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Potassium Carbonate Promoted Nucleophilic Addition of Alkenes with Phosphites

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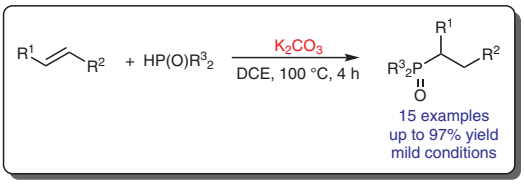

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Abstract A facile hydrophosphonylation of alkenes by phosphites promoted by potassium carbonate was developed. The reaction features include easy handling, environmental friendliness, and avoidance of the use of strong bases. A variety of alkenes are tolerated in this reaction, with moderate to excellent yields.

Key words potassium carbonate, addition, alkenes, phosphites, hydrophosphonylation

Organophosphorus compounds are widely found in natural products, pharmaceuticals, functional materials, and ligands.[1] Consequently, the development of synthetic methods for the formation of these compounds has attracted much attention in organic chemistry. Among these methods, the addition of P(O)–H bonds to alkenes plays an important role because this method is straightforward and atom economical.[2] During recent decades, a variety of strategies have been developed to permit this addition, for example by using transition-metal salts, acids, or PBu_3 as catalysts,[3–5] by using AIBN or other radical initiators, or by the application of microwave-assisted conditions.[6,7] Organic and inorganic bases, including EtONa,[8] *t*-BuOK,[9] $Ca(OH)_2$,[10] NaH,[11] amines,[12] or Et_2Zn,[13] have recently been found to accelerate the addition reactions, making them more convenient, generating less organic waste, and being easier to handle. Although great advances have been made, most of the bases used are strong, which might limit the functional compatibility of the substrates. Here, we report a weak-base-promoted hydrophosphonylation of alkenes with phosphine oxides as phosphorus sources under mild conditions.

Because of our ongoing interest in phosphonylation reactions,[14] we selected diphenylphosphine oxide (**1a**) and butyl acrylate (**2a**) as model substrates to optimize the reaction. When the reaction was carried out without a base in CH_3CN at 100 °C under N_2 for four hours, no addition product was obtained (Table 1, entry 1). Interestingly, when Na_2CO_3 was employed as a base, the reaction gave the expected product in 79% yield (entry 2), whereas K_2CO_3 gave the desired product in 80% yield (entry 3) and Cs_2CO_3 was less efficient (4). Strong bases such as *t*-BuOK and KOH were not good bases in this transformation (entries 5 and 6). Similarly, unsatisfactory yields were obtained when inorganic bases were used; for example, when DABCO or Et_3N was used in the reaction, moderate yields were obtained (entries 7 and 8). Next, the effects of the solvent on the reaction were studied. CH_2Cl_2 delivered the desired product in 75% yield (entry 9), whereas THF, toluene, and DMF were poorer solvents for this transformation (entries 10–12). DCE was the best solvent, giving the desired product in 95% yield (entry 13), while switching the base to Na_2CO_3 gave a 91% yield (entry 14). Finally, the effect of the loading of K_2CO_3 was examined. Reducing the loading of the base to one equivalent decreased yield of the addition product to 45% yield, whereas increasing the amount of K_2CO_3 did not promote the conversion (entries 15 and 16). Because the reaction is sensitive to O_2, the yield of product dropped to 74% when the reaction was performed under air (entry 17).

Having determined the optimal reaction conditions, we explored the substrate scope of the K_2CO_3-promoted addition reaction (Scheme 1). Ethyl acrylate delivered the desired product **3b** in 93% yield. Methyl acrylate and methyl methacrylate gave the corresponding products **3c** and **3d** in yields of 71 and 67%, respectively. Interestingly, when dimethyl fumarate was subjected to the reaction, the expect-

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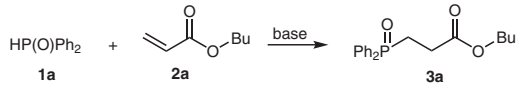
Table 1 Optimization of the Reaction[a]

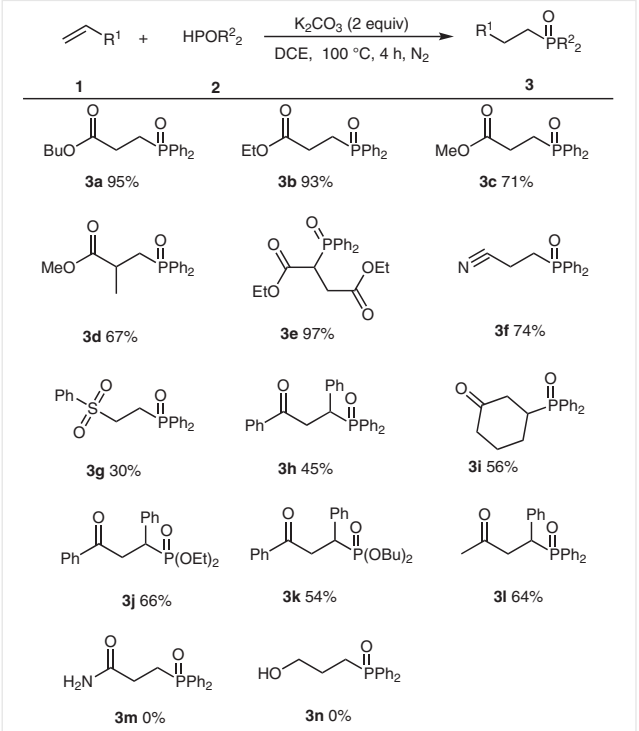


Entry	Base	Solvent	Yield[b] (%)
1	–	CH_3CN	–
2	Na_2CO_3	CH_3CN	79
3[c]	K_2CO_3	CH_3CN	80
4	Cs_2CO_3	CH_3CN	67
5	*t*-BuOK	CH_3CN	36
6	KOH	CH_3CN	46
7	DABCO	CH_3CN	42
8	Et_3N	CH_3CN	75
9	K_2CO_3	CH_2Cl_2	75
10	K_2CO_3	THF	68
11	K_2CO_3	toluene	58
12	K_2CO_3	DMF	72
13	**K_2CO_3**	**DCE**	**95**
14	Na_2CO_3	DCE	91
15[c]	K_2CO_3	DCE	45
16[d]	K_2CO_3	DCE	94
17[e]	K_2CO_3	DCE	74

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2 equiv), base (200 mol%), solvent (2 mL), 100 °C, N_2, 4 h.
[b] Isolated yield.
[c] K_2CO_3 (1 equiv).
[d] K_2CO_3 (3 equiv).
[e] Under air.

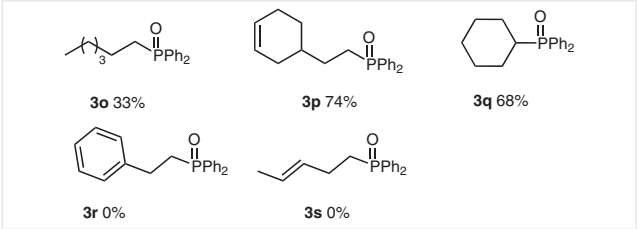
ed product **3e** was isolated in 97% yield. Furthermore, the acrylonitrile delivered the addition product **3f** in 74% yield, whereas, (vinylsulfonyl)benzene gave the desired product **3g** in only 30% yield. The nonterminal alkene chalcone was also tolerated, giving the corresponding addition product **3h** in 45% yield. Cyclohex-2-en-1-one gave the corresponding product **3i** in 56% yield. Notably, alkyl phosphonates were suitable reactants. For example, when diethyl and dibutyl phosphonates were used as reaction partners with chalcone, the corresponding addition products **3j** and **3k** were isolated in yields of 66 and 54% yield. 4-Phenylbut-3-en-2-one also gave the desired product **3l** in 64% yield. Unfortunately, alkenes with active hydrogens, such as acrylamide or prop-2-en-1-ol, did not undergo the addition reaction under the standard conditions (**3m** and **3n**).

Interestingly, the unsubstituted terminal alkene hex-1-ene were found to be a suitable substrate for this hydrophosphonylation reaction, although its reactivity was relatively low and the anti-Markovnikov product **3o** was obtained (Scheme 2). In addition, 4-vinylcyclohex-1-ene gave the desired product **3p** in 74% yield. Inspired by this, we applied the reaction to cyclohexene and isolated the desired



Scheme 1 The scope of substrates for the reaction

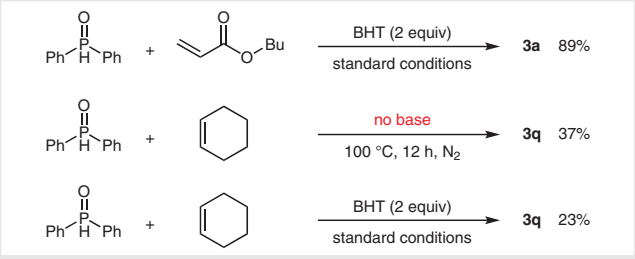
product **3q** in 68% yield. Unfortunately, the conjugated olefins styrene and penta-1,3-diene did not deliver the corresponding addition products **3r** and **3s**.



Scheme 2 The scope of other substrates for the reaction

Several control experiments were conducted to gain insight into the reaction mechanism (Scheme 3). When butylated hydroxytoluene (BHT) was added to the model reaction system, the desired product **3a** was isolated in 89% yield, indicating that a radical process did not occur in this reaction. However, with cyclohexene, we found that the reaction proceeded in the absence of a base, albeit with less efficiency, giving the desired product **3q** in 37% yield. This provided two pieces of information: first, a base is essential for this hydrophosphonylation, and secondly, the formation of an anti-Markovnikov product shows the reaction might proceed through a radical mechanism in the presence of a trace of air.[6d] When we added the radical scavenger BHT to

the reaction of cyclohexene under standard conditions, the yield of the addition product **3q** fell to 23%, confirming that our hypothesis was correct.



Scheme 3 Control experiment

In conclusion, we have developed a weak-base-promoted hydrophosphonylation reaction of alkenes with disubstituted phosphine oxides under mild conditions.[15] A series of electron-deficient olefins with terminal nonactivated alkene groups, as well as chalcones, are suitable substrates for this transformation, giving moderate to good yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707852.

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(15) **Butyl 3-(Diphenylphosphoryl)propanoate (3a); Typical Procedure**

A mixture of **1a** (0.4 mmol), **2a** (0.8 mmol), and K_2CO_3 (0.8 mmol) in DCE (2 mL) was heated at 100 °C under N_2 for 4 h. The mixture was then extracted with DCE (3 × 5 mL) and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by TLC [silica gel, PE–EtOAc (3:1)] to give a colorless liquid; yield: 132 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 10.9, 7.6 Hz, 4 H), 7.43 (dd, *J* = 21.7, 6.4 Hz, 6 H), 3.96 (t, *J* = 6.6 Hz, 2 H), 2.55 (s, 4 H), 1.48 (pent, *J* = 6.8 Hz, 2 H), 1.25 (hept, *J* = 7.3 Hz, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H). HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{24}O_3P$: 331.1458; found: 331.1467.

