Triethylborane-Initiated Room Temperature Radical Addition of Hypophosphites to Olefins: Synthesis of Monosubstituted Phosphinic Acids and Esters

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A novel and practical approach to monosubstituted phosphinic acid (alkylphosphonous acid) derivatives from hypophosphite salts or esters is described. Phosphorus-centered radical formation is initiated with Et_3B/O_2, and the reaction is conveniently conducted at room temperature in an open flask. In contrast to previously reported conditions for the radical reaction of hypophosphorous acid and sodium hypophosphite (peroxide initiators, acid catalysis, heat), the method proceeds under neutral conditions and therefore tolerates a wide range of functional groups. Previously inaccessible phosphinic acids can be prepared in a single step from cheap starting materials. Excellent selectivity is observed for monoaddition, and symmetrical dialkyl phosphinates do not form in significant amounts. Monosubstituted phosphinic acids are usually obtained in better than 90% purity by a simple extractive workup; however, isolated yields are diminished if the substituent is polar. Because radicals derived from hypophosphites are electrophilic, the reaction is limited to the use of electron-rich olefins. The reaction conditions can also be employed in the room temperature radical reduction of alkyl halides and provide an exceptionally mild and environmentally friendly alternative to the use of tributyltin hydride. The remarkable mild nature of the reaction conditions allows for the radical reaction of sensitive alkyl hypophosphites to occur, in which case, a catalytic amount of Et_3B suffices to deliver alkyl phosphinate esters in reasonable yield.

Introduction

In connection with our continuing efforts to develop novel approaches toward the preparation of functionalized monosubstituted phosphinic acids (alkylphosphonous acids) and their derivatives, we have been investigating the reactivity of hypophosphite salts with unsaturated compounds under radical conditions. We now report the convenient, mild, and selective reaction of sodium hypophosphite and related species with alkenes, initiated at ambient temperature, by trialkylboranes and air.

Monosubstituted phosphinic acids and esters are important intermediates in the syntheses of biologically active compounds[1] and can be prepared by a variety of methods.[2] However, hydrolysis of dichlorophosphines is limited by the lack of functionalized precursors available.[2] Also, the reaction of bis(trimethylsiloxy)phosphine (BTSP) with alkyl halides,[3] although somewhat general, normally requires a large excess of reagent to limit the formation of disubstituted phosphinic acids and is limited to iodides and reactive halides.[4] In addition, workup is rarely straightforward due to the phosphine stench usually associated with the reaction mixture.[3c,5] Ultimately, the development of alternate approaches based on phosphinate synthons with a masked P−H bond has solved a number of difficulties and provided a general entry into monosubstituted phosphinic acids.[6] However, cleavage of the protecting group to unmask the P−H bond requires

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(1) Representative examples: (a) Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935. (b) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little, D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323. (c) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508. (d) Baillie, A. C.; Cornell, C. L.; Wright, B. J.; Wright, K. *Tetrahedron Lett.* **1992**, *33*, 5133. (e) Karanewsky, D. S.; Badia, M. C. *Tetrahedron Lett.* **1986**, *27*, 1751. (f) Sampson, N. A.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500. (g) 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. (h) Qiao, L.; Nan, F.; Kunkel, M.; Gallegos, A.; Powis, G.; Kozikowski, A. P. *J. Med. Chem.* **1998**, *41*, 3303. (i) 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. (j) Willems, H. A. M.; Veeneman, G. H.; Westerduin, P. *Tetrahedron Lett.* **1992**, *33*, 2075. (k) Tian, F.; Montchamp, J.-L.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 7313.

(2) Reviews: (a) Frank, A. W. *Chem. Rev.* **1960**, *60*, 389. (b) Nifant'ev, E. E. *Russ. Chem. Rev.* **1978**, *47*, 835. (c) *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: New York, 1996; Vol. 4. (d) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000.

(3) (a) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223. (b) Boyd, E. A.; Corless, M.; James, K.; Regan, A. C. *Tetrahedron Lett.* **1990**, *31*, 2933. (c) Issleib, K.; Mögelin, W.; Balszuweit, A. *Z. Anorg. Allg. Chem.* **1985**, *530*, 16.

(4) For example, see: (a) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502. (b) Nan, F.; Bzdega, T.; Pshenichkin, S.; Wroblewski, J. T.; Wroblewska, B.; Neale, J.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 772. An, H.; Wang, T.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789. (c) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119. (d) Jones, P. B.; Parrish, N. M.; Houston, T. A.; Stapon, A.; Bansal, N. P.; Dick, J. D.; Townsend, C. A. *J. Med. Chem.* **2000**, *43*, 3304. (e) Grobelny, D. *Synth. Commun.* **1989**, *19*, 1177. (f) Montchamp, J.-L.; Tian, F.; Frost, J. W. *J. Org. Chem.* **1995**, *60*, 6076.

(5) $(TMSO)_2PH$ (BTSP) is a hazardous, pyrophoric compound. Decomposition to a polymeric yellow solid of high phosphorus content is commonly observed in Arbuzov reactions with this compound, and disproportionation leads to formation of PH_3. See for example: Voronkov, M. G.; Marmur, L. Z.; Dolgov, O. N.; Pestunovich, V. A.; Pokrovskii, E. I.; Popel, Y. I. *J. Gen. Chem. USSR* **1971**, *41*, 2005.

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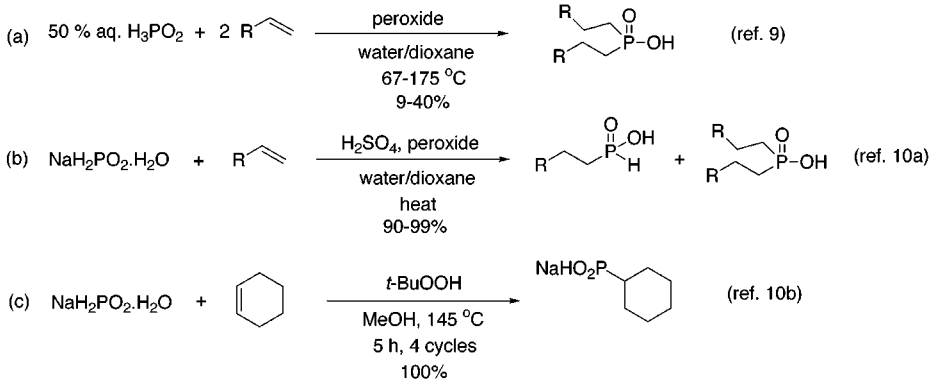
Scheme 1. Radical Reaction between Hypophosphite Derivatives and Alkenes



acidic or basic conditions which are often not compatible with highly functionalized molecules. Nevertheless, this three-step sequence (synthon preparation, functionalization, deprotection) is currently the most general approach, partly because the functionalization step can be conducted under a wide range of conditions.

Alternatively, conceiving a direct approach from inexpensive precursors such as hypophosphorous acid or its salts would be ideal, and provided that the reaction is controlled to stop at the monophosphinic acid stage, it is the most direct approach conceivable. Furthermore, if the hazard associated with the use of anhydrous hypophosphorous acid is avoided, such an approach would also be most practical. For these reasons, we have been interested in developing the chemistry of hypophosphite salts for the preparation of organophosphorus compounds and recently reported a general preparation of aryl phosphinic acids via palladium-catalyzed cross-coupling.[7] To extend the range of monosubstituted phosphinic acids available, we have investigated the radical reaction of sodium, anilinium, and alkyl hypophosphites with olefins.

Preparative radical additions of phosphorus-centered radicals as P−C bond-forming reactions have been known for several decades.[8] Hypophosphorous acid is known to react with alkenes under the influence of radical initiators (Scheme 1). Williams and Hamilton studied the reaction of aqueous H_3PO_2, as early as 1955 (Scheme 1a).[9] However, Nifant'ev and co-workers were chiefly responsible for the synthetic development of this reaction, which has become one of the most convenient methods for the preparation of phosphinic acids (Reactions b and c of Scheme 1).[10] More recently, hypophosphorous acid and some of its salts have emerged as inexpensive and environmentally benign hydrogen atom donors for the replacement of tributyltin hydride in radical reductions and radical cyclizations.[11] However, the latter reactions do not result in the formation of phosphorus-containing products.

During studies aimed at the preparation of building blocks for the synthesis of nonhydrolyzable DNA analogues, we required a method to prepare functionalized monosubstituted acids or esters. While the addition of hypophosphorous acid to properly functionalized olefins appeared most expeditious, it soon became obvious that the Nifant'ev conditions were not compatible with many functional groups, due to the strongly acidic nature of the reaction medium. A neutral source of the phosphorus radical, such as sodium hypophosphite, might solve this problem. In fact, Nifant'ev had also investigated the radical reaction of sodium hypophosphite and found that good yields of adducts could be obtained (Scheme 1c).[10b] Unfortunately, the reaction requires very high temperatures (130−150 °C), a pressurized apparatus (autoclave), since sodium hypophosphite is soluble only in water or low-boiling alcohols (methanol, ethanol), and multiple additions of a peroxide initiator, thereby significantly complicating the reaction in practice. In an attempt to diminish these experimental difficulties, Nifant'ev found it better to generate hypophosphorous acid in situ, by treating sodium hypophosphite with sulfuric acid. The acidic nature of the medium thus catalyzes the breakdown of the peroxide initiators, allowing for lower reaction temperatures and more efficient radical formation. A modification of these conditions was recently introduced by Karenewsky who found that even AIBN could be employed in refluxing ethanol.[1g] While providing a major practical breakthrough, these conditions remained incompatible with acid-sensitive functionalities.

Confronted with this situation, we decided to study alternate conditions to initiate the radical reaction of hypophosphite salts and found organoboranes to be effective and practical for this purpose. Trialkylboranes, and especially Et_3B, have been extensively employed as

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(7) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510.

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(10) (a) Nifant'ev, E. E.; Magdeeva, R. K.; Shchepet'eva, N. P. *J. Gen. Chem. USSR* **1980**, *50*, 1416. (b) Nifant'ev, E. E.; Koroteev, M. P. *J. Gen. Chem. USSR* **1967**, *37*, 1366. (c) Nifant'ev, E. E.; Solovetskaya, L. A.; Maslennikova, V. I.; Magdeeva, R. K.; Sergeev, N. M. *J. Gen. Chem. USSR* **1986**, *56*, 680.

(11) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838. (c) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun.* **1998**, 2691. (d) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071. (e) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415. (f) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973. (g) Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145. (h) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157.

low-temperature initiators, for example, in asymmetric radical additions.[12] Yet, to our knowledge, they were never employed to generate phosphorus-centered radicals for P−C bond formation, although one report does describe the use of sodium hypophosphite and 2 equiv of Et_3B as the initiator, as a Bu_3SnH replacement.[13] We now report a novel synthesis of monosubstituted phosphinic acids and esters at ambient temperature and under neutral conditions, which allows the preparation of previously inaccessible building blocks. The scope and limitations of the process are discussed, and the use of hypophosphite salts is compared with the use of alkyl hypophosphites.

Results and Discussion

Hypophosphite Salts. At the outset, we selected hypophosphite salts as radical precursors, because they are readily available, safely handled, and either essentially neutral or much less acidic than hypophosphorous acid ($pK_a = 1.23$). Some years ago, Barton introduced *N*-ethylpiperidinium hypophosphite (EPHP) as a superior alternative to the use of tributyltin hydride for radical reductions.[11a,11b] While this work provided an encouraging example of the reactivity of hypophosphites in radical reactions, based on our experience, we preferred anilinium hypophosphite ($PhNH_3{\cdot}H_2PO_3$, AHP), which is a more easily handled and relatively nonhygroscopic crystalline salt.[7,14] In addition, sodium hypophosphite (NaH_2PO_2) was also chosen since it is neutral, widely available, and inexpensive. An immediate problem with NaH_2PO_2 is its insolubility in most organic solvents. A recent report from the Abbott Laboratories addressed this problem, by describing the use of a phase-transfer agent in alcoholic solvents for the large scale deoxygenation of an erythromycin derivative, and demonstrated the usefulness of NaH_2PO_2 in radical reductions.[15] However, investigations aimed at the preparation of organophosphorus compounds from hypophosphites under radical conditions have apparently not been conducted since Nifant'ev's studies.

In preliminary experiments, a methanolic solution of sodium hypophosphite and 1-octene (or 1-decene) was treated with 0.1 equiv of triethylborane (as a 1 M solution in hexane or THF) at room temperature under nitrogen, and air was introduced in a controlled manner. Unfortunately, the reactions were sluggish and irreproducible. These reactions were followed by ^{31}P NMR, to measure the formation of the phosphinate product and the disappearance of sodium hypophosphite (yields determined by integrating all the resonances), as well as by capillary gas chromatography, to monitor the disappearance of 1-octene using an internal standard. Good agreement was found between 1-octene consumption and sodium octylphosphinate formation.

Radical reactions initiated by Et_3B are often conducted with a stoichiometric amount and even a 2- to 5-fold excess of the borane.[12] Indeed, better results were obtained with an equimolar amount of Et_3B relative to the alkene, but the introduction of air still appeared to be a delicate parameter. Fortunately, we soon discovered that when the reaction mixture was treated with Et_3B in an open vessel and at room temperature, a rapid (<2 h) and essentially quantitative reaction took place. In one key experiment leading to this discovery, a methanol solution of NaH_2PO_2 (2.5 equiv) and 1-decene (1 equiv) was treated with Et_3B (1 equiv) at room temperature, under N_2. After 18 h, sodium decylphosphinate was obtained in only 18% yield, but exposure of the reaction mixture to air, at that point, rapidly resulted in a 95% yield of product.

As expected, stepwise addition of substoichiometric quantities of Et_3B also worked well, but this protocol was not retained (nor further optimized) because it was found less practical. Due to its convenience, the procedure where Et_3B is added to a solution of reactants in an open vessel was subsequently adopted, and the role of concentration and NaH_2PO_2 stoichiometry (relative to the alkene) on the yield and selectivity (monoalkylphosphinate vs dialkylphosphinate) was investigated (Table 1). Again, these runs were conveniently monitored by ^{31}P NMR. Reaction times were fixed at 2 h, as the reactions were usually fast and no change was observed beyond that point. As Nifant'ev had also noticed under his thermal conditions,[10a] telomer formation was insignificant. It was not possible to explore subambient temperatures because hypophosphite salts rapidly become insoluble upon cooling. Similarly, concentrations of NaH_2PO_2 above 0.5 M were not studied because the reaction mixtures become saturated.

Some disubstitution occurred at high olefin/hypophosphite ratios (entries 13 and 14 of Table 1), but monophosphinates were always the major products. AHP has a slightly greater propensity for disubstitution than NaH_2PO_2 (entries 1 vs 9 and 2 vs 10 of Table 1). The conversion was lowered when either the reaction was conducted with lower alkene concentration (entry 1 vs 4 and 5 and entry 9 vs 11 of Table 1) or the hypophosphite was employed as a limiting reagent (entries 7, 8, and 14). This can be explained by inefficient chain propagation and is consistent with previous work on P-centered radicals.[8,10a,b]

Besides NaH_2PO_2 and AHP, other hypophosphite salts (triethylammonium, ammonium, and *N*-ethylpiperidinium) could also be employed with equally satisfactory results (entries 15−17). Interestingly, even concentrated H_3PO_2 adds itself to 1-octene, although in this case some methyl octylphosphinate is also formed (entry 18).

Reducing the amount of Et_3B also reduces the amount of product formed (entry 1 vs 3), although the use of 0.5 equiv of Et_3B is almost as effective as a stoichiometric

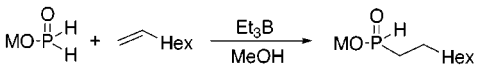
(12) The autooxidation of organoboranes is widely used to generate alkyl radicals, even at low temperature, see for example: (a) Davies, A. G.; Ingold, K. U.; Roberts, B. P.; Tudor, R. *J. Chem. Soc. B* **1971**, 698. (b) Brown, H. C.; Midland, M. M. *Tetrahedron* **1987**, *43*, 4059. (c) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681. (d) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403. (e) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923. (f) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059. (g) Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron Lett.* **1998**, *39*, 5437. Asymmetric examples: (h) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (i) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (j) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528. (k) Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794. (l) Mase, N.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 2797. (m) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780.

(13) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104. In one instance, P-C bond formation was observed as a side reaction (15% yield).

(14) Anilinium hypophosphite (mp 113−114 °C) can be stored at room temperature for months and is handled in air. Commercially available EPHP (Aldrich) is a low-melting solid (mp 40−43 °C) and is highly hygroscopic (see ref 11b).

(15) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem.* **2000**, *65*, 2583.

Table 1. Influence of the Reaction Parameters on Yield[a]



entry	hypophosphite[b]	MH_2PO_2 equiv	Et_3B equiv[c]	conc[d]	^{31}P NMR % yield[e]
1	NaH_2PO_2	2.5	1.0	0.2	95
2	NaH_2PO_2	2.5	0.5	0.2	83
3	NaH_2PO_2	2.5	0.1	0.2	25
4	NaH_2PO_2	2.5	1.0	0.12	70
5	NaH_2PO_2	2.5	1.0	0.05	47
6	NaH_2PO_2	1.5	1.0	0.2	66
7	NaH_2PO_2	1.0	1.0	0.2	40
8	NaH_2PO_2	0.2	1.0	0.5	52
9	$PhNH_3{\cdot}H_2PO_2$	2.5	1.0	0.2	92 (5)
10	$PhNH_3{\cdot}H_2PO_2$	2.5	0.5	0.2	90 (6)
11	$PhNH_3{\cdot}H_2PO_2$	2.5	1.0	0.12	75
12	$PhNH_3{\cdot}H_2PO_2$	2.0	1.0	0.09	73
13	$PhNH_3{\cdot}H_2PO_2$	1.5	1.0	0.09	67 (5)
14	$PhNH_3{\cdot}H_2PO_2$	0.5	1.0	0.2	30 (12)
15	$Et_3NH{\cdot}H_2PO_2$	2.5	1.0	0.2	99
16	$NH_4{\cdot}H_2PO_2$	2.5	1.0	0.2	90
17	EPHP	3.0	1.0	0.2	83
18	H_3PO_2	2.5	1.0	0.2	71[f]

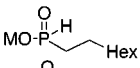
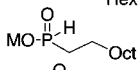
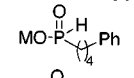
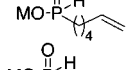
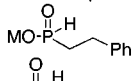
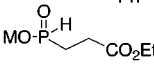
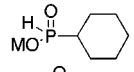
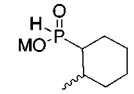
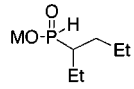
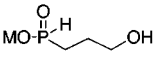
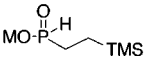
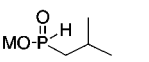
[a] All reactions were conducted in reagent grade MeOH for 1.5−2 h, at room temperature in an open flask. Concentration and number of equivalents are relative to the alkene. [b] $NaH_2PO_2{\cdot}H_2O$ was used. EPHP: 1-ethylpiperidine hypophosphite. H_3PO_2 was obtained by concentrating a 50% by wt solution in vacuo. [c] Et_3B (1.0 M in hexane or THF was employed). [d] Alkene concentration after addition of the borane solution. [e] Determined by integration of all the signals. The number in parentheses indicates the amount of disubstituted phosphinate formed. When no number is indicated, disubstituted phosphinate was not observed (<2%). The balance of material is unreacted hypophosphite. [f] Several other components are present, including methyl octylphosphinate (20%).

amount (entries 2 and 10). The same results were observed with *sec*-Bu_3B in place of Et_3B (data not shown).

It should be noted that running the reaction at ambient temperature results in a much greater intrinsic selectivity for monosubstitution, whereas Nifant'ev showed that with a 1:2 hypophosphite/olefin ratio disubstituted phosphinates can be formed in very high yield.[10a] Also, our results clearly indicate that the formation of a radical is significantly more difficult from RP(O)(OM)H than from MH_2PO_2. Indeed, when monosubstituted phosphinate esters or salts and an olefin were treated with Et_3B, a low yield of addition was observed, with the exception of butyl phenylphosphinate (74% yield with 1-decene). However, these substrates can be reacted under standard thermal or photochemical initiation, since the solvent, pH, or selectivity is not an issue.[8] From the data shown in Table 1, a molar ratio of 2.5:1:1 of NaH_2PO_2/alkene/Et_3B and an alkene concentration of 0.1−0.2 M in methanol were subsequently adopted as the standard conditions for the formation of the corresponding sodium monoalkylphosphinate. It is noteworthy that no special precaution is required as the reaction is not moisture sensitive (in fact, reagent grade methanol and sodium hypophosphite hydrate were employed).

With this preliminary data in hand, we then explored the scope of the reaction with respect to olefinic substrates (Table 2). A variety of alkenes reacted uneventfully to deliver good to excellent yields of monosubstituted phosphinates. Terminal-, 1,2-disubstituted-, and trisubstituted-alkenes (entries 1−4, 11−12, and 8−10 of Table 2) undergo the reaction with the expected regioselectivity. 1,5-Hexadiene (entry 4) gives the monophosphinic acid as the major product. A small amount of bis addition

Table 2. Radical Reaction of Sodium Hypophosphite with Alkenes[a]

Entry	Alkene	Product	^{31}P NMR yield[b] %	Isolated yield[c] %
1			90	80
2			95	92
3			89	87
4			70	40
5			9	-
6			18	-
7		—	0	-
8			98	86
9			86[d]	-
10			46	-
11			89	-
12			85	50
13			38[e]	10

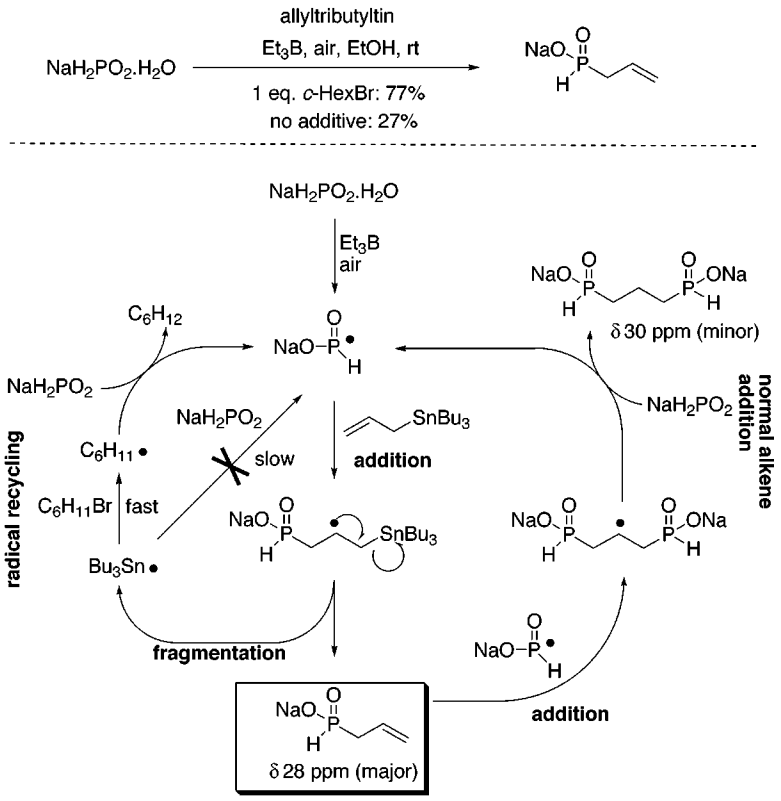
[a] All reactions were conducted in reagent grade MeOH (0.2 M in alkene) for 1.5−2 h, at room temperature in an open flask. NaH_2PO_2/Et_3B/alkene = 2.5:1:1. [b] Yield of phosphinate salt (M = Na), as determined by integration of all the signals. [c] Isolated by extraction with aqueous $KHSO_4$/EtOAc (see Experimental Section). Monosubstituted phosphinic acid products (M = H) were >90% pure. [d] 1:1 ratio of diastereoisomers. [e] Isobutylene was bubbled through the reaction mixture. Yield based on NaH_2PO_2.

product is also observed in this reaction mixture, but this component is not extracted upon workup. As expected, no intramolecular cyclization of the intermediate radical was observed, in agreement with the Beckwith/Baldwin rules.[16]

Some limitations were observed when the reaction was attempted with electron-deficient olefins. Ethyl acrylate and styrene were unreactive (5−20% yields, entries 5 and 6), and removal of the stabilizers present in the commercial reagents did not change this situation. Although this has not been discussed in any great detail in the literature, it appears that hypophosphite radicals are electrophilic and are electronically mismatched with electron-poor alkenes. Fortunately, the corresponding phosphinates are accessible from reaction with BTSP[4b,17] or via the Michael addition of alkyl hypophosphites $ROP(O)H_2$.[17] While this was not thoroughly investigated in the present study, an additional factor responsible for the failed reactions with some olefins may be the increased stability of the intermediate radical, resulting in inefficient hydrogen abstraction from the hypophosphite

(16) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

Scheme 2. Postulated Mechanism in the Reaction of NaH_2PO_2 with Allyltributyltin, with and without Radical Recycling



salt, and thus the failure to maintain chain propagation through the regeneration of the P-centered radical. Some olefinic substrates supporting this hypothesis are isoprene (entry 7) and allyltributyltin, both of which did not produce useful amounts of phosphinate products (0% and 27%, respectively). Interestingly, when allyltributyltin was reacted in the presence of cyclohexyl bromide as an alkyl radical recycling stratagem, the yield of adduct increased to 77% (27−28 ppm). Although this reaction is of little synthetic use, it illustrates how the radical chain propagation can be sustained through the use of such a recycling strategy. The postulated mechanism is shown in Scheme 2. The tin radical does not efficiently abstract the hypophosphite hydrogen, but it rapidly reduces cyclohexyl bromide to produce an alkyl radical capable of carrying the chain by generating the required P-centered radical (similar to Roberts' polarity reversal catalysis[18]). Depending on the conditions, addition to sodium allylphosphinate can be observed to form the corresponding bisphosphinate. The latter radical reaction is representative of the addition to other alkenes, which does not require a separate radical-recycling step (see "normal alkene addition" pathway in Scheme 2). In this experiment, after acidification of the aqueous layer, identification of the products was conducted by ^{1}H NMR analysis of the crude reaction mixture and comparison with the spectrum of an authentic sample[4a] of allylphosphinic acid.

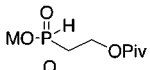
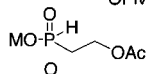
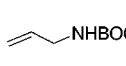
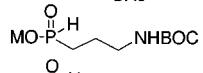
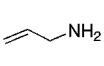
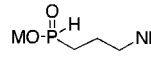
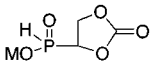
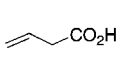
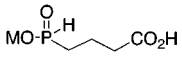
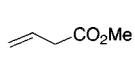
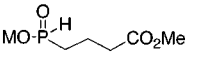
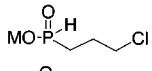
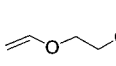
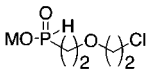
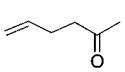
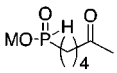
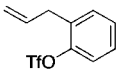
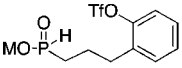
Besides the practical convenience of ambient temperature, an open vessel, and short reaction time, the usefulness of our reaction is better demonstrated with more elaborate substrates (Table 3), especially alkenes displaying acid-sensitive functionalities not compatible with the Nifant'ev conditions (entries 1−3, 5, and 9 of Table 3). In an ongoing synthetic project, we required 2-hydroxyethylphosphinic acid, which is a type of synthon that is not readily available. Using our reaction, protected 2-hydroxyethylphosphinic acid can be obtained in good yield and in a single step from NaH_2PO_2 and enol esters. Vinyl pivalate and vinyl acetate were reacted with NaH_2PO_2 under the standard conditions (entries 1 and 2 of Table 3) to provide the corresponding esters in 60−80% yields, which could be isolated in good purity after a simple extractive workup. If the phosphinate ester is desired, the acid can be esterified as previously reported.[19] Other acid-sensitive (or base-sensitive) substrates were tolerated without further complication (Table 3). If desired, the protecting group can be cleaved during workup, although this was generally avoided in order to facilitate further manipulations. Another interesting application is the formation of (3-aminopropyl)-phosphinic acid (CGP27492), which is a GABA mimic and a precursor to other biologically active compounds developed by Ciba-Geigy.[1i,6c,20] This compound had been previously synthesized in three steps, using the protect-

(17) BTSP reaction: (a) Jackson, P. F.; Cole, D. C.; Slusher, B. S.; Stetz, S. L.; Ross, L. E.; Donzanti, B. A.; Trainor, D. A. *J. Med. Chem.* **1996**, *39*, 619. (b) Kurdyumova, N. R.; Rozhko, L. F.; Ragulin, V. V.; Tsvetkov, E. N. *Russ. J. Gen. Chem.* **1997**, *67*, 1852. (c) Kurdyumova, N. R.; Rozhko, L. F.; Ragulin, V. V.; Tsvetkov, E. N. *Russ. J. Gen. Chem.* **1997**, *67*, 1857. Hypophosphite esters: (d) Gallagher, M. J.; Sussman, J. *Phosphorus* **1975**, *5*, 91. (e) Maier, L. *Helv. Chim. Acta* **1973**, *56*, 489. (f) Caldwell, C. G.; Sahoo, S. P.; Polo, S. A.; Eversole, R. R.; Lanza, T. J.; Mills, S. G.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Durette, P. L.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 323. (g) Wroblewski, A. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 10168.

(18) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

(19) Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. *Org. Lett.* **2000**, *2*, 3341 and references cited. For example, $PivOCH_2CH_2P(O)(OBu)H$ was obtained in ca. 50% overall yield after esterification of the crude acid, followed by chromatographic purification.

Table 3. Radical Reaction of Sodium Hypophosphite with Functionalized Alkenes[a]

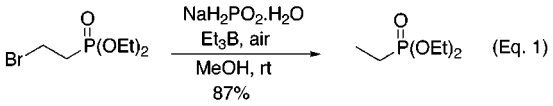
Entry	Alkene	Product	^{31}P NMR yield[b] %	Isolated yield[c] %
1			77	49
2			69	-
3			100	51
4			100[d]	42
5			86	-
6			95	-
7			98	-
8			72	71
9			58	-
10			94[e]	-
11			82	80

[a] All reactions were conducted in reagent grade MeOH (0.2 M in alkene) for 1.5−2 h, at room temperature in an open flask. NaH_2PO_2/Et_3B/alkene = 2.5:1:1. [b] Yield of phosphinate salt (M = Na), as determined by integration of all the signals. [c] Isolated by extraction with aqueous $KHSO_4$/EtOAc (see Experimental Section). Monosubstituted phosphinic acid products (M = H) were >90% pure. [d] A 1 equiv portion of AcOH was added. [e] Side products formed during attempted extraction.

ing group methodology devised in the same laboratories. Unfortunately, allylamine did not react well with NaH_2PO_2 (0−20%) under the standard conditions. We reasoned that it might be due to the formation of an amine−borane complex which would inhibit the autooxidation of Et_3B. To test our hypothesis, 1 equiv of acetic acid was added to the reaction mixture prior to borane addition. We were rewarded with an essentially quantitative yield of the desired product (Table 3, entry 4). An additional run supporting the initial hypothesis came from the treatment of free allylamine with 2 equiv of Et_3B to deliver the adduct in 77% yield.

Similarly, the present methodology was applied to the one-step preparation of an advanced intermediate employed by a Schering group for the synthesis of potential inhibitors of pantothenate synthetase.[1d] Once again, these researchers prepared (3-methoxycarbonyl-propyl)-phosphinic acid using Ciba's protection/reaction/deprotection sequence. With our methodology, methyl allylacetate and allylacetic acid reacted with NaH_2PO_2 to afford the corresponding phosphinate adducts in 98 and 95% yield, respectively (entries 6 and 7 of Table 3). This novel reaction should therefore prove useful for the preparation of a variety of functional intermediates, avoiding the use of protection/deprotection sequences, and the use of anhydrous hypophosphorous acid.

Next, we explored the preparation of possible precursors to P-heterocycles via tandem radical addition−polar cyclizations (entries 8−11 of Table 3). Haloalkenes were studied as substrates in the radical addition step. As expected, some competing reduction was observed with bromides (allyl bromide and 5-bromo-1-pentene), although the desired product was formed as part of a relatively complex product mixture. In contrast, chlorides were tolerated, which with no doubt is due to the fact that the reactions were run at ambient temperature. For example, allyl chloride and chloroethyl vinyl ether gave the corresponding adducts in 55−72 and 50−58% yields, respectively (entries 8 and 9). Although heating the latter intermediates with HMDS in toluene did produce some amount of the corresponding heterocycles, these experiments were not optimized and merely constituted a proof of concept. Similarly, nonconjugated ketones are another type of precursor amenable to tandem reactions, and 5-hexen-2-one reacted to give the corresponding phosphinate salt in 94% yield (entry 10). Cyclization was not tested because attempted extraction did not give the pure ketone (although it was the major component in the product mixture). Finally, *o*-(2-propenyl)phenyl trifluoromethanesulfonate[21] reacted uneventfully to deliver the corresponding phosphinate salt in 82% yield (entry 11), which offers the possibility for subsequent Pd-catalyzed cyclization. These experiments will be the basis for future research.[22]



(Eq. 1)

On the basis of the data obtained through the reactions of allyltributyltin and bromoalkenes, the simple radical reduction of alkyl bromides was modeled with diethyl 2-bromoethylphosphonate (eq 1). Not surprisingly, the corresponding diethyl ethylphosphonate was obtained in 95% NMR yield (and a simple extraction delivered the desired product in 87% isolated yield). In their experiments, Oshima and co-workers employed a 10-fold excess of hypophosphite salts and a 2-fold excess of Et_3B relative to their aryl iodide substrates (aryl bromides were unreactive).[13] In our study with an alkyl bromide, both reagents were used in significantly smaller quantities, and in fact, reduction proceeded satisfactorily even with 0.1 equiv of Et_3B (66% yield). While this was not further investigated, since our focus remained on P−C bond formation, this methodology provides a useful alternative to Barton's EPHP and related radical reductions initiated thermally with AIBN.

(20) 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.

(21) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557.

(22) Although the Pd-catalyzed cross-coupling of phosphinate esters is well established, aryl triflates have apparently not been used as substrates in these reactions: (a) Xu, Y.; Zhang, J. *Synthesis* **1984**, 778. (b) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377. (c) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1984**, 781. (d) Xu, Y.; Li, Z. *Synthesis* **1986**, 240. (e) Xu, Y.; Xia, J.; Guo, H. *Synthesis* **1986**, 691. (f) Xu, Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606. (g) Xu, Y.; Wej, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949. (h) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255. (i) Schwabacher, A. W.; Zhang, S.; Davy, W. *J. Am. Chem. Soc.* **1993**, *115*, 6995. (j) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206. (k) See also ref 6f.

Overall, the Et_3B-promoted reaction of hypophosphite salts with olefins proceeds in high yield under mild conditions. However, the isolated yields were significantly lower due to the high aqueous solubility of many of the products, and they have not been optimized. No attempt was made to utilize continuous extraction techniques, precipitation with adamantanamine, or ion-exchange chromatography. Esterification of the products is the most convenient isolation procedure, and we have already reported a new protocol for the selective esterification of monosubstituted phosphinic acids.[19] Nonetheless, an alternate direct method to prepare phosphinate esters would be useful when sodium (or anilinium) phosphinates are difficult to handle. With this idea in mind, we decided to investigate the reactivity of alkyl hypophosphites in radical reactions.

Hypophosphite Esters. Since our Et_3B/air procedure worked well with hypophosphite salts and was tolerant of acid-sensitive functionalities, it occurred to us that sensitive alkyl hypophosphites ($ROP(O)H_2$) might be employed as well. Alkyl hypophosphites are air and moisture sensitive and thermally unstable. The latter property precludes their use in AIBN-initiated reactions since, for example, methyl hypophosphite decomposes in about an hour at 80 °C.[22h]

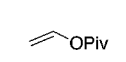
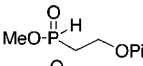
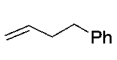
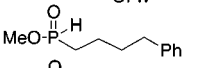
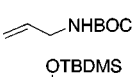
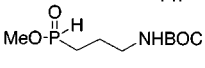
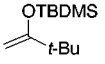
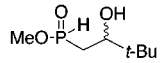
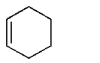
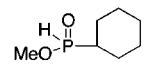
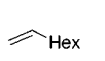
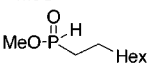
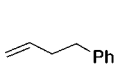
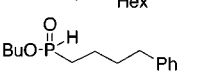
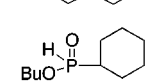
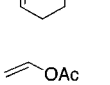
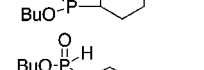
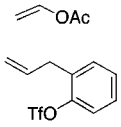
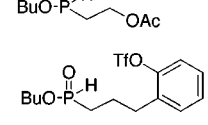
To the best of our knowledge, a single report describes the radical reaction of an alkyl hypophosphite.[23] Butyl hypophosphite was reacted with allyl acetate, in a sealed tube at 130−140 °C for 10 h in the presence of di-*tert*-butyl peroxide, to produce butyl bis-(3-acetoxypropyl)-phosphinate in 25% yield. The extent of decomposition under such conditions was not discussed.[23]

Since Fitch's original report in 1964,[24] alkyl hypophosphites ($ROP(O)H_2$) have seldom been used. A few exceptions can be found, for example, in the works of Gallagher, Stawinski, and Schwabacher, among others.[25] There are two major methods to prepare alkyl hypophosphites: (1) esterification of anhydrous H_3PO_2 with orthoformates (R = Me, Et)[24] and (2) esterification of H_3PO_2 with an alcohol with azeotropic removal of water (Dean−Stark trap).[26] Both methods were employed in this study. Other methods[27] such as esterification with diazoalkanes or triethyloxonium tetrafluoroborate are much less convenient and were not considered.

Room Temperature Radical Reaction of Methyl Hypophosphite (Entries 1−6 of Table 4). Methyl hypophosphite ($MeOP(O)H_2$) was prepared by the orthoformate method and then reacted with 1-octene at room temperature with 1 equiv of Et_3B in an open flask. Once again, a rapid reaction took place and the desired ester was formed as the major product. A detailed analysis of this reaction requires prior discussion of several important parameters. First, 2 equiv of $(MeO)_3CH$ was employed, because crystalline anhydrous H_3PO_2 is relatively inconvenient to prepare, and excess orthoformate removes the traces of moisture remaining in H_3PO_2 after high vacuum concentration of the commercial (50% by wt) aqueous solution. The resulting crude reaction mixture was directly used in the following step. Second, the yield of methyl hypophosphite under these conditions is usually 85−90% (^{31}P NMR) and never exceeded 90% in our hands, yet in the following discussion the number of equivalents refers to the total amount of phosphorus (H_3PO_2 starting material) and not that of methyl hypophosphite formed. Third, the reaction concentration for the radical step was controlled by adding anhydrous dioxane (although other solvents, including methanol, can also be used for this purpose).

The results of various runs have been collected in Table 4 (entries 1−6). The H_3PO_2 and Et_3B equivalents are the two key variables that are crucial to obtain good yields of the desired phosphinate product (some of these experiments are summarized in Supporting Information).

Table 4. Radical Reaction of Methyl and Butyl Hypophosphites with Alkenes[a]

Entry	Alkene	Product	^{31}P NMR yield[b] %	Isolated yield[c] %
1			93	40
2			93	45
3			100	37
4			66[d]	55[e]
5			97	60
6			-	96[f]
7			76	65
8			-	60
9			-	52
10			62	59

[a] All reactions were conducted for 1.5−2 h, at room temperature in an open flask. See Experimental Section for details. [b] Yield of phosphinate ester, as determined by integration of all the signals. [c] Isolated by extraction with aqueous $KHSO_4$/EtOAc followed by chromatography (see Experimental Section). [d] TBDMS ether, 1:1 mixture of diastereoisomers. [e] Desilylated during workup, 1:1 mixture of diastereoisomers. A small amount of contaminating silyl ether is also present. [f] Obtained in ca. 90% purity after extraction.

(23) Aleksandrova, I. A.; Ufimtseva, L. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1971**, *6*, 1218.

(24) Fitch, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 61.

(25) For examples on the use of hypophosphite esters, see: (a) Ivanov, B. E.; Kudryavtseva, L. A. *Bull. Acad. Sci., USSR* **1968**, *7*, 1544. (b) Ivanov, B. E.; Kudryavtseva, L. A. *Bull. Acad. Sci., USSR* **1967**, *7*, 1447. (c) Vysotskii, V. I.; Skobun, A. S.; Tilichenko, M. N. *J. Gen. Chem. USSR* **1979**, *49*, 1721. (d) Livantsov, M. V.; Prishchenko, A. A.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1986**, *56*, 2195. (e) Livantsov, M. V.; Prishchenko, A. A.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1986**, *56*, 1976. (f) Natchev, I. A. *Phosphorus, Sulfur* **1988**, *37*, 133. (g) Natchev, I. A. *Liebigs Ann. Chem.* **1988**, 861. (h) Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125. (i) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389. (j) Grice, I. D.; Harvey, P. J.; Jenkins, I. D.; Gallagher, M. J.; Ranasinghe, M. G. *Tetrahedron Lett.* **1996**, *37*, 1087. (k) Gallagher, M. J.; Honegger, H. *J. Chem. Soc., Chem. Commun.* **1978**, 54. (l) Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425. (m) Devedjiev, I.; Ganev, V.; Stefanova, R.; Borisov, G. *Phosphorus Sulfur* **1987**, *31*, 7. (n) Gallagher, M. J.; Ranasinghe, M. G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *115*, 255. (o) Gallagher, M. J.; Ranasinghe, M. G. *J. Org. Chem.* **1996**, *61*, 436. (p) Jankowska, J.; Cieslak, J.; Kraszewski, A.; Stawinski, J. *Tetrahedron Lett.* **1997**, *38*, 2007. (q) See also refs 17d−g, 22h−j, and 27b.

(26) Nifant'ev, E. E.; Levitan, L. P. *J. Gen. Chem. USSR* **1965**, *35*, 762.

(27) (a) Pinnick, H. W.; Reynolds, M. A. *Synth. Commun.* **1979**, *9*, 535. (b) Stawinski, J.; Thelin, M.; Westman, E.; Zain, R. *J. Org. Chem.* **1990**, *55*, 3503.

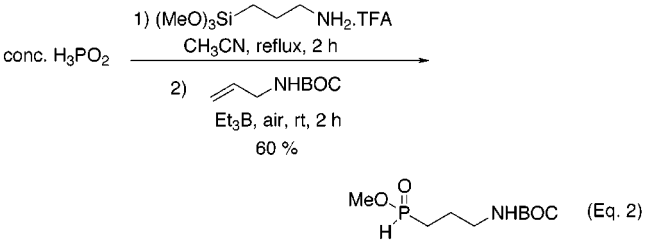
Interestingly, alkyl hypophosphites appear much more prone to H-abstraction resulting in more efficient chain reactions than of the salts, and consistently higher yields were obtained with as little as 0.1−0.2 equiv of Et_3B. A diminished amount of alkyl hypophosphite results in significantly lower yields; therefore, 3 equiv of $MeOP(O)H_2$ was used per olefin (assuming quantitative esterification). The crude reaction mixtures are always much more complex than those with the hypophosphite salts, due to the fact that the formation and decomposition of $MeOP(O)H_2$ is responsible for several side products, as previously reported in the literature.[24,28] For this reason, the yields determined by ^{31}P NMR are somewhat less accurate than those determined with hypophosphite salts and should only be used as a qualitative measurement for comparison between different runs. Nonetheless, the desired ester was always the major product of P−C bond formation, although some of the corresponding phosphinic acid was a common contaminant.[29] Purification was also difficult. Extractive workup can be used to hydrolyze $MeOP(O)H_2$ and remove the H_3PO_2 formed, but here again, the polarity of the phosphinate esters causes loss of material in the aqueous phase. Direct purification by chromatography could also be used, but slow hydrolysis of the ester on silica gel can decrease the isolated yield.

Ethyl hypophosphite[24] reacted similarly (see table in Supporting Information).

Room Temperature Radical Reaction of Butyl Hypophosphite (Entries 7−10 of Table 4). Butyl hypophosphite ($BuOP(O)H_2$) was obtained by esterification of hypophosphorous acid with butanol under azeotropic water removal.[26] It was chosen as a representative example of the direct esterification method pioneered by Nifant'ev.[26] In the literature, the conditions for this reaction (concentration, reaction time, scale, amount, and nature of the alcohol employed) have not been studied in great detail. The scope of alcohols which can be employed has apparently not been investigated beyond the simple alkyls (*i*-Pr, Bu, Hex, *n*-$C_{12}H_{25}$) and certain polyols. Therefore, after our own limited investigation, we settled on a "standard" set of conditions. As expected, temperature (i.e., the solvent employed), reaction time, concentration, and number of equivalents of alcohol are all important factors. The first two interrelated parameters are especially important, as the ester that is formed can decompose over time. The reaction could be monitored by NMR, but in all the runs that were conducted, we never found conditions which provided quantitative formation of the alkyl hypophosphite. We selected cyclohexane as the solvent to replace toxic benzene while maintaining the same reaction temperature. (Although this may not be a widely known fact, cyclohexane is an excellent benzene replacement in azeotropic distillation and possesses properties essentially identical to that of benzene, including azeotropic composition.) Butyl hypophosphite was thus prepared by directly refluxing a mixture of a commercial aqueous solution of hypophosphorous acid and butanol (2 equiv) in cyclohexane for 4−6 h in a Dean−Stark apparatus under N_2. The final concentration in phosphorus was ~1 M. Since the concentration of aqueous H_3PO_2 in vacuo prior to esterification gave similar results, the former more practical direct procedure was adopted routinely. Under these conditions, the yield of $BuOP(O)H_2$ was typically 80−90%, the remainder being H_3PO_2. After being cooled, the reaction solution is used directly for the radical reaction (alkene concentration = ~0.3 M).

Results (entries 7−10 of Table 4) of the radical reaction with $BuOP(O)H_2$ were similar to the ones observed with $MeOP(O)H_2$, except that the crude ^{31}P NMR spectra were simpler, with less side products being present in the reaction mixtures. In addition, isolated yields were typically higher, possibly because the butyl phosphinates are more robust during chromatography. When menthyl hypophosphite ($MenOP(O)H_2$) was used, no induction ("desymmetrization" at phosphorus) was observed. This might not be surprising since the chirality is far away from the diastereotopic phosphinylidene hydrogens. Nonetheless, this type of approach might still be adapted to the asymmetric synthesis of new carbon or phosphorus chiral centers, and the ester group may ultimately be designed to increase diastereotopicity. This and the development of a low-temperature protocol are the directions we will be actively following with this project.

The radical reactions of alkyl hypophosphites and hypophosphite salts are complementary, and the choice of one vs the other is dictated by the olefinic substrate. On one hand, hypophosphite salts provide the highest yields and can be reacted without any special precaution (moisture tolerant) but require 0.5−1.0 equiv of organoborane initiator and a separate esterification step if the ester is desired. On the other hand, alkyl hypophosphites directly deliver a phosphinate ester even with a catalytic amount of Et_3B and circumvent the acidification step usually required prior to esterification. In the case of highly sensitive compounds, the latter method remains advantageous even if the yields of radical addition are lowered due to the competing formation of alkylphosphinic acid from residual H_3PO_2.[29]



(Eq. 2)

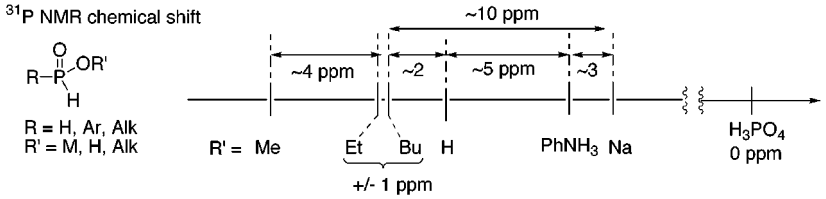
Methodological advances for the preparation of hypophosphite esters would further increase the synthetic value of this reaction, as both yields and isolation procedures might improve. Indeed, we recently developed a new esterification reaction which consistently affords almost quantitative yields of alkyl hypophosphites.[30] Under these conditions, the radical reactions proceed with significantly higher yields, particularly with methyl hypophosphite, and little or no phosphinic acid is produced. For example,[30] *N-tert*-butyl-allylcarbamate reacted with methyl hypophosphite to provide the corresponding methyl phosphinate in 60% isolated yield (eq 2, compare to entry 3 of Table 4).

(28) (a) Gallagher, M. J.; Honegger, H. *Tetrahedron Lett.* **1977**, *34*, 2987. (b) Gallagher, M. J.; Honegger, H. *Aust. J. Chem.* **1980**, *33*, 287. (c) Gallagher, M. J.; Garbutt, R.; Hua, L. Y.; Lee, G. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *75*, 201.

(29) As shown in Table 1, entry 18, H_3PO_2 also reacts with alkenes under these conditions. Thus, residual H_3PO_2, present in the alkyl hypophosphite solution, leads to monosubstituted phosphinic acid.

(30) Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.*, in press.

Chart 1. ^{31}P NMR Chemical Shift Prediction of Phosphinate Derivatives



Conclusion

In conclusion, we have found a novel and practical method for the formation of P−C bonds under mild conditions. Functional groups are well tolerated, and previously inaccessible compounds have been prepared. For hypophosphite salts, the yields of adducts are usually excellent and the crude reaction mixtures are very clean, but isolation can be cumbersome particularly with relatively polar alkenes, and at least 0.5 equiv of Et_3B is required for reproducible results. An alternative protocol employs highly sensitive alkyl hypophosphites to directly produce a monosubstituted phosphinate ester and has the advantage of requiring only a catalytic quantity of borane while producing a more easily handled phosphinate ester. Nonetheless, difficulties still exist in the isolation of the products, and the yields of the radical reaction are intrinsically lower than with the hypophosphite salts. A cleaner and more convenient preparation of hypophosphite esters would therefore be desirable in order to further develop this methodology.[30] Ultimately, the choice between hypophosphorous ester or salt will be dictated by the particular reaction under study. The novel reaction disclosed herein opens up a number of research avenues. Future work will focus on further optimization of the methodology, particularly in tandem processes, and on the development of an asymmetric version.

Experimental Section

General Chemistry. ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported (in ppm) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in ppm) relative to $CDCl_3$ ($\delta = 77.0$ ppm). ^{31}P NMR spectra were recorded at 121 MHz, and chemical shifts are reported (in ppm) relative to external 85% phosphoric acid ($\delta = 0.0$ 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). Ethyl acetate/hexanes mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by immersion in anisaldehyde stain (by volume: 93% ethanol, 3.5% sulfuric acid, 1% acetic acid, and 2.5% anisaldehyde) followed by heating. Organic solutions of products were dried over $MgSO_4$ and filtered.

Reagents and Solvents. Unless otherwise noted, reagents were used as received. 3,3-Dimethyl-2-{[(1,1-dimethylethyl)-dimethylsilyl]oxy}-1-butene was prepared as follows: TBDMSOTf (2.0 mL, 8.7 mmol) was added neat to a solution of pinacolone (0.833 g, 8.3 mmol) and anhydrous Et_3N (1.8 mL, 13 mmol) in anhydrous benzene (20 mL), at room temperature under N_2. The dark reaction mixture was refluxed for 4 h. Water and ether were added to the cool reaction mixture. The organic layer was washed with 0.5 N aqueous HCl, saturated aqueous $CuSO_4$, water, and brine. Concentration afforded the enol ether in quantitative yield. Its spectral data was identical to that reported in: Bach, T.; Jödicke, K. *Chem. Ber.* **1993**, *126*, 2457.

Hypophosphorous Derivatives. Sodium hypophosphite hydrate and aqueous hypophosphorous acid (50% by wt) were obtained from Aldrich and used as received. Before the reaction, hypophosphorous acid was concentrated in vacuo on a rotary evaporator at room temperature for 20−30 min. Anilinium hypophosphite was prepared as previously described by us.[7,30] Triethylammonium hypophosphite was prepared according to ref 27b. Ammonium hypophosphite was prepared as described in ref 4f. EPHP was purchased from Aldrich and used as received.

Solvents. Reagent grade methanol was used in all reactions involving hypophosphite salts (Tables 1−3). Anhydrous solvents were prepared as follows: dioxane was dried over activated 4A molecular sieves and stored under N_2; pyridine and triethylamine were distilled from calcium hydride and stored under N_2 over activated 4A molecular sieves; benzene was distilled, immediately before use, from calcium hydride under N_2.

^{31}P NMR Yield Measurements. NMR yields were determined by integration of all the ^{31}P signals. During our studies of phosphinates and related compounds, we realized that a chart for the prediction of ^{31}P chemical shifts of salts, acids, and esters, based on the knowledge of one of these chemical shifts, would be useful to us and others. On the basis of our data, we compiled Chart 1 which, surprisingly, is applicable over a wide range of concentrations and solvents (within 1 or 2 ppm). For example, if the chemical shift of OctP(O)(OBu)H is known at 38.5 ppm, one could predict the following chemical shifts: ethyl ester at 38.5 + 1 = 39.5 (experimental value = 39.0); methyl ester at 38.5 + 4 + 1 = 43.5 (experimental value = 42.6); acid at 38.5 − 2 = 36.5 (experimental value = 37.8); anilinium salt at 38.5 − (2 + 5) = 31.5 (experimental value = 31.0); sodium salt at 38.5 − 10 = 28.5 (experimental value = 29).

Room Temperature Radical Reaction of Sodium Hypophosphite: Representative Procedure (Tables 1−3). To a solution of $NaH_2PO_2 \cdot H_2O$ (5 mmol) and alkene (2 mmol) in methanol (10 mL) was added Et_3B (1.0 M, 2 mL, 2 mmol), at room temperature in an open reaction vessel. The solution was stirred at room temperature for 2 h. ^{31}P NMR analysis of the crude reaction mixture was used to calculate the NMR yield at that time. The reaction mixture was concentrated on a rotary evaporator, and the residue was partitioned between aqueous $KHSO_4$ and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried and concentrated to afford the crude phosphinic acid (typically in greater than 90% purity). The same procedure was employed with other hypophosphite salts.

Octylphosphinic Acid (Table 2, Entry 1).[10a] ^{1}H NMR ($CDCl_3$) δ 10.72 (bs, 1H), 7.08 (d, $J = 540$ Hz, 1H), 1.1−1.80 (m, 16H), 0.88 (t, $J = 6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 31.6, 30.3 (d, $J_{PCCC} = 16$ Hz), 29.1 (d, $J_{PC} = 94$ Hz), 29.0, 28.9, 22.5, 20.6 (d, $J_{PCC} = 3$ Hz), 14.0; ^{31}P NMR ($CDCl_3$) δ 37.8 (dt, $J_{P-H} = 540$, 14 Hz).

Decylphosphinic Acid (Table 2, Entry 2).[1g,10a] ^{1}H NMR ($CDCl_3$) δ 10.39 (bs, 1H), 7.05 (d, $J = 537$ Hz, 1H), 1.15−1.90 (m, 18H), 0.88 (t, $J = 6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 31.8, 30.4 (d, $J_{PCCC} = 16$ Hz), 29.2 (d, $J_{PC} = 94$ Hz), 29.5, 29.3, 29.2, 29.1, 22.6, 20.5 (d, $J_{PCC} = 3$ Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 38.8 (dt, $J_{P-H} = 537$ Hz).

4-Phenylbutylphosphinic Acid (Table 2, Entry 3).[1g] ^{1}H NMR ($CDCl_3$) δ 11.40 (bs, 1H), 7.04 (d, $J = 540$ Hz, 1H), 7.0−7.45 (m, 5H), 2.61 (t, $J = 7$ Hz, 2H), 1.5−2.0 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 144.2, 128.3, 125.8, 35.3, 32.1 (d, $J_{PCCC} = 16$ Hz),

29.0 (d, J_{PC} = 94 Hz), 20.3 (d, J_{PCC} = 3 Hz), 14.1; ^{31}P NMR ($CDCl_3$) δ 37.5 (dt, J_{P-H} = 540 Hz).

5-Hexenylphosphinic Acid (Table 2, Entry 4). ^{1}H NMR ($CDCl_3$) δ 10.89 (bs, 1H), 7.02 (d, J = 530 Hz, 1H), 5.65−5.9 (m, 1H), 4.9−5.1 (m, 2H), 1.95−2.25 (m, 2H), 1.35−1.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 138.0, 114.9, 33.2, 29.6 (d, J_{PCCC} = 16 Hz), 29.2 (d, J_{PC} = 94 Hz), 20.3; ^{31}P NMR ($CDCl_3$) δ 37.8 (dm, J_{P-H} = 530 Hz).

Cyclohexylphosphinic Acid (Table 2, Entry 8).[10a] ^{1}H NMR ($CDCl_3$) δ 12.13 (bs, 1H), 6.81 (d, J = 532 Hz, 1H), 1.6−2.15 (m, 7H), 1.05−1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 37.2 (d, J_{PC} = 96 Hz), 25.7, 25.5, 23.8; ^{31}P NMR ($CDCl_3$) δ 41.9 (dm, J_{P-H} = 535 Hz).

(2-Trimethylsilyl)ethylphosphinic Acid (Table 2, Entry 12). ^{1}H NMR ($CDCl_3$) δ 11.68 (bs, 1H), 6.99 (d, J = 540 Hz, 1H), 1.5−1.75 (m, 2H), 0.3−0.4 (m, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 22.6 (d, J_{PC} = 92 Hz), 5.9 (d, J_{PCC} = 7 Hz), −2.3; ^{31}P NMR ($CDCl_3$) δ 41.1 (dm, J_{P-H} = 540 Hz).

(2-Pivaloyloxy)ethylphosphinic Acid (Table 3, Entry 1). ^{1}H NMR ($CDCl_3$) δ 9.60 (bs, 1H), 7.20 (d, J = 560 Hz, 1H), 4.25−4.45 (m, 2H), 2.05−2.3 (m, 2H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 60.0, 38.7, 29.6 (d, J_{PC} = 94 Hz), 27.1; ^{31}P NMR ($CDCl_3$) δ 30.8 (dm, J_{P-H} = 560 Hz).

(3-(*tert*-butoxycarbonylamino)propyl)phosphinic Acid (Table 3, Entry 3). ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J = 558 Hz, 1H), 3.1−3.35 (bm, 2H), 1.65−1.95 (bm, 4H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.1, 79.0, 40.4 (m), 28.2, 26.4 (d, J_{PC} = 95 Hz), 21.3; ^{31}P NMR ($CDCl_3$) δ 38.5 (dm, J_{P-H} = 558 Hz).

(3-Aminopropyl)phosphinic Acid (CGP27492, Table 3, Entry 4).[6c] ^{1}H NMR (D_2O) δ 7.13 (d, J = 540 Hz, 1H), 3.1−3.3 (bm, 2H), 1.7−2.2 (bm, 4H); ^{31}P NMR (D_2O) δ 36.5 (d, J_{P-H} = 540 Hz).

(3-Chloropropyl)phosphinic Acid (Table 3, Entry 8). ^{1}H NMR ($CDCl_3$) δ 12.07 (bs, 1H), 7.14 (d, J = 549 Hz, 1H), 3.63 (t, J = 6 Hz, 2H), 1.8−2.2 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 45.1 (d, J_{PCCC} = 18 Hz), 27.0 (d, J_{PC} = 95 Hz), 24.4; ^{31}P NMR ($CDCl_3$) δ 36.5 (dm, J_{P-H} = 549 Hz).

(3-(*o*-Trifluoromethanesulfonyl)phenylpropyl)-phosphinic Acid (Table 3, Entry 11). ^{1}H NMR ($CDCl_3$) δ 10.36 (bs, 1H), 7.2−7.4 (m, 4H), 7.08 (d, J = 545 Hz, 1H), 2.81 (t, J = 7 Hz, 3H), 1.6−2.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 147.9, 133.5, 131.2, 128.5, 128.3, 121.4, 118.5 (q, J_{CF} = 320 Hz), 30.3 (d, J_{PCCC} = 17 Hz), 28.5 (d, J_{PC} = 94 Hz), 20.9; ^{31}P NMR ($CDCl_3$) δ 37.0 (d, J_{P-H} = 550 Hz).

Room Temperature Radical Reaction of Alkyl Hypophosphites: Representative Procedures (Table 4). (1) Methyl Esters. H_3PO_2 (50% aqueous solution by wt, 0.8 g, 6 mmol) was concentrated in vacuo for 20−30 min at room temperature. $(MeO)_3CH$ (1.3 mL, 12 mmol) was added under N_2, and the solution was stirred for 1−2 h at room temperature. Anhydrous dioxane (5 mL), the alkene (2 mmol), and then Et_3B (1.0 M, 0.2−2.0 mL, 0.2−2.0 mmol) were successively added to the open flask. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated on a rotary evaporator, and then aqueous $KHSO_4$ and EtOAc were added. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine. Drying and concentration afforded the crude methyl phosphinate, which was purified by chromatography over silica gel. The same protocol could also be scaled up to 20−30 mmol of alkene.

Methyl (2-Pivaloyloxy-ethyl)phosphinate (Table 4, Entry 1). ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 548 Hz, 1H), 4.25−4.45 (m, 2H), 3.83 (d, J = 12 Hz, 3H), 2.15−2.35 (m, 2H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 177.6, 57.2, 52.7 (d, J_{POC} = 7 Hz), 38.4, 28.5 (d, J_{PC} = 94 Hz), 26.8; ^{31}P NMR ($CDCl_3$) δ 36.4 (dm, J_{P-H} = 548 Hz).

Methyl (4-phenylbutyl)phosphinate (Table 4, Entry 2).[19] ^{1}H NMR ($CDCl_3$) δ 7.02 (dt, J = 530, 2 Hz, 1H), 7.1−7.3 (m, 5H), 3.75 (d, J = 12 Hz, 3H), 2.63 (t, J = 7 Hz, 2H), 1.55−1.85 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 141.4, 128.2, 128.1, 125.7, 52.6 (d, J_{POC} = 7 Hz), 35.2, 31.9 (d, J_{PCC} = 15 Hz), 28.2 (d, J_{PC} = 93 Hz), 20.1 (d, J_{PCCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 42.2 (d, J_{P-H} = 530 Hz).

Methyl [3,3-dimethyl-2-hydroxy-butyl]phosphinate (Table 4, Entry 4). (1:1 mixture of diastereoisomers). ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 541 Hz, 1H), 7.17 (d, J = 540 Hz, 1H), 3.78 (d, J = 12 Hz, 6H), 3.7−3.9 (m, 2H), 2.05−2.25 (m, 2H), 1.8−2.0 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 74.2, 74.1, 52.8 (d, J_{POC} = 7 Hz), 52.5 (d, J_{POC} = 7 Hz), 36.2, 36.1, 34.2 (d, J_{PC} = 94 Hz), 34.0 (d, J_{PC} = 94 Hz), 25.9, 25.8; ^{31}P NMR ($CDCl_3$) δ 41.4 (dm, J_{P-H} = 538 Hz), 40.4 (dm, J_{P-H} = 537 Hz).

Methyl cyclohexylphosphinate (Table 4, Entry 5). ^{1}H NMR ($CDCl_3$) δ 6.80 (dd, J = 521, 2 Hz, 1H), 3.78 (d, J = 11 Hz, 3H), 1.6−2.0 (m, 6H), 1.15−1.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.8 (d, J_{POC} = 8 Hz), 37.4, 36.1, 35.7 (d, J_{PC} = 89 Hz), 25.0−26.2 (multiple peaks, could not be deconvoluted), 23.9 (d, J_{PCC} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 46.7 (d, J_{P-H} = 521 Hz).

Methyl octylphosphinate (Table 4, Entry 6). ^{1}H NMR ($CDCl_3$) δ 7.05 (dt, J = 529, 2 Hz, 1H), 3.78 (d, J = 12 Hz, 3H), 1.5−1.85 (m, 4H), 1.2−1.45 (m, 10H), 0.88 (t, J = 7 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 42.6 (dq, J_{P-H} = 528, 14 Hz).

(2) Butyl Esters. A flask containing H_3PO_2 (50% aqueous solution by wt, 33 mmol) and butanol (6 mL, 66 mmol) in cyclohexane (reagent grade, 40 mL) was equipped with a Dean−Stark trap prefilled with cyclohexane and fitted with a condenser. The solution was refluxed under N_2 for 4−6 h and then cooled to room temperature. The alkene (11 mmol) and Et_3B (1.0 M, 1.1−11 mL, 1.1−11 mmol) were successively added to the open flask, and the resulting solution was stirred at room temperature for 2 h. EtOAc and aqueous $KHSO_4$ were added, and the resulting organic layer was washed with saturated aqueous $NaHCO_3$ and then with brine. Drying and concentration afforded the crude butyl phosphinate, which was purified by chromatography over silica gel.

Butyl (4-phenylbutyl)phosphinate (Table 4, Entry 7).[19] ^{1}H NMR ($CDCl_3$) δ 7.1−7.3 (m, 5H), 7.05 (d, J = 528 Hz, 1H), 3.9−4.2 (m, 2H), 2.62 (t, J = 7 Hz, 2H), 1.5−1.85 (m, 6H), 1.25−1.45 (m, 2H), 0.93 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.4, 128.9, 125.6, 65.8 (d, J_{POC} = 7 Hz), 35.1, 32.1 (d, J_{PCCCC} = 6 Hz), 31.8 (d, J_{PCCC} = 16 Hz), 28.3 (d, J_{PC} = 94 Hz), 20.1 (d, J_{PCC} = 3 Hz), 18.5, 13.3; ^{31}P NMR ($CDCl_3$) δ 39.5 (d, J_{P-H} = 528 Hz).

Butyl cyclohexylphosphinate (Table 4, Entry 8). ^{1}H NMR ($CDCl_3$) δ 6.82 (dd, J = 518, 2 Hz, 1H), 3.9−4.2 (m, 2H), 1.6−2.0 (m, 8H), 1.2−1.5 (m, 7H), 0.95 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 65.9 (d, J_{POC} = 7 Hz), 37.0 (d, J_{PC} = 96 Hz), 32.3, 32.2, 25.7(2), 25.5, 24.1, 24.0, 18.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 44.3 (d, J_{P-H} = 519 Hz).

Butyl (2-acetoxy)ethylphosphinate (Table 4, Entry 9). ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 546 Hz, 1H), 4.3−4.45 (m, 2H), 3.95−4.25 (m, 2H), 2.1−2.25 (m, 2H), 2.07 (s, 3H), 1.6−1.75 (m, 2H), 1.3−1.45 (m, 2H), 0.95 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 66.2 (d, J_{POC} = 6 Hz), 57.2, 32.0, 28.5 (d, J_{PC} = 94 Hz), 20.4, 18.4, 13.2; ^{31}P NMR ($CDCl_3$) δ 33.5 (dm, J_{P-H} = 547 Hz).

Butyl (3-(*o*-Trifluoromethanesulfonyl)phenylpropyl)-phosphinate (Table 4, Entry 10). ^{1}H NMR ($CDCl_3$) δ 7.2−7.4 (m, 4H), 7.10 (d, J = 531 Hz, 1H), 3.9−4.2 (m, 2H), 2.84 (t, J = 8 Hz, 3H), 1.7−2.05 (m, 4H), 1.6−1.7 (m, 2H), 1.3−1.5 (m, 2H), 0.94 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 133.4, 131.1, 128.5, 128.3, 121.4, 118.4 (q, J_{CF} = 320 Hz), 66.2 (d, J_{POC} = 7 Hz), 32.3, 30.3 (d, J_{PCCC} = 16 Hz), 28.1 (d, J_{PC} = 94 Hz), 20.9, 18.6, 13.4; ^{31}P NMR ($CDCl_3$) δ 38.2 (dm, J_{P-H} = 531 Hz).

Radical Reduction (eq 1). To a solution of $NaH_2PO_2 \cdot H_2O$ (5 mmol) and diethyl 2-bromoethylphosphonate (2 mmol) in methanol (10 mL) was added Et_3B (1.0 M, 2 mL, 2 mmol), at room temperature in air. The solution was stirred at room temperature for 2 h (95% yield by ^{31}P NMR analysis). The reaction mixture was concentrated under reduced pressure. Ether and water were added. The organic layer was dried and concentrated to afford diethyl ethylphosphonate, identical to the commercially available material.

Methyl (3-(*tert*-butoxycarbonylamino)propyl)phosphinate (eq 2).[30] Concentrated H_3PO_2 (initially 50% aqueous solution by wt, 0.681 g, 5.1 mmol) was dissolved in CH_3CN (HPLC grade, 10 mL), and the reaction flask was equipped

with a reflux condenser and placed under N_2. Trifluoroacetic acid (0.39 mL, 5.1 mmol) and 3-aminopropyltrimethoxysilane (0.90 mL, 5.1 mmol) were then added successively at room temperature. An exothermic reaction took place immediately, and the mixture was heated to reflux. After 2 h, the reaction mixture was allowed to cool to room temperature. The flask was open to air, *N-tert*-butyl-allylcarbamate (0.326 g, 2.1 mmol) was added, followed by triethylborane (1 M in hexanes, 2.0 mL, 2 mmol), and the heterogeneous mixture was stirred in air at room temperature for 2 h. The crude reaction mixture (94% NMR yield) was treated with EtOAc and aqueous $KHSO_4$. The organic layer was washed successively with saturated aqueous $NaHCO_3$ (1×) and brine (1×). Drying, concentration, and purification by radial chromatography (4 mm thickness, EtOAc/hexane 1:1, v/v, EtOAc) afforded the adduct (0.296 g, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.09 (d, J = 533 Hz, 1H), 4.93 (bs, 1H), 3.79 (d, J = 12 Hz, 2H), 3.15−3.25 (m, 2H), 1.7−1.9 (m, 4H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.9, 52.8 (d, J_{POC} = 7 Hz), 40.5 (d, J_{PCCC} = 6 Hz), 40.4, 28.3, 25.8 (d, J_{PC} = 94 Hz), 21.4 (d, J_{PCC} = 3 Hz); ^{31}P NMR ($CDCl_3$) δ 40.5 (dm, J_{P-H} = 521 Hz).

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Supporting Information Available: Representative spectroscopic data and table summarizing the study of reaction parameters for the radical reaction of methyl and ethyl hypophosphites. This material is available free of charge via the Internet at http://pubs.acs.org.

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