 30.2 (d, J_{PC} = 94 Hz), 32.6 (d, J_{POCC} = 6 Hz), 39.9 (d, J_{PCCCC} = 3.5 Hz), 66.6 (d, J_{POC} = 7.2 Hz), 110.6 (d, J_{PCC} = 8.9 Hz), 123.9. 132.0, 142.2 (d, J_{PCCC} = 14.1 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 38.4 (dm, J_{PH} = 537 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{14}H_{27}O_2P$: 258.1749; found: 258.1747.

Butyl Farnesyl-H-phosphinate (4) (Scheme 2, Table 1, Entry 18)
Yield: 80%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3 H), 1.51 (sext, J = 7.3 Hz, 2 H), 1.59 (s, 3 H), 1.63–1.75 (m, 11 H), 1.94–2.13 (m, 8 H), 2.55–2.66 (m, 2 H), 3.98, 4.10 (tdd, J_{HP} = 6.5 Hz, J = 8.5, 10.2 Hz, 2 H), 5.05–5.16 (m, 3 H), 7.04 (ddd, J_{HP} = 537 Hz, J = 1.5, 2.6 Hz, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 16.2, 16.8 (d, J_{PCCCC} = 3.2 Hz), 17.9, 19.0, 25.9, 26.6 (d, J_{PCCCCC} = 3.7 Hz), 26.9, 30.2 (d, J_{PC} = 91.6 Hz), 32.6 (d, J_{POCC} = 6 Hz), 39.9, 66.6 (d, J_{POC} = 7.2 Hz), 110.6 (d, J_{PCC} = 9.2 Hz), 123.9. 124.5, 131.6, 135.7, 142.2 (d, J_{PCCC} = 14.0 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 38.36 (dm, J_{PH} = 537 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_{19}H_{35}O_2P$: 326.2375; found: 326.2374.

(*E*,*E*)-3-[Butoxy(3,7,11-trimethyl-2,6,10-dodecatrienyl)phosphinyl]propanoic Acid Benzyl Ester (5) (Scheme 2)
To a mixture of benzyl acrylate (0.0348 g, 1 equiv, 0.214 mmol) and butyl farnesyl-H-phosphinate (**4**; 0.07 g, 1 equiv, 0.214 mmol) in CH_2Cl_2 (0.5 mL) was added BSA (0.053 mL, 1 equiv, 0.214 mmol), dropwise at r.t. After stirring at r.t. for 14 h, the reaction mixture was quenched with a solution of $NaHSO_4$ (0.5 mL, 20% in water) and extracted with EtOAc (3 ×). The combined organic phases were washed with brine, then dried over $MgSO_4$ and concentrated under vacuum. The crude oil obtained was purified by chromatography over silica gel (hexane–EtOAc, 80:20) to produce compound **5** (0.048 g, 49%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3 H), 1.51 (sext, J = 7.3 Hz, 2 H), 1.53–1.69 (m, 14 H), 1.91–2.11 (m, 10 H), 2.49–2.71 (m, 4 H), 3.93–4.03 (m, 2 H), 5.05–5.11 (m, 2 H), 5.12 (s, 2 H), 5.13–5.23 (m, 1 H), 7.32–7.41 (m, 5 H).

^{13}C {^{1}H} NMR (22.63 MHz, $CDCl_3$): δ = 13.3, 15.7, 16.2 (d, J_{PCCCC} = 2.2 Hz), 17.4, 18.5, 23.4 (d, J_{PC} = 93 Hz), 25.4, 26.1 (d, J_{PCCCCC} = 3.2 Hz), 26.4, 26.5, 28.9 (d, J_{PC} = 89.5 Hz), 32.4 (d, J_{POCC} = 5.6 Hz), 39.4, 64.0 (d, J_{POC} = 6.9 Hz), 66.4, 112.2 (d, J_{PCC} = 8.7 Hz), 123.0, 123.4, 127.9, 128.0, 128.3, 130.9, 135.4, 140.4 (d, J_{PCCC} = 12.8 Hz), 171.5.

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 53.91 (s).

Butyl (3-Methylbut-2-en-1-yl)-H-phosphinate (Table 1, Entry 19)
Yield: 81%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.6 Hz, 3 H), 1.40 (sext, J = 7.6 Hz, 2 H), 1.59 (s, 3 H), 1.65–1.78 (m, 8 H), 2.55–2.66 (m, 2 H), 3.98–4.16 (m, 2 H), 5.07–5.16 (m, 1 H), 7.04 (dm, J_{HP} = 535, 1 H).

^{13}C {^{1}H} NMR (75.45 MHz, $CDCl_3$): δ = 13.8, 18.1 (d, J_{PCCCC} = 3.5 Hz), 18.7, 26.0 (d, J_{PCCCC} = 3.5 Hz), 29.8 (d, J_{PC} = 91.8 Hz), 32.7 (d, J_{POCC} = 6 Hz), 66.4 (d, J_{POC} = 7.5 Hz), 110.7 (d, J_{PCC} = 9.2 Hz), 138.3 (d, J_{PCCC} = 14.4 Hz).

^{31}P NMR (121.47 MHz, $CDCl_3$): δ = 37.99 (dm, J_{PH} = 535 Hz).

HRMS (EI$^+$): *m*/*z* calcd for $C_9H_{19}O_2P$: 190.1123; found: 190.1127.

Acknowledgment

The National Institute of General Medical Sciences/NIH (1R01 GM067610) is gratefully acknowledged for financial support.

References

(1) Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *115*, 255.
(2) (a) Gallagher, M. J.; Sussman, J. *Phosphorus* **1975**, *5*, 91. (b) Maier, L. *Helv. Chim. Acta* **1973**, *56*, 489. (c) Wroblewski, A. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 10168. (d) See also reference 6.
(3) (a) Fookes, C. J. R.; Gallagher, M. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1876. (b) Fookes, C. J. R.; Gallagher, M. J.; Honneger, H. *J. Chem. Soc., Chem. Commun.* **1978**, 324.
(4) Nifant'ev, E. E.; Levitan, L. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1965**, *35*, 762.

(5) (a) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G.; Jack, J. *Phosphorus Sulfur Relat. Elem.* **1987**, *30*, 571. (b) McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319. (c) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787. (d) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385. (e) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389. (f) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297. (g) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1145.

(6) Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *643-644*, 154.

(7) For example: Ribière, P.; Bravo-Altamirano, K.; Antczak, M.; Hawkins, J. D.; Montchamp, J.-L. *J. Org. Chem.* **2005**, *70*, 4064.

(8) The purification of H-phosphinate esters is often complicated by the very polar nature of these compounds, and their relative ease of hydrolysis. Benzyl alkyl-H-phosphinate esters are more labile than other alkyl esters.

(9) (a) Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745. (b) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.

(10) Bravo-Altamirano, K.; Huang, Z.; Montchamp, J.-L. *Tetrahedron* **2005**, *61*, 6315.

(11) See for example: (a) Nifant'ev, E. E.; Magdeeva, R. K.; Shchepet'eva, N. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1980**, *50*, 1416. (b) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W. Jr.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204. (c) Kabachnik, M. I.; Tsvetkov, E. N.; Chang, C.-Y. *Dokl. Chem. (Engl. Transl.)* **1959**, *125*, 309.

(12) See for example: (a) [$CH_3P(O)(OEt)H$, 81%]: Kehler, J.; Ebert, B.; Dahl, O.; Krogsgaard-Larsen, P. *Tetrahedron* **1999**, *55*, 771. (b) [$CH_3P(O)(OEt)H$, 88%]: Renard, P.-Y.; Vayron, P.; Taran, F.; Miokowski, C. *Tetrahedron Lett.* **1999**, *40*, 281. (c) [$CH_3P(O)(OAr)H$, 32–75%]: Barabanov, V. I.; Abramov, V. S. *J. Gen. Chem. USSR (Engl. Transl.)* **1965**, *35*, 2215. (d) [$CH_3P(O)(OAlk)H$, 60–75%]: Gruzdev, V. G.; Karavanov, K. V.; Ivin, S. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1968**, *38*, 1499. (e) [$CH_3P(O)(OBu)H$, 68%]: Gladshtein, B. M.; Shitov, L. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1969**, *39*, 1913. (f) Murata, Y.; Woodward, R. M.; Miledi, R.; Overman, L. E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2073.

(13) Kehler, J.; Ebert, B.; Dahl, O.; Krogsgaard-Larsen, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3241.

(14) We thank Jakob Heid, Klemens Kaupmann, and Wolfgang Froestl (Novartis Pharma) for conducting the GTPgammaS binding assay.

(15) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223.

(16) (a) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119. (b) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517.

(17) (a) Patel, D. V.; Gordon, E. M.; Schmidt, R. J.; Weller, H. N.; Young, M. G.; Zahler, R.; Barbacid, M.; Carboni, J. M.; Gullo-Brown, J. L.; Hunihan, L.; Ricca, C.; Robinson, S.; Seizinger, B. R.; Tuomari, A. V.; Manne, V. *J. Med. Chem.* **1996**, *38*, 435. (b) Valentijn, A. R. P. M.; van den Berg, O.; van der Marel, G. A.; Cohen, L. H.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 563.

(18) For the conversion of RP(O)(OR′)H into RP(O)(OR′)Cl and esterification, see for example: (a) Bartlett, P. A.; Giangiordano, M. A. *J. Org. Chem.* **1996**, *61*, 3433. (b) Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743.

(19) Based on this NMR data, it is not possible to unambiguously distinguish between the anion and the proposed hydrogen-bonded or tight ion-pair structures [for example for phosphites, $(RO)_3P$ and $(RO)_2PO^-$ appear in the same range of chemical shift (δ = 130–150 ppm in ^{31}P NMR), though there too ion-pairs are possible]: (a) Galkin, V. I.; Khabibullina, A. B.; Smirnov, V. N.; Cherkasov, R. A.; Pudovik, A. N. *Dokl. Chem. (Engl. Transl.)* **1987**, *292*, 21. (b) Moedritzer, K. *J. Inorg. Nucl. Chem.* **1961**, *22*, 19. However, it is not likely that DBU is sufficiently basic to deprotonate the alkyl phosphinate. Related P(III) compounds have been characterized, for example: (c) $(MeO)_2PH$ [δ = 171 (J_{P-H} = 203 Hz)]: Centofanti, L. F. *Inorg. Chem.* **1973**, *12*, 1131. (d) $(i\text{-BuO})_2PH$ [δ = 163 (J_{P-H} = 200 Hz)]: Lutsenko, I. F.; Proskurnina, M. V.; Borisenko, A. A. *Dokl. Chem. (Engl. Transl.)* **1970**, *193*, 553. (e) $(NeoO)_2PH$ [δ = 162 (J_{P-H} = 198 Hz)]: Stec, W.; Uznanski, B.; Houalla, D.; Wolf, R. *C. R. Acad. Sci. Ser. C* **1975**, *281*, 727. (f) (EtO)P(OTMS)H [δ = 154 (J_{P-H} = 184 Hz)], $(TMSO)_2PH$ [δ = 140 (J_{P-H} = 176 Hz)]: Livantsov, M. V.; Prishchenko, A. A.; Lutsenko, I. F. *J. Gen. Chem. USSR (Engl. Transl.)* **1986**, *56*, 1976. (g) ROP(OR′)H has been proposed as a likely intermediate in the transesterification of alkyl phosphinates but could not be detected: Gallagher, M. J.; Honneger, H. *J. Chem. Soc., Chem. Commun.* **1978**, 54.

(20) Review: Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388.

(21) (a) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (b) Anilinium hypophosphite is now also commercially available from Aldrich.

(22) Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.

(23) (a) Yamagishi, T.; Kusano, T.; Yokomatsu, T.; Shibuya, S. *Synlett* **2002**, 1471. (b) Yamagishi, T.; Kusano, T.; Kaboudin, B.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767.

(24) Petnehazy, I.; Jaszay, Z. M.; Szabo, A.; Everaert, K. *Synth. Commun.* **2003**, *33*, 1665.

(25) Kabachnik, M. I.; Chang, J.-Y.; Tsvetkov, E. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1962**, *32*, 3351.