Convenient Mild and Selective Hydrophosphination of Functionalized Alkenes: Access to P,O and P,S Derivatives

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Received 2 May 2008; revised 20 June 2008

Abstract: The synthesis of new functionalized phosphines is carried out through the easy and atom economic hydrophosphination reaction of functionalized alkenes such as vinyl ethers and vinyl thioethers. The reactions occur under mild conditions without catalyst using phosphine-boranes as hydrophosphinating agents.

Key words: addition reactions, alkenes, boron, phosphorus, radical reactions

Phosphines are important ligands in transition-metal-catalyzed reactions. Among the variety of methods employed for their synthesis, hydrophosphination (i.e., the addition of a P–H bond to an unsaturation) is a straightforward and efficient process, which fulfills the atom economy principle. The main promoters used are metal complexes, strong bases, acids, and free radicals. However, this approach continues to pose considerable challenges in the preparation of oxygen-sensitive phosphines. An alternate approach using phosphine-boranes as hydrophosphinating agent has solved a number of difficulties. Hence, the borane group acts as a protecting group and prevents the oxidation of the phosphine. It also activates the reaction of functionalized alkenes such as vinyl ethers and vinyl thioethers, which are available substrates.

Equation 1

Only one regioisomer was detected by 31P NMR spectroscopy. 1H NMR revealed the exclusive formation of the anti-Markovnikov adduct 2. The observed regioselectivity is similar to that obtained under radical activation with free phosphines. However, in our system, only a slight excess (1.2 equiv) of alkenes was used instead of the 2 or 3 equivalents, which are required in radical-activated process. Moreover, the reaction requires neither thermal activation nor UV irradiation, thus avoiding the polymerization of the alkene. Finally, in contrast with ‘free’ phosphines, no workup was required. The adduct was easily purified in air by flash filtration on a pad of silica gel (flash chromatography using toluene as eluent) affording 2 in 76% yield. In the first trial, the reaction was carried out on a 100 mg precursor scale but the reaction can easily be scaled up to grams under the previously defined conditions.
As shown in Table 1, the methodology can be successfully applied to other acyclic and cyclic vinyl ethers. Butyl vinyl ether was totally hydrophosphinated in 24 hours while 2-methoxypropene required 96 hours for a full conversion (Equation 2, Table 1, entries 2, 3). As in the previous example, no competing decomplexation of the phosphine-borane was noticed. Tertiary phosphate-boranes 3 and 4 having a predictable regiochemistry (anti- Markovnikov adducts) were isolated in 74 and 60% yields, respectively, and fully characterized. With 3,4-dihydro-2H-pyran, no strong influence of the cyclic structure on the reactivity was observed and hydrophosphination could be carried out in 48 hours at room temperature. Regioselectively, the phosphorus atom enters exclusively at the carbon in the β-position producing as expected the phosphine-borane 5, which was isolated in 69% yield after flash chromatography (Equation 2, Table 1, entry 4).

\[
\text{Equation 2}
\]

<table>
<thead>
<tr>
<th>Entry X</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>r.t.</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>Bu</td>
<td>H</td>
<td>H</td>
<td>r.t.</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>r.t.</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r.t.</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>S</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>35</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 1 Reaction of 1 with Vinyl Ethers and Thioethers

P,S ligands have a different behavior than P,O ligands due to the bulkiness of the sulfur atom and to its electronic properties, which makes sulfur a softer ligand, according to Pearson’s theory. We were consequently interested to check our method in the synthesis of such P,S derivatives. Ethyl vinyl sulfide was selected as a model substrate and reacted with 1 under the previously defined conditions for the oxygenated counterpart (24 h, r.t.). However, the conversion remained low (58%). Upon slightly increasing the temperature to 35 °C, an almost complete conversion was obtained after 24 hours. Again, as with vinyl ethers, no decomposition of the phosphine borane was noticed and only the anti-Markovnikov regioisomer was formed. Phosphine-borane 6 was isolated after purification in 69% yield (Equation 2, Table 1, entry 5). With phenyl vinyl sulfide, the hydrophosphination was complete at 35 °C in 48 hours affording phosphine-borane 7 in 64% yield after purification (Equation 2, Table 1, entry 6).

All the substrates being easily hydrophosphinated by 1 under mild conditions (r.t. or 35 °C), we then extended our study to more electron-rich phosphine precursors, which are known to be less reactive than diarylphosphine derivatives. Methylphenylphosphine-borane 8 was first selected. Addition of 8 to ethyl vinyl ether was performed at room temperature. The reaction was completed in 24 hours and phosphine-borane 11 was isolated in 73% yield (Equation 3, Table 2, entry 1).

\[
\begin{align*}
\text{Equation 3} \\
8: R¹ = \text{Me}, R² = \text{Ph} \\
9: R¹ = \text{t-Bu}, R² = \text{Ph} \\
10: R¹ = \text{Cy}, R² = \text{Cy}
\end{align*}
\]

Table 2 Reaction of Phosphine-boranes 8–10 with Vinyl Ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor R³</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>Et</td>
<td>r.t.</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>Et</td>
<td>r.t.</td>
<td>7 d</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Bu</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Bu</td>
<td>75</td>
<td>30 min</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Bu</td>
<td>r.t.</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Et</td>
<td>r.t.</td>
<td>96</td>
</tr>
</tbody>
</table>

a Microwave activation.  
b Amount of Et3B used: 1.2 equiv.

The reactivity of tert-butylphenylphosphine-borane 9 was, as expected, lower due to the steric bulkiness of the tert-butyl group. Nevertheless, after seven days at room temperature, hydrophosphination product 12 could be isolated in a reasonable yield of 47% (Equation 3, Table 2, entry 2). Finally, we selected dicyclohexylphosphine-borane 10 as precursor. It soon became obvious that the conditions defined for phosphines 2, 8, and 9 were inappropriate with such a bulky and electron-rich phosphine. Hence after four days at room temperature, no hydrophosphination product was observed with ethyl vinyl ether. Former studies on the hydrophosphination of alkenes with such phosphine derivatives showed that the reaction required a thermal activation. Ethyl vinyl ether having a low boiling point (bp 36 °C), we turned to butyl vinyl ether, which was more adapted for a thermal activation (bp 94 °C). Various temperatures were tested without success. Only high temperature (70 °C, 48 h) afforded some hydrophosphination product 13 although in a rather low amount (36%), as determined by 31P NMR spectroscopy. The expected product was accompanied by various side-
products and phosphine-oxides indicating decomplexation of phosphine-borane derivatives. Nevertheless, phosphine 13 was isolated in 22% yield (Equation 3, Table 2, entry 3). To improve the yield we used a microwave irradiation (MWI) device. Former studies had shown the compatibility of this device with phosphine-boranes and its advantage with bulky and electron-rich hydrophosphinating agents. However, the reaction afforded mainly decomplexed and oxidized secondary phosphines. The expected adduct 13 was isolated only in low yield (14%) (Equation 3, Table 2, entry 4). These last results show the importance of avoiding high temperature in order to limit the decomplexation-oxidation of phosphine-boranes and the formation of side-products when using ethers as substrates.

Since thermal activation was inappropriate, our next study focused on the use of a radical activator. This choice was based on the fact that: i) we had previously proposed that the mechanism of the uncatalyzed hydrophosphination reaction using phosphine-borane derivatives could involve a radical intermediate, and ii) a radical mechanism was recently proposed for the addition of phosphate oxides to alkenes in the presence of a catalytic amount of oxygen.

To prevent the formation of side-products and the polymerization of the alkenes, we avoided AIBN, which requires the use of a high temperature (65–70 °C) and selected Et3B as a radical initiator. Trialkylboranes and especially Et3B have been widely used as low temperature initiators. To the best of our knowledge, they were never employed with phosphine-borane derivatives although they have been used in one report dealing with C–P bond activation using Et3B as low temperature initiators.

Before the start of the reaction, the uncatalyzed hydrophosphination reaction using phosphine-borane precursors could involve a radical intermediate, and a radical mechanism was recently proposed for the addition of phosphate oxides to alkenes in the presence of a catalytic amount of oxygen.

To prevent the formation of side-products and the polymerization of the alkenes, we avoided AIBN, which requires the use of a high temperature (65–70 °C) and selected Et3B as a radical initiator. Trialkylboranes and especially Et3B have been widely used as low temperature initiators.

To the best of our knowledge, they were never employed with phosphine-borane derivatives although they have been used in one report dealing with C–P bond formation by hydrophosphination using hypophosphite as hydrophosphinating agent. Et3B in hexane (1.2 equiv) was simply added to the reaction mixture and the reaction was run at room temperature using a 1:1.2 ratio of phosphine-borane 10/butyl vinyl ether in a small amount of toluene. Under these conditions, the reaction was complete in 96 hours at room temperature and compound 13 was isolated in 54% yield (Equation 3, Table 2, entry 5). To verify that the reaction was indeed radical activated, the experiment was repeated in the presence of a radical trap (duroquinone). After 24 hours, secondary phosphine-borane 10 was recovered unreacted and no trace of phosphine-borane 13 was detected by 31P NMR spectroscopy, confirming the radical activation induced by Et3B. The reaction was next carried out with ethyl vinyl ether in the presence of Et3B, and 14 was isolated in 53% yield (Equation 3, Table 2, entry 6). The Et3B activation was also observed, although less impressive, in the reaction between butyl vinyl ether and phosphine-borane 1, the reaction being completed in 13 hours compared to 24 hours in the absence of the radical catalyst. All these results are in agreement with a radical-catalyzed process.

In summary, we have devised a fully regioselective hydrophosphination of functionalized alkenes, which gives an efficient and easy access to a new family of ether and thioether/phosphine-borane derivatives. All the reactions were carried out under mild conditions (r.t. to 35 °C) and do not require any catalyst except for the very bulky and electron-rich dicyclohexylphosphine-borane, where a radical activation using Et3B was applied at room temperature. Application in homogeneous catalysis of the potential phosphate-ether ligands, which have been prepared by this methodology, is under investigation.

Phosphine-boranes 1, 8, 9, 10 were synthesized following published procedures. Toluene was dried by an Innovative Technology Pure Solvent device. Solvents used for column chromatography were directly used from commercial bottles. The microwave irradiation apparatus was a Discover from CEM Company with a maximal power of 300 watts.

1H, 13C, and 31P NMR spectra were recorded on Bruker DPX 250 and Bruker AC 400 spectrometers. 11B NMR spectra were recorded on a Bruker AC 400 spectrometer. TMS was used as internal reference for recording the 1H and 13C NMR spectra. 85% H3PO4 and BF3·OEt2 were used as external reference for 31P and 31P NMR spectroscopy, respectively. Coupling constants are reported in Hz.

Uncatalyzed Hydrophosphination of Vinyl Derivatives; General Procedure

An oven-dried Schlenk-tube was charged with phosphine-borane precursor 1, 8 or 9 (1 equiv). After three cycles with oil pump vacuum/N2 purge, the respective alkene (1.2 equiv) was added under a N2 flow. Then, toluene (0.25 mL) was added to the solution. The mixture was stirred for the time and at temperature indicated in Tables 1 and 2, and then cooled to r.t. as required. The crude product was directly purified by silica gel chromatography. The pure product was obtained after drying under vacuum.

Et3B-Catalyzed Hydrophosphination of Vinyl Derivatives with 10; General Procedure

An oven-dried Schlenk-tube was charged with phosphine-borane precursor 10 (1 equiv). After three cycles with oil pump vacuum/N2 purge, the respective alkene (1.2 equiv) was added under a N2 flow. Then, toluene (0.25 mL) and Et3B (1.2 equiv) were added to the solution. The mixture was stirred for 96 h at r.t. The crude product was directly purified by silica gel chromatography. The pure product was obtained after drying under vacuum.

(2-Ethoxyethyl)diphenylphosphine-borane (2)

Prepared from phosphine-borane 1 (100 mg, 0.5 mmol) and ethyl vinyl ether (58 μL, 0.6 mmol); yield: 76%; translucent oil; Rf = 0.35 (toluene).

1HNMR (250 MHz, CDCl3): δ = 7.75–7.72 (m, 1 H), 7.72–7.68 (m, 2 H), 7.68–7.64 (m, 1 H), 7.56–7.37 (m, 6 H), 3.65 (dt, JH,P = 15.2 Hz, JH,P = 7.5 Hz, 2H), 3.41 (q, JH,P = 7.0 Hz, 2 H), 2.60 (dt, JH,P = 11.4 Hz, JH,P = 7.5 Hz, 1 H), 2.55 (dt, JH,P = 11.4 Hz, JH,P = 7.5 Hz, 1 H), 1.096 (t, JH,P = 7.0 Hz, 3 H, 3 H), 0.90 (q, JH,P = 9.1 Hz, 3 H, 3 H).

13CNMR (63 MHz, CDCl3): δ = 132.1 (d, JCP = 9.4 Hz), 131.2 (d, JCP = 1.9 Hz), 129.3 (d, JCP = 56.6 Hz), 128.8 (d, JCP = 10.1 Hz), 66.3 (s), 64.9 (d, JCP = 5.0 Hz), 26.4 (d, JCP = 36.48 Hz), 15.0 (s).

31PNMR (101 MHz, CDCl3): δ = 13.53 (dd, JCP = 71.0 Hz). HRMS: m/z calculated for [M – H]+: 258.1174; found: 258.1182.

(2-Butoxyethyl)diphenylphosphine-borane (3)

Prepared from phosphine-borane 1 (100 mg, 0.5 mmol) and butyl vinyl ether (78 μL, 0.6 mmol); yield: 74%; translucent oil; Rf = 0.2 (toluene).
Pyran-2-ylidophenylphosphine-borane (5)
Prepared from phosphine-borane 1 (100 mg, 0.5 mmol) and 3,4-dihydro-2H-pyran (55 μL, 0.6 mmol); yield: 69%; translucent oil; \( R_f = 0.3 \) (toluene).

1H NMR (250 MHz, CDC13); \( \delta = 7.83-7.66 \) (m, 4 H), 7.57-7.40 (m, 6 H), 4.01-3.90 (m, 1 H), 3.90-3.79 (m, 1 H), 3.59 (dt, \( J_{C,P} = 2.0 \) Hz, \( J_{H,P} = 1.15 \) Hz, 1 H), 3.40 (dt, \( J_{C,P} = 3.25 \) Hz, \( J_{H,P} = 11.0 \) Hz, 1 H), 2.89-2.68 (m, 4 H), 1.87-1.54 (m, 3 H).

13C NMR (63 MHz, CDC13); \( \delta = 132.6 \) (d, \( J_{C,P} = 8.8 \) Hz), 132.4 (d, \( J_{C,P} = 8.8 \) Hz), 131.6 (d, \( J_{C,P} = 2.5 \) Hz), 131.5 (d, \( J_{C,P} = 2.5 \) Hz), 129.1 (d, \( J_{C,P} = 9.4 \) Hz), 129.0 (d, \( J_{C,P} = 9.4 \) Hz), 127.6 (d, \( J_{C,P} = 54.7 \) Hz), 127.5 (d, \( J_{C,P} = 54.1 \) Hz), 68.4 (s), 68.2 (d, \( J_{C,P} = 8.7 \) Hz), 32.7 (d, \( J_{C,P} = 34.3 \) Hz), 29.9 (s), 26.5 (d, \( J_{C,P} = 9.9 \) Hz), 24.1 (s).

31P NMR (101 MHz, CDCl3); \( \delta = 16.63 \) (dm, \( J_{P,B} = 61.5 \) Hz).


Dicyclohexyl(2-butoxy)ethylphosphine-borane (6)
Prepared from phosphine-borane 1 (100 mg, 0.5 mmol) and ethyl vinyl ether (58 μL, 0.6 mmol); yield: 69%; translucent oil; \( R_f = 0.3 \) (CHCl3).

1H NMR (250 MHz, CDC13); \( \delta = 7.80-7.67 \) (m, 2 H), 7.57-7.40 (m, 3 H), 3.82-3.68 (m, 1 H), 3.53-3.30 (m, 1 H), 3.43 (t, \( J_{C,P} = 7.1 \) Hz, 2 H), 2.59-2.39 (m, 1 H), 2.32-2.14 (m, 1 H), 1.47-1.28 (m, 1 H), 1.11 (t, \( J_{H,P} = 7.1 \) Hz, 3 H), 1.11 (d, \( J_{C,P} = 14.0 \) Hz, 9 H), 0.60 (q, \( J_{H,B} = 88.4 \) Hz, 3 H).

13C NMR (63 MHz, CDC13); \( \delta = 133.4 \) (d, \( J_{C,P} = 8.2 \) Hz), 131.4 (d, \( J_{C,P} = 1.9 \) Hz), 128.5 (d, \( J_{C,P} = 9.4 \) Hz), 125.9 (d, \( J_{C,P} = 48.4 \) Hz), 66.4 (s), 65.5 (d, \( J_{C,P} = 5.0 \) Hz), 29.2 (d, \( J_{C,P} = 33.3 \) Hz), 25.4 (d, \( J_{C,P} = 2.5 \) Hz), 19.9 (d, \( J_{C,P} = 33.3 \) Hz).

31P NMR (101 MHz, CDCl3); \( \delta = 27.82 \) (q, \( J_{P,B} = 69.7 \) Hz).

Dicyclohexyl(2-ethoxy)ethylphosphine-borane (14)

Prepared from phosphine-borane 10 (106 mg, 0.5 mmol), ethyl vinyl ether (58 μL, 0.6 mmol), and Et3B (600 μL, 1 mol·L⁻¹ in hexane); yield: 53%; translucent oil; Rf = 0.3 (toluene).

1H NMR (250 MHz, CDCl₃): δ = 3.63 (dt, J_H,B = 15.5 Hz, J_H,H = 7.4 Hz, 2 H), 3.49 (q, J_H,H = 7.0 Hz, 2 H), 1.98–1.62 (m, 13 H), 1.48–1.13 (m, 11 H), 1.20 (t, J_H,H = 7.0 Hz, 3 H), 0.25 (qm, J_H,H = 9.2 Hz, 3 H).

13C NMR (63 MHz, CDCl₃): δ = 66.2 (s), 65.7 (d, J_C,P = 3.4 Hz), 31.9 (d, J_C,P = 32.9 Hz), 26.8 (d, J_C,P = 1.1 Hz), 26.8 (s), 26.7 (d, J_C,P = 2.5 Hz), 26.6 (d, J_C,P = 2.5 Hz), 25.9 (d, J_C,P = 1.2 Hz), 19.8 (d, J_C,P = 30.9 Hz), 15.2 (s).

31P NMR (101 MHz, CDCl₃): δ = 23.83 (dm, J_P,B = 74.0 Hz).

HRMS: m/z calc for [M – H]⁺: 283.2362; found: 283.2367.

Acknowledgment

This work was performed within the ‘CRUNCH’ interregional network. We gratefully acknowledge financial support from the ‘Ministère de la Recherche et des Nouvelles Technologies’, CNRS (Centre National de la Recherche Scientifique), the ‘Région Basse-Normandie’ and the European Union (FEDER funding) for financial support.

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