Manganese(III)-mediated direct phosphonation of arylalkenes and arylalkynes†

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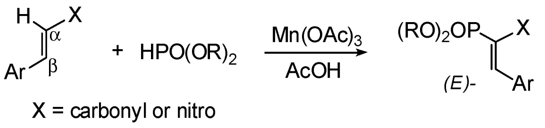
Mn(III)-mediated phosphonations of carbon–carbon double and triple bonds to form alkenylphosphonates are introduced.

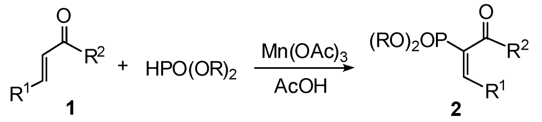
Alkenylphosphonate is a synthetically versatile functional group,[1] which is also responsible for many biologically active compounds.[2] The synthesis of alkenylphosphonates can be accomplished by Knoevenagel condensations of phosphonacetate esters with aldehydes and ketones,[3] or by Pudovik-type hydrophosphonations of alkynes under ionic,[4] free radical,[5] and transition metal-catalyzed conditions.[6] Introduced in this paper are $Mn(OAc)_3$-promoted oxidative free radical reactions[7] of dialkylphosphites with arylalkenes (Scheme 1), a new approach to preparing alkenylphosphonates *via* direct phosphonation of sp^2 C–H bonds.

The Ishii and our groups recently reported the $Mn(OAc)_3$-promoted phosphonations for the preparation of aryl- and heteroarylphosphonates.[8,9] There are two challenges in applying this method of preparing alkenylphosphonates: (1) how to control radical additions to avoid polymerization of alkenes, and (2) how to control the regio- and stereo-(*E*/*Z*)-selectivities of the phosphonation process. From the initial experiments using simple conjugated terminal alkenes such as methyl acrylate **1a**, acrylonitrile **1b**, and styrene **1c**, we found that the reactions with dimethylphosphite only gave mixtures of polymers.[10] Reactions with conjugated non-terminal alkenes **1d–g** produced much lesser amounts of polymerization products, but alkenylphosphonate products were the mixtures of regio- and *E*/*Z* isomers. These results suggest that these conjugated alkenes are too reactive for selective dialkylphosphonyl radical-based phosphonations. Since dialkylphosphonyl radicals are electrophilic and the α-position of the arylalkene has a high electron density, we envisioned that the reaction selectivity might be improved if an electron-withdrawing group is attached to the α-position of the arylalkene.



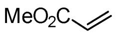
Scheme 1

Table 1 Phosphonation of α,β-unsaturated arylketones



Entry	R^1	R^2	R	% Yield
1	Ph	Ph	Et	73
2	Ph	*p*-$MeOC_6H_4$	Et	78
3	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	Et	76
4	Ph	*p*-MeC_6H_4	Et	71
5	*p*-ClC_6H_4	Ph	Et	64
6	Ph	Me	Et	80
7	Ph	Ph	Me	77
8	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	Me	73
9	Ph	Me	Me	71
10	*p*-$NO_2C_6H_4$	Ph	Me	43
11	Ph	*p*-$NO_2C_6H_4$	Me	40

Thus, 1,3-diphenylpropenone (chalcone, Table 1, entry 1) was used as a model compound to test the hypothesis. Remarkably, the reaction of chalcone and diethylphosphite with 3.0 equiv. of $Mn(OAc)_3$ in acetic acid at 60 °C for 1 h gave (*E*)-1,3-diphenyl-2-phosphonylpropenone, a regioselective α-phosphonation product, in 73% isolated yield. By-products that could be generated from alkenylphosphonation at the β-position, phenylphosphonation, and hydrophosphonation were not detected in the reaction mixture. A series of phosphonation reactions of conjugated ketones with diethyl- and dimethylphosphites were carried out. Products shown in Table 1 are regioselective with good isolated yields (64–80%) except for entries 10 and 11 which have the electron-withdrawing nitro group on the benzene rings. Dimethylphosphite and diethylphosphite have shown a similar reactivity for alkenylphosphonations.



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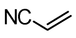

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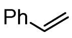

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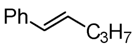

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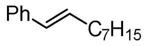

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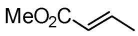

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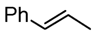

1g

A mechanism for selective phosphonation of conjugated arylalkenes is proposed in Scheme 2. The electrophilic dialkylphosphonyl radicals are more reactive toward the conjugated alkene than the phenyl rings.[11] Since the α-position of the conjugated alkene has a higher electron density than the β-position, it induces dialkylphosphonyl radical attacking at the α-position to generate benzyl radical **3a**, which has a more stable conformation **3b**. Radical **3b** is oxidized with $Mn(OAc)_3$

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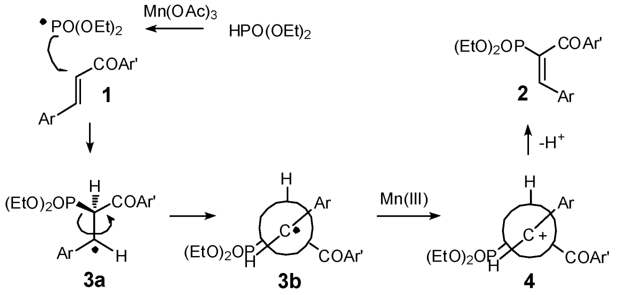
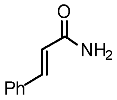
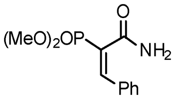
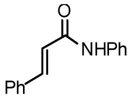
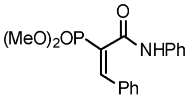
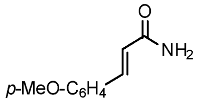
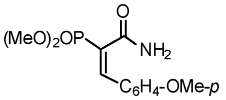
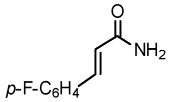
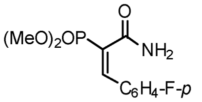
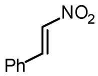
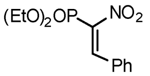
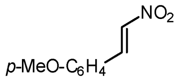
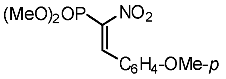
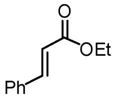
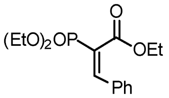
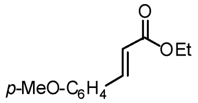
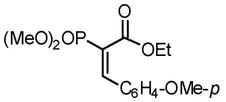
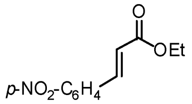
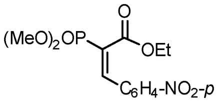
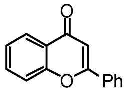
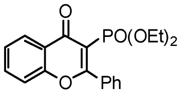
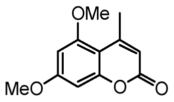
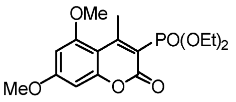
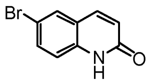
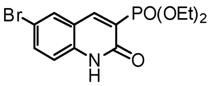
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, NMR spectra and X-ray crystal structures. CCDC 743887 & 743888. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b925951a



Scheme 2

Table 2 Phosphonation of conjugated arylalkenes

Entry	Conjugated arylalkene	Product	% Isolated yield
1			75
2			74
3			71
4			74
5			64
6			70
7			77
8			73
9			37
10		 75% SM conversion	44
11			87
12			72

to carbocation **4** followed by deprotonation to regenerate the conjugated system and afford the phosphonation product **2** as an *E*-isomer. Both the carbonyl and aryl groups in the conjugated alkenes **1** are required to control the reactivity of the alkene and the regioselectivity of the dialkylphosphonation process.

To explore the reaction scope, other conjugated arylalkenes including arylacrylamides (Table 2, entries 1–4), nitroalkenes (entries 5 and 6), α,β-unsaturated esters (entries 7–9), and derivatives of flavone, coumarine and quinolinone (entries 10–12) were used as the substrates for phosphonations. The reactions gave good yields with the exception of using the nitro-substituted arylalkene (entry 9) and flavone derivative (entry 10). The reaction shown in entry 12 produced a precursor of oxoquinoline-3-phosphonic acid, a biologically interesting compound which requires several steps to prepare if using the literature procedure.[12] We have noticed that the addition of the dialkoxyphopsphonyl radical to the conjugated nitroalkenes occurred without the loss of the nitro group (entries 5 and 6). This result suggests that the oxidation of the intermediate radical at the β-position of arylalkene to form a carbocation is more competitive than the β-scission of the NO_2 radical. The later process usually happens in the non-oxidative radical reactions.[13] The structure of (*E*)-3-phenyl-2-phosphonylacrylamide (Table 2, entry 1) has been confirmed by X-ray crystal analysis (Fig. 1). The *E*/*Z* assignment of other products is based on ^{1}H NMR analysis. The coupling constant of vinylphosphonate is 10–20 Hz for *cis* P–H and 30–50 Hz for *trans* P–H.[14] Most of our alkenylphosphonate products have a $^3J_{\text{P–H}}$ value smaller than 25 Hz, so they are determined to be *E* isomers. We have also explored other oxidation agents and the preliminary experiment indicated that ceric ammonium nitrate (CAN)[15] could be used as a $Mn(OAc)_3$ alternative for alkenylphosphonation reactions similar to those shown in Table 1, entry 1 and Table 2, entry 7.

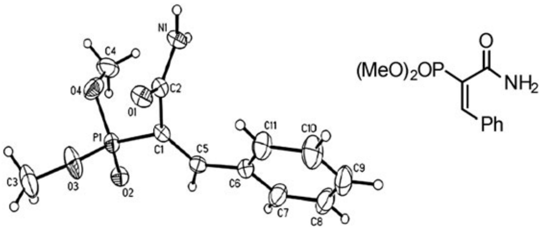
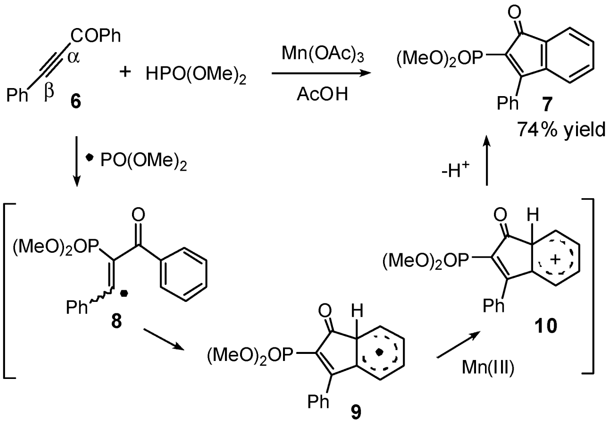


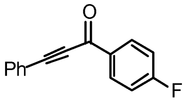
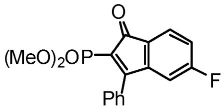
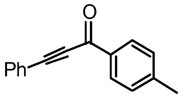
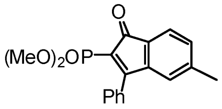
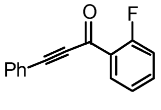
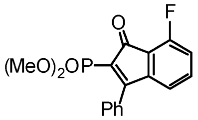
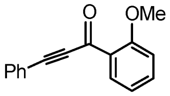
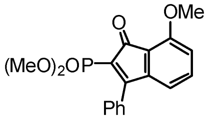
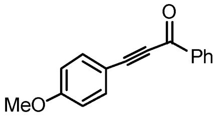
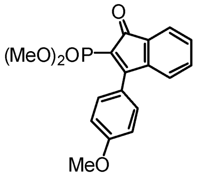
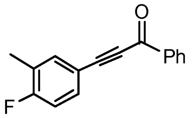
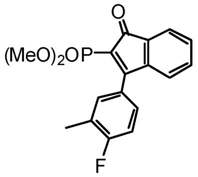
Fig. 1 X-Ray crystal structure of (*E*)-3-phenyl-2-phosphonylacrylamide, each unit consists of three identical molecules.[16]

Conjugated arylalkynes (benzoylphenylacetylenes) have been employed for phosphonation reactions. Instead of giving direct phosphonation or hydrophosphonation products, the reaction of 1,3-diphenylprop-2-yn-1-one **6** afforded substituted 1*H*-inden-1-one **7** in 74% yield (Scheme 3). Reactions with analogous alkynes produced corresponding indenones in good yields (Table 3). The addition of the initial dialkylphosphonyl radical occurs at the α-position of the conjugated arylalkyne to form vinyl radical **8**. This radical undergoes cyclization to form radical **9** followed by oxidation to carbocation **10** and affords product **7** after rearomatization. More reactions of conjugated alkynes are shown in Table 3. Both the aryl groups in the arylalkyne **6** are proved to be important for this transformation since the reactions of alkynes **6a–d** all

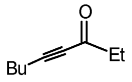


Scheme 3 Phosphonation of a conjugated arylalkyne.

Table 3 Phosphonation of conjugated alkynes

Entry	Conjugated alkyne	Product	% Isolated yield
1			70
2			79
3			66
4			75
5			73
6			72

produced mixtures of regio- and *E*/*Z* isomers of hydrophosphonation products.



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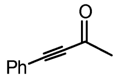

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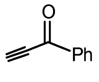

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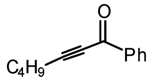

6d

In summary, we have successfully developed a Mn(III)-mediated regioselective phosphonation reaction of arylalkenes bearing conjugated groups such as ketone, amide, nitro, or ester at the α-position. The reactions are straightforward and highly efficient. The reactions can be used for arylalkynes to prepare 1*H*-inden-1-one derivatives. Since the intermediate carbon radical has the tendency to undergo rearrangement, this reaction process could be further developed for making more complicated ring systems bearing the dialkylphosphonyl functionality.

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Notes and references

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16 Crystal data for (*E*)-3-phenyl-2-phosphonylacrylamide $C_{11}H_{14}NO_4P$, M = 255.21, monoclinic, a = 24.732(4) Å, b = 9.2832(11) Å, c = 18.052(3) Å, β = 105.924(4)°, U = 3985.5(9) Å^3, T = 293 K, space group P 2_1/c, Z = 12, Dc = 1.276 g cm^{-3}, Nonius Kappa CCD diffractometer, μ(Mo-Kα) = 0.209 mm^{-1}, 37451 independent reflections (7277 observed), 466 parameters, R_{int} = 0.0649, R = 0.0837, wR(F2) = 0.1495, thermal ellipsoids probability level is 20%. CCDC 743887.