

Radical-Mediated Anti-Markovnikov  
Hydrophosphonation of Olefins

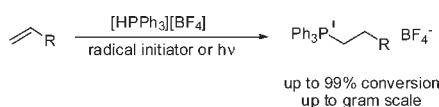
Christopher S. Daeffler and Robert H. Grubbs\*

Division of Chemistry and Chemical Engineering, California Institute of Technology,  
MC 164-30, Pasadena, California 91125, United States

rhg@caltech.edu

Received October 17, 2011

## ABSTRACT



The radical-mediated addition of triphenylphosphonium tetrafluoroborate to olefins (hydrophosphonation) is reported. Both standard radical initiators and photochemical conditions are effective, up to the gram scale. The phosphonium salts are shown to serve as *Z*-selective Wittig olefination reagents, even without purification.

Phosphines are a diverse and valuable class of compounds employed in a range of applications from organometallic ligands to organocatalysts to olefination reagents. One common way to synthesize phosphines is the addition of the P–H bond to a carbon–carbon multiple bond, called hydrophosphination. Modern hydrophosphination methods include transition metal catalysis and radical-mediated additions to multiple bonds.<sup>1,2</sup> One application of phosphorus-based radical reactions is the synthesis of structurally complex Horner–Wadsworth–Emmons (HWE) phosphonate esters, which are precursors to *E*-olefins.<sup>3</sup> HWE reagents may also be subjected to conditions that preferentially provide *Z*-olefins, but this requires specialized

phosphonate esters.<sup>4</sup> An alternative synthesis for *Z*-olefins uses alkyltriphenylphosphonium salts, or Wittig reagents.<sup>5</sup> To our knowledge, there are no radical-based analogous methods to generate Wittig phosphonium salts from olefins. Herein we describe a method to functionalize olefins by the radical-mediated addition of phosphonium salts (Figure 1).

In order to produce the desired phosphonium salts, the reaction conditions need to generate a triphenylphosphoniumyl radical cation ( $\text{PPh}_3^{\bullet+}$ ) from a triphenylphosphonium salt,  $[\text{HPPH}_3][\text{X}]$  (Figure 1). Triphenylphosphonium salts have been studied in the context of their acidity, not P–H bond homolysis, so we decided to investigate their reactivity under radical conditions.<sup>6</sup> We first attempted to hydrophosphonate a model substrate, 4-allylanisole, with a common radical initiator, azobisisobutyronitrile (AIBN), and a variety of  $[\text{HPPH}_3][\text{X}]$ . We found that a monatomic anion, bromide, did not give the desired product  $1[\text{Br}]$ , but the noncoordinating anions  $\text{BF}_4^-$  and  $\text{PF}_6^-$  gave 50% and 13% conversion of  $1[\text{BF}_4]$  and  $1[\text{PF}_6]$ , respectively (Scheme 1). Encouraged by the initial results, we embarked on a screen of conditions, seeking to improve the efficiency of the hydrophosphonation reaction with  $[\text{HPPH}_3][\text{BF}_4]$  and to gain a more complete understanding of the triphenylphosphoniumyl radical cation.

(1) Examples of transition-metal catalyzed hydrophosphination: (a) Wicht, D. K.; Kourkine, I. V.; Lew, B. M.; Nthenge, J. M.; Glueck, D. S. *J. Am. Chem. Soc.* **1997**, *119*, 5039. (b) Costa, E.; Pringe, P. G.; Worboys, K. *Chem. Commun.* **1998**, 49. (c) Wicht, D. K.; Kourkine, I. V.; Kovacic, I.; Glueck, D. S. *Organometallics* **1999**, *18*, 5381. (d) Kovacic, I.; Wicht, D. K.; Grewal, N. S.; Glueck, D. S. *Organometallics* **2000**, *19*, 950.

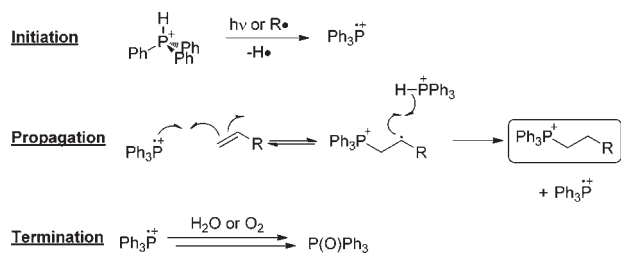
(2) Examples of radical-mediated hydrophosphination: (a) Cho, D. H.; Jang, D. O. *Synlett* **2005**, *1*, 59. (b) Robertson, A.; Bradaric, C.; Frampton, C. S.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2001**, *42*, 2609. (c) Lopin, C.; Gouhier, G.; Gautier, A.; Pietre, S. R. *J. Org. Chem.* **2003**, *68*, 9916. (d) Beaufils, F.; Dénès, F.; Renaud, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 5273. (e) Leca, D.; Fensterbank, L.; Laçote, E.; Malacra, M. *Chem. Soc. Rev.* **2005**, *34*, 858. (f) Semezin, D.; Emetad-Moghadam, G.; Albouy, D.; Diallo, O.; Koenig, M. *J. Org. Chem.* **1997**, *62*, 2414.

(3) Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T. *Org. Lett.* **2005**, *7*, 1597.

(4) (a) Breuer, E.; Bannet, D. M. *Tetrahedron Lett.* **1977**, *18*, 1141. (b) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

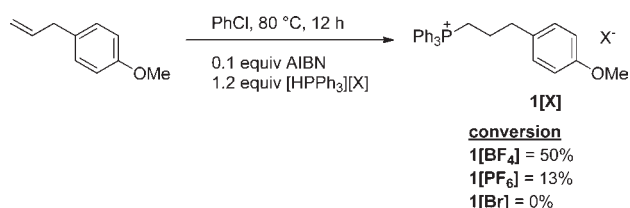
(5) (a) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(6) (a) Abdur-Rashid, K.; Fing, T. P.; Greaves, B.; Gusev, D. G.; Hinman, J. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 9155. (b) Li, T.; Lough, A. J.; Zuccaccia, C.; Macchioni, A.; Morris, R. H. *Can. J. Chem.* **2006**, *84*, 164. (c) Li, T.; Lough, A. J.; Morris, R. H. *Chem.—Eur. J.* **2007**, *13*, 3796.



**Figure 1.** Proposed hydrophosphonation mechanism.

**Scheme 1.** Anion Effect



We sought to optimize the hydrophosphonation conditions by examining the effects of the initiator, temperature, and triphenylphosphine (PPh<sub>3</sub>) additive (Table 1). The initiator 1,1'-azobis(cyclohexanecarbonitrile) (ACN), activated at 110 °C, appears to be the most effective. Dibenzoyl peroxide (DBP) is the least effective, likely due to its oxidative ability. Triphenylphosphine is a useful additive to the reaction mixture, increasing the yield slightly from 81% to 86% (entries 3 and 4). If the amount of PPh<sub>3</sub> is increased further, from 0.1 equiv to 0.5 equiv to 1 equiv, the conversion actually drops to 76% and 65%, respectively (entries 5 and 6). We believe that, in small amounts, PPh<sub>3</sub> acts to prevent termination. Previous work has shown that PPh<sub>3</sub><sup>•+</sup>, generated by laser flash photolysis from PPh<sub>3</sub>, will react with water and oxygen, with further PPh<sub>3</sub> participating to preserve the radical chain.<sup>7</sup> Under hydrophosphonation conditions, PPh<sub>3</sub> may play a similar role as the sacrificial link in the radical chain.

A Lewis acid–base pair of PPh<sub>3</sub><sup>•+</sup>–PPh<sub>3</sub> may be responsible for the deleterious effect of high PPh<sub>3</sub> concentration. When bound to PPh<sub>3</sub>, PPh<sub>3</sub><sup>•+</sup> would not be able to react with an olefin in the desired manner. This interaction would be favored at high concentration, leading to reduced conversions. Pulsed addition of both ACN and PPh<sub>3</sub> half-way through the reaction time provides the best conversions (entry 12).

Although standard radical conditions give **1[BF<sub>4</sub>]** in high conversion (94%), we surmised that a complementary

(7) (a) Nakamura, M.; Miki, M.; Majima, T. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1447. (b) Yasui, S.; Tojo, S.; Majima, T. *J. Org. Chem.* **2005**, *70*, 1276. (c) Yasui, S.; Tojo, S.; Majima, T. *Org. Biomol. Chem.* **2006**, *4*, 2969.

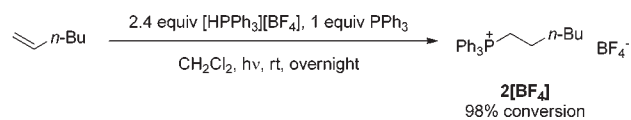
**Table 1.** Hydrophosphonation Optimization

entry	initiator <sup>a</sup>	x <sup>b</sup>	y	z <sup>b</sup>	conv (%) <sup>c</sup>
1	ACN	0.01	2.4	0	78
2	ACN	0.02	2.4	0	72
3	ACN	0.02	2.4	0	81
4	ACN	0.02	2.4	0.1	86
5	ACN	0.02	2.4	0.5	76
6	ACN	0.02	2.4	1	65
7	ACN	0.1	1.2	0	50
8	ACN	0.2	1.5	0	57
9	ACN	0.2	1.5	0.1	67
10	ACN	2×(0.1)	1.5	0.1	72
11	ACN	2×(0.1)	2	0	81
12	ACN	2×(0.1)	2.4	2×(0.1)	94
13	AIBN	0.02	2.4	0	34
14	AIBN	0.2	1.2	0	36
15	AIBN	0.5	2	0	52
16	DBP	0.2	2.4	0	35
17	DBP	2×(0.1)	2.4	0	17

<sup>a</sup> ACN and DBP were activated at 110 °C. AIBN was activated at 80 °C. <sup>b</sup> 2×(0.1) indicates that 0.1 equiv of initiator was added at the beginning and halfway through the reaction. <sup>c</sup> Conversion measured by <sup>1</sup>H NMR and based on recovered starting material.

photochemical method could be developed.<sup>8</sup> The aforementioned photolysis gave us a clue that this might be possible.<sup>7</sup> To test this hypothesis, 1-hexene was subjected to photochemical conditions, with the reaction monitored by NMR (Scheme 2). Phosphonium salt **2[BF<sub>4</sub>]** was produced quantitatively in approximately 2 h.<sup>9</sup> The effect of PPh<sub>3</sub> was also investigated. While there appears to be a general trend, as increasing amounts of PPh<sub>3</sub> gave higher conversions (Figure 2), the mechanistic underpinnings for this phenomenon are unknown. The photochemical hydrophosphonation method is scalable: 1 g batches of **1[BF<sub>4</sub>]** are easily prepared with 77% isolated yield by simple trituration of the crude reaction mixture with EtOAc.<sup>10</sup>

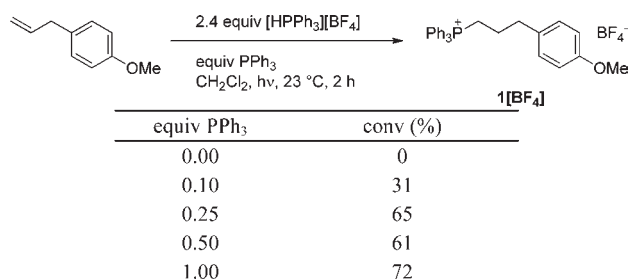
**Scheme 2.** Photochemical Hydrophosphonation of 1-Hexene



(8) Additionally, standard radical conditions produce the P(O)–Ph<sub>3</sub>–BF<sub>3</sub> adduct as a side product that is difficult to separate from the crude reaction mixture.

(9) [HPPH<sub>3</sub>][PF<sub>6</sub>] and [HPPH<sub>3</sub>][Br] are not effective as hydrophosphonating reagents under photochemical conditions. Further experiments showed that the reaction would not continue without irradiation.

(10) All reactions were carried out in Pyrex glassware with a water-cooled, quartz-jacketed UV lamp. See Supporting Information for more details.



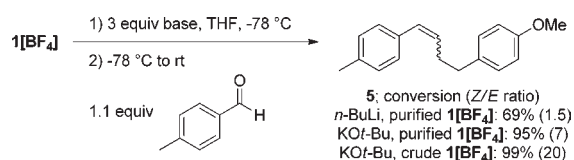
**Figure 2.** Effect of PPh<sub>3</sub> in photochemical hydrophosphonation.

**Table 2.** Substrate Scope

entry	olefin	product	yield (%) <sup>a</sup>
1			95
2			93
3			41
4			96
5			62

With two hydrophosphonation methods in hand, the reaction was expanded to incorporate an array of functional groups and olefin substitution patterns (Table 2).

**Scheme 3.** Wittig Reaction with Hydrophosphonation-Derived Phosphonium Salts



Hydrophosphonation conditions were shown to tolerate ethers and a nitrogenous heterocycle. The PPh<sub>3</sub><sup>+</sup> species will add to monosubstituted olefins with a preference over 1,2-disubstituted olefins. Radical 5-*exo*-trig ring closures are also possible, simultaneously adding complexity and functionality to these substrates.

Importantly, the phosphonium salts should be viable Wittig reagents. To examine its efficacy, **1[BF<sub>4</sub>]** was treated with *n*-BuLi or KO*t*-Bu at -78 °C. The phosphorus ylide intermediate was reacted with *p*-tolaldehyde and allowed to warm to room temperature. As expected, dissociating KO*t*-Bu conditions possess a better Z/E selectivity than *n*-BuLi for the production of 1,2-disubstituted styrene product **3** (Z/E = 1.5 versus 7), Scheme 3). Furthermore, crude **1[BF<sub>4</sub>]** can be used in the Wittig reaction with comparable yield and selectivity of **5** when compared to the reaction with purified **1[BF<sub>4</sub>]**.<sup>11</sup> This obviates the need for a purification step.

We have developed a reliable method for the radical-mediated P-H bond addition of [HPPH<sub>3</sub>][BF<sub>4</sub>] to unactivated olefins. This reaction, called hydrophosphonation, may be performed using either standard radical initiators or photochemical conditions and was applied to a range of olefins. The alkyltriphenylphosphonium tetrafluoroborate products are shown to be Z-selective Wittig reagents. Future work in this area will pursue mechanistic studies and generalization to other classes of olefins.

**Acknowledgment.** The authors would like to thank Amgen and the U.S. Department of Energy for funding. Prof. Christopher J. Douglas (University of Minnesota), Dr. Cheol K. Chung (Merck), and Prof. Guangbin Dong (University of Texas) are thanked for helpful discussions.

**Supporting Information Available.** Experimental procedures; spectroscopic data; and selected <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(11) Crude **1[BF<sub>4</sub>]** was obtained from photochemical hydrophosphonation conditions, where the mixture contains unreacted 4-allylanisole, [HPPH<sub>3</sub>][BF<sub>4</sub>], and PPh<sub>3</sub>.