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An Efficient Conjugate Addition of Dialkyl Phosphite to Electron-Deficient Olefins: The Use of a Nucleophilic Organocatalyst to Form a Strong Base

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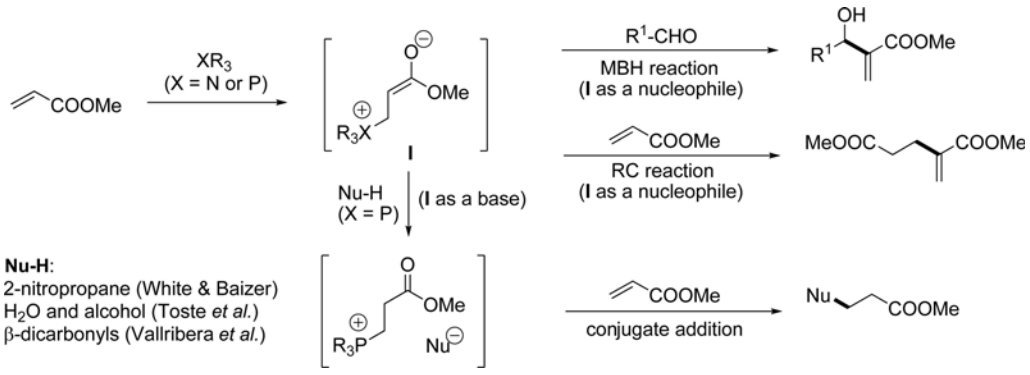
The formation of a zwitterionic species between electron-deficient olefins and tertiary amine or phosphine is a pivotal and the starting point for the Morita-Baylis-Hillman (MBH) reaction[1] and Rauhut-Currier (RC) reaction.[2] A subsequent 1,2-addition of the zwitterion **I**, which was generated from methyl acrylate as an example, to aldehyde and a proton movement furnished the Morita-Baylis-Hillman adduct, whereas a conjugate addition to electron-deficient olefins is the Rauhut-Currier reaction, as shown in Scheme 1. Basically, the zwitterion is an ester enolate and could act as a base.[3,4] In this respect, White and Baizer reported a phosphine-catalyzed conjugate addition of 2-nitropropane to various electron-deficient olefins, as also shown in Scheme 1.[3a] Toste and co-workers reported a phosphine-catalyzed conjugate addition of alcohol or water to electron-deficient olefins.[3b] Later, Pedduri and Williamson have applied the concept to make tetrahydrofurans.[3c] Vallribera and co-workers also reported the conjugate addition of β-dicarbonyl compounds to electron-deficient olefins.[3d] The mechanism of the conjugate additions likely involves the zwitterion **I** behaving as a base to deprotonate the nitroalkane, alcohol, water and β-dicarbonyl; the nitronate, alkoxide, hydroxide or the enolate of β-dicarbonyl then undergoes the following conjugate additions to electron-deficient olefins. Recently, Tian and co-workers have developed an efficient alternative way to Henry reaction involving a deprotonation of a nitroalkane with the zwitterionic ester enolate to form a nitronate and a subsequent reaction with aldehyde.[4]

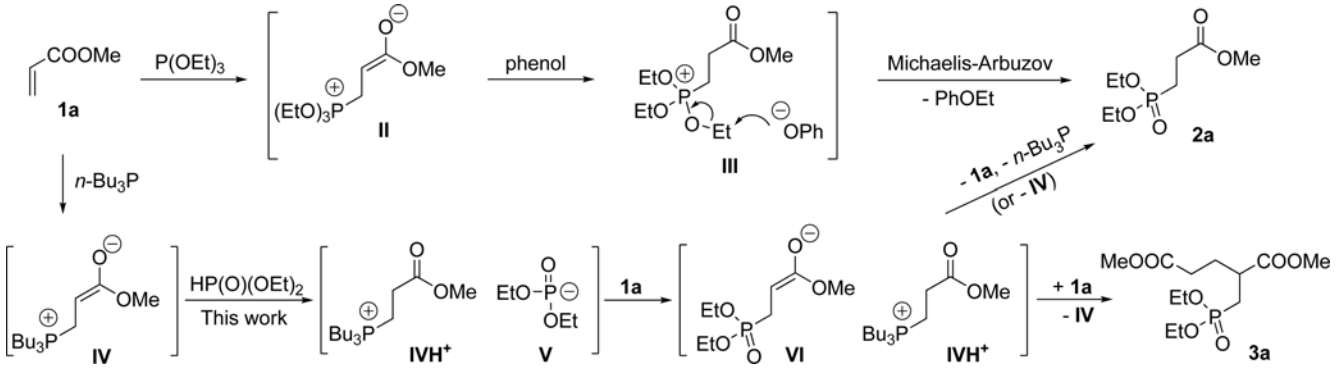
The conjugate addition of a dialkylphosphonate anion to electron-deficient olefins provided an efficient way to alkyl-substituted phosphonates;[5,6] however, the method required usually a strong base[6a,b,d-h] or somewhat drastic conditions.[6c] Thus, an alternative way has been used more widely involving the use of trialkyl phosphite.[7] The reaction between electron-deficient olefins such as methyl acrylate and trialkyl phosphite generated a zwitterionic species at elevated temperature. A subsequent Michaelis-Arbuzov type rearrangement in the presence of phenol afforded the desired alkyl phosphonate, as shown in Scheme 2. In these respects, we presumed that the conjugate addition reactions catalyzed by a nucleophilic organocatalyst such as tributylphosphine could be applied for the synthesis of alkyl phosphonate, as also shown in Scheme 2.

At the outset of our experiment we examined the reaction of methyl acrylate and diethyl phosphite in the presence of various nucleophilic catalyst including DABCO, *n*-Bu_3P and PPh_3 in CH_3CN. The use of DABCO (10 mol %, rt, 6 days) did not produce **2a** in any trace amount.[3b] The use of *n*-Bu_3P (20 mol %, rt, 2 h) produced **2a** in good yield (72%), whereas the reaction in the presence of PPh_3 (20 mol %, reflux, 24 h) produced **2a** in a trace amount (< 5%).[3b] Further studies revealed that the use of 5-10 mol % of *n*-Bu_3P showed cleaner reaction and increased the yield of **2a**.

The reaction mechanism for the formation of **2a** could be suggested, as shown in Scheme 2. A conjugate addition of *n*-Bu_3P to **1a** produced a zwitterionic intermediate **IV**. Diethyl



Scheme 1



Scheme 2

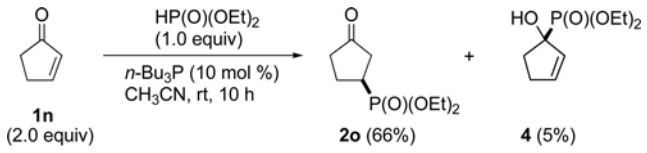
phosphite was deprotonated by the intermediate **IV** to form **IV**H$^+$ and the diethylphosphonate anion **V**. The anion **V** attacks **1a** in a conjugate manner to produce **VI**, which abstracts a proton from **IV**H$^+$ and forms **2a**. The formation of a side product **3a**, which could be formed by the reaction of **VI** and **1a**, was observed in a trace amount (4%).

Encouraged by the successful result, we examined the synthesis of various phosphonates *via* *n*-Bu$_3$P-catalyzed conjugate addition of dialkyl phosphites to some representative electron-deficient olefins. The results are summarized in Table 1. The reaction of methyl acrylate (**1a**) and diethyl phosphite (entry 1) afforded **2a** in good yield (86%) in the presence of *n*-Bu$_3$P (5 mol %) for 1 h.[8] The use of dimethyl- and diisopropyl phosphites afforded the corresponding phosphonates **2b** and **2c** in good yields (entries 2 and 3). The reaction of acrylonitrile (**1c**) showed a similar result (entry 4). When we used phenyl vinyl sulfone (**1d**), somewhat longer reaction time (20 h) was required even in the presence of 10 mol % of *n*-Bu$_3$P (entry 5). Acrylamide (**1e**) and *N,N*-dimethylacrylamide (**1f**) also required 20 h for the completion (entries 6 and 7). The reaction with methyl vinyl ketone (**1g**) was somewhat complex (entry 8), and a desired product **2h** was isolated in moderate yield (51%). Many side products were formed including a 1,2-addition product.[6h,i] Three α-substituted electron-deficient olefins **1h-j** (entries 9-11) gave the products **2i-k** in good yields (81-86%). However, the protocol could not be applied to β-substituted vinyl compounds such as ethyl crotonate (**1k**), chalcone (**1l**), and 3-penten-2-

Table 1. *n*-Bu$_3$P-catalyzed conjugate addition of dialkyl phosphite[a]

Entry	Substrate	Product (%)	Entry	Substrate	Product (%)
1[b]	COOMe **1a**	$(EtO)_2(O)P$ COOMe **2a** (86)	8[b]	COMe **1g**	$(EtO)_2(O)P$ COMe **2h** (51)
2[b]	COOEt **1b**	$(MeO)_2(O)P$ COOEt **2b** (78)	9[c]	COOMe **1h**	$(EtO)_2(O)P$ COOMe **2i** (86)
3[b]	**1b**	$(i\text{-PrO})_2(O)P$ COOEt **2c** (83)	10	NC CN **1i**	$(EtO)_2(O)P$ NC CN **2j** (81)
4[b]	CN **1c**	$(EtO)_2(O)P$ CN **2d** (82)	11	Ph COPh **1j**	$(EtO)_2(O)P$ Ph COPh **2k** (84)
5	SO_2Ph **1d**	$(EtO)_2(O)P$ SO_2Ph **2e** (84)	12	COOEt **1k**	$(EtO)_2(O)P$ COOEt **2l** (0)
6	$CONH_2$ **1e**	$(EtO)_2(O)P$ $CONH_2$ **2f** (88)	13	COPh Ph **1l**	$(EtO)_2(O)P$ COPh Ph **2m** (0)
7	$CONMe_2$ **1f**	$(EtO)_2(O)P$ $CONMe_2$ **2g** (90)	14	COMe **1m**	$(EtO)_2(O)P$ COMe **2n** (0)

[a]Conditions: Michael acceptor **1** (1.0 mmol), dialkyl phosphite (0.5 mmol), *n*-Bu$_3$P (10 mol %), CH$_3$CN, rt, 20 h. [b]Conditions: Michael acceptor **1** (1.0 mmol), dialkyl phosphite (0.5 mmol), *n*-Bu$_3$P (5 mol %), CH$_3$CN, rt, 1 h. [c]Reaction time was 30 h.



Scheme 3

one (**1m**), unfortunately (entries 12-14). The failure might be due to insufficient formation of a zwitterionic species between the organocatalyst (*n*-Bu_3P) and β-substituted vinyls because of the steric hindrance.

As a last entry, we also examined the reaction of 2-cyclopenten-1-one (**1n**), as shown in Scheme 3. As in the case of methyl vinyl ketone (entry 8 in Table 1), 1,4-addition product **2o** was obtained as a major product (66%) along with a trace amount of 1,2-addition product **4** (5%).

In summary, an efficient organocatalyst-catalyzed conjugate addition of dialkyl phosphite was disclosed. The reaction of dialkyl phosphites and β-unsubstituted electron-deficient olefins in the presence of a catalytic amount of *n*-Bu_3P produced alkylphosphonates in good yields.

Experimental Section

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Unity Plus 300 spectrometer using tetramethylsilane (TMS, δ = 0 ppm) as an internal standard. ^{31}P NMR (121 MHz) spectra were recorded on Varian Unity Plus 300 spectrometer using 85% H_3PO_4 (δ = 0 ppm) as an external standard.

Typical Procedure for the Synthesis of 2a. To a stirred solution of methyl acrylate (86 mg, 1.0 mmol) and diethyl phosphite (69 mg, 0.5 mmol) in CH_3CN (1.0 mL) was added *n*-Bu_3P (5 mg, 5 mol %), and the reaction mixture was stirred for 1 h at room temperature. After removal of solvent under reduced pressure and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 1:1:1), compound **2a**[6e,i,7e] was obtained as colorless oil, 96 mg (86%) along with a trace amount of **3a** (6 mg, 4%).[9a] Other compounds **2b**,[9b] **2c**,[9c] **2d**,[6a,k] **2e**,[6i] **2f**,[6a,7f] **2g**, **2h**,[6h,i] **2i-k**, **2o**,[6i,7c,d] and **4**[6i] were synthesized similarly, and the spectroscopic data of unknown compounds, **2g**, **2i**,[9d] **2j** and **2k**, are as follows.

Compound 2g: 90%; colorless oil; IR (film) 1649, 1497, 1398, 1244, 1163, 1057, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, *J* = 7.2 Hz, 6H), 1.98-2.09 (m, 2H), 2.49-2.58 (m, 2H), 2.89 (s, 3H), 2.96 (s, 3H), 3.97-4.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.10 (J_{PC} = 5.7 Hz), 20.62 (J_{PC} = 142.6 Hz), 26.09 (J_{PC} = 2.3 Hz), 35.31, 36.70, 61.31 (J_{PC} = 6.2 Hz), 170.48 (J_{PC} = 17.7 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 31.98; ESIMS *m/z* 238 [M^++H]. Anal. Calcd for $C_9H_{20}NO_4P$: C, 45.57; H, 8.50; N, 5.90. Found: C, 45.82; H, 8.39; N, 5.78.

Compound 2i:[9d] 86%; colorless oil; IR (film) 1740, 1458, 1256, 1240, 1163, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.67-1.80 (m, 1H), 2.15-2.29 (m, 1H), 2.70-2.86 (m, 1H), 3.63 (s, 3H), 3.97-4.07 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.22 (J_{PC} = 6.3 Hz), 18.55 (J_{PC} = 9.7 Hz), 29.08 (J_{PC} = 141.4 Hz), 34.29 (J_{PC} = 4.0 Hz), 51.83, 61.49 (J_{PC} = 6.9 Hz), 61.51 (J_{PC} = 6.3 Hz), 175.58 (J_{PC} = 12.0 Hz); ESIMS *m/z* 239 [M^++H]. Anal. Calcd for $C_9H_{19}O_5P$: C, 45.38; H, 8.04. Found: C, 45.69; H, 7.95.

Compound 2j: 81%; pale yellow oil; IR (film) 2247, 1447, 1393, 1246, 1163, 1051, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, *J* = 7.2 Hz, 6H), 1.90-2.12 (m, 4H), 2.46-2.66 (m, 2H), 2.98-3.13 (m, 1H), 4.04-4.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.08, 16.27 (J_{PC} = 5.7 Hz), 16.29 (J_{PC} = 5.7 Hz), 25.58 (J_{PC} = 4.0 Hz), 28.11 (J_{PC} = 143.7 Hz), 28.67 (J_{PC} = 9.2 Hz), 62.47 (J_{PC} = 6.3 Hz), 62.50 (J_{PC} = 6.3 Hz), 117.60, 119.08 (J_{PC} = 11.5 Hz); ESIMS *m/z* 245 [M^++H]. Anal. Calcd for $C_{10}H_{17}N_2O_3P$: C, 49.18; H, 7.02; N, 11.47. Found: C, 49.03; H, 7.34; N, 11.29.

Compound 2k: 84%; colorless oil; IR (film) 1682, 1597, 1449, 1244, 1051, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 2.10-2.22 (m, 1H), 2.77-2.90 (m, 1H), 3.72-3.98 (m, 4H), 4.93-5.02 (m, 1H), 7.09-7.15 (m, 1H), 7.17-7.34 (m, 6H), 7.38-7.44 (m, 1H), 7.89-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.09 (J_{PC} = 6.3 Hz), 16.22 (J_{PC} = 6.3 Hz), 29.71 (J_{PC} = 139.1 Hz), 44.57 (J_{PC} = 2.3 Hz), 61.53 (J_{PC} = 6.3 Hz), 61.57 (J_{PC} = 6.9 Hz), 127.45, 128.16, 128.50, 128.80, 129.02, 133.03, 136.00, 138.69 (J_{PC} = 10.4 Hz), 197.83 (J_{PC} = 8.0 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 29.27; ESIMS *m/z* 347 [M^++H]. Anal. Calcd for $C_{19}H_{23}O_4P$: C, 65.89; H, 6.69. Found: C, 65.95; H, 6.47.

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