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$Mn(OAc)_3$-mediated synthesis of β-hydroxyphosphonates from P(O)–H compounds and alkenes†

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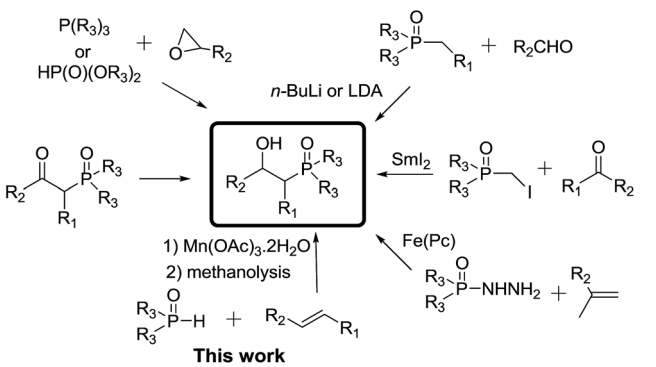
A new and general method for the synthesis of β-hydroxy phosphonates has been achieved through $Mn(OAc)_3$-mediated radical oxidative phosphonation of alkenes with *H*-phosphonates and *H*-phosphine oxide. The starting materials of P(O)–H compounds and alkenes are stable and cheap. $Mn(OAc)_3$ can be readily prepared from $Mn(OAc)_2$ in the laboratory. This method can be easily adapted to large-scale preparations.

β-Hydroxyphosphonates are extremely valuable compounds in organic chemistry for their potential applications in herbicides, horticulture agents, antioxidants, and moisture-resistant compounds.[1] Treatment of β-hydroxyphosphonates with oxidizing agents results in the formation of β-ketophosphonates which could be used in the preparation of α, β-unsaturated carbonyl compounds *via* the well-known HWE (Horner–Wadsworth–Emmons) reaction.[2] Furthermore, the hydroxyl group in β-hydroxyphosphonates could be converted into a variety of functional groups, such as esters, amines, phenyl ethers and so on, which have interesting biological properties.[3]

Generally, β-hydroxyphosphonates have been prepared by the hydrogenation of β-ketophosphonates[4] or the ring-opening reaction of epoxy compounds with phosphorus nucleophiles[5] (Scheme 1). Alternative procedures have been reported including reaction of alkylphosphonates with aldehydes *via* an aldol-like reaction in the presence of strong bases[6] and reaction of dialkyl(iodomethyl)phosphonate with aldehydes by employing SmI_2.[7] In 2011, Taniguchi's group described iron-catalyzed aerobic oxidative phosphonation of alkenes by using phosphorohydrazidates as starting materials, but only *gem*-dialkyl/aryl-substituted alkenes could afford satisfactory yields.[8]

Reactions involving organophosphorus radicals have a long history, and are useful reactive species in organic synthetic chemistry.[9] Economically and environmentally benign manganese salts are attractive because manganese is one of the most abundant metals in the world. Manganese salts have been used for many transformations in the last few years.[10] $Mn(OAc)_3$-promoted phosphonations are important methods for the formation of P–C bond.[11] Our continued interest in the synthesis of α-hydroxy-,[12] α-amino-phosphonates[13] and the formation of C–P bonds[2c,d,14] prompted us to explore a general method for the synthesis of β-hydroxyphosphonates *via* P-centered radical difunctionalization of alkenes.

This idea was first examined by using styrene (**1a**) and diisopropyl *H*-phosphonate (**2a**) as reaction partners (Table 1). In the beginning, various copper and silver salts were tested (entries 1–4), most of which behaved poorly. Other oxidants such as $AgNO_3/K_2S_2O_8$ and TBHP were also investigated, but the reaction did not work well under these conditions (entries 5 and 6). Pleasingly, when $Mn(OAc)_3 \cdot 2H_2O$ was chosen as the oxidant, and HOAc as the solvent, the product **3a** was obtained in 73% yield at 80 °C under nitrogen atmosphere (entry 7). It should be



Scheme 1 Synthetic routes to β-hydroxyphosphonates.

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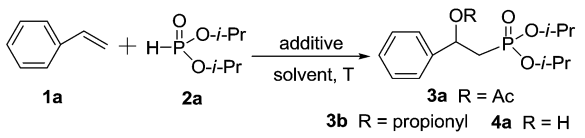
† Electronic supplementary information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **3a**, **3b**, **4a–4w** and **5–7**. See DOI: 10.1039/c4ra10593a

Table 1 Reaction conditions optimization[a]



Entry	Additive	Solvent	T [°C]	Yield [%]
1	$AgNO_3$ (0.5)	CH_3CN	100	16 (**4a**)
2	CuCl (0.5)	CH_3CN	100	Trace
3	$CuCl_2$ (0.5)	CH_3CN	100	Trace
4	AgOAc (3)	DMF	100	Trace
5	Bu_4NI (0.2) + TBHP (3)	CH_3CN	100	Trace
6	$AgNO_3$ (0.2) + $K_2S_2O_8$ (2)	CH_3CN	100	Trace
7	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	80	73 (**3a**)
8[b]	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	80	35 (**3a**)
9[c]	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	80	62 (**3a**)
10	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	100	43 (**3a**)
11	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	60	87 (**3a**)
12	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	50	66 (**3a**)
13	$Mn(acac)_3$ (3)	HOAc	60	n.d.
14	—	HOAc	60	0
15	$Mn(OAc)_3 \cdot 2H_2O$ (3)	CH_3CN	60	70 (**3a** + **4a**)
16	$Mn(OAc)_3 \cdot 2H_2O$ (3)	Propionic acid	60	73 (**3b**)
17	$Mn(OAc)_3 \cdot 2H_2O$ (3)	Pivalic acid	60	n.d.

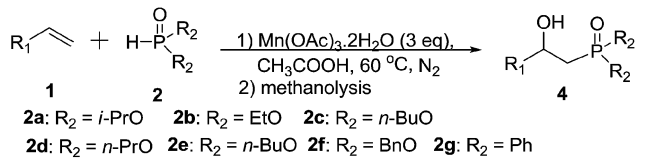
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), additive in solvent (3 mL) stirring under nitrogen for 8 h. Oil bath temperature. Yield of the isolated product; n.d.: not detected. [b] Under O_2. [c] Under air.

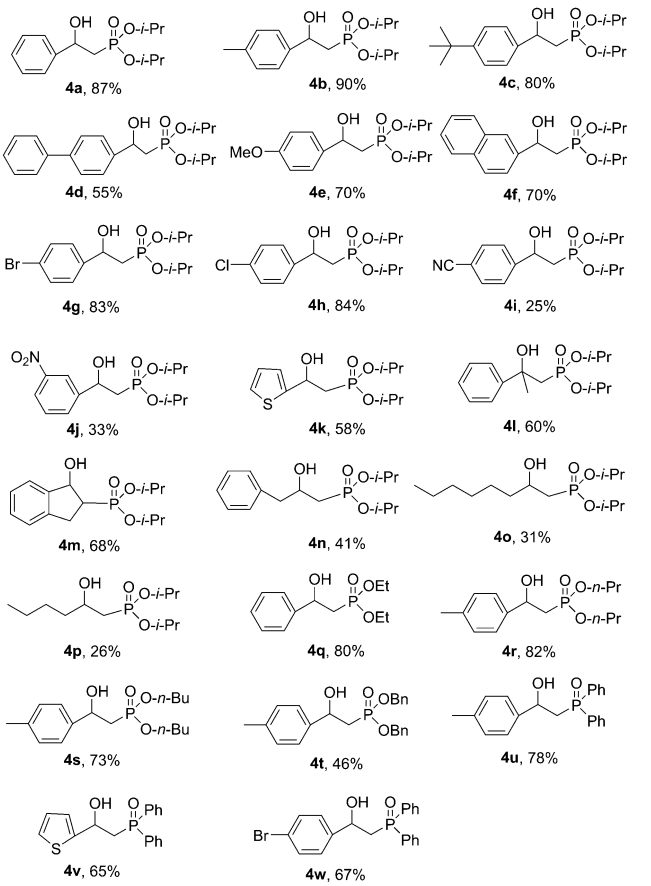
noted that **3a** could transform into β-hydroxyphosphonate **4a** quantitatively through a simple alcoholysis process. The reaction gave much lower yields when carried out under O_2 and air conditions (entries 8 and 9).

Further screening indicated that the choice of temperature is also very crucial for the reaction (entries 10–12). The reaction performed well at 60 °C and gave **3a** in 87% yield. However, the yield of product **3a** decreased greatly when the temperature was raised to 100 °C or decreased to 50 °C. No desired product was obtained when $Mn(acac)_3$ was chosen as the oxidant (entry 13). The reaction did not occur at all in the absence of $Mn(OAc)_3 \cdot 2H_2O$ (entry 14). A mixture of **3a** and **4a** was obtained when CH_3CN was chosen as the solvent (entry 15). When propionic acid was chosen as the solvent, the only product **3b** was obtained in 73% yield (entry 16). Unfortunately, when the bulky pivalic acid was selected as solvent, no product was detected (entry 17). After optimization of the reaction conditions, we established a highly efficient route to formation of β-hydroxyphosphonate. The optimal reaction conditions are: (1) 3.0 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ as the oxidant, and HOAc as the solvent at 60 °C for 8 h under nitrogen atmosphere (entry 11 and (2) alcoholysis using 1 M NaOH in CH_3OH at room temperature for 1 hour.

Having the optimal conditions in hand, we next examined the reaction by using various alkenes including aromatic alkenes and aliphatic alkenes with different *H*-phosphonates **2a–2g** to understand the scope of the reaction. As shown in Table 2, most of the functional groups were tolerated under the present oxidative conditions. Various aromatic alkenes with electron-donating substituents on the benzene ring were investigated, and the corresponding products were obtained in high yields (**4b–4e**). When 2-naphthalenylethene was examined, 70% yield was obtained (**4f**). Halogen atoms such as bromo and chloro on the aromatic ring were unaffected under the present reaction conditions, giving products **4g** and **4h** in 83% and 84% yields, respectively. However, 4-cyano and 3-nitrostyrene were examined for their reactivity with **2a** under similar reaction conditions, gave the expected products **4i** and **4j** in 25% and 33% yield, respectively. These examples imply that the reaction involves cationic intermediates. 2-Vinylthiophene also reacted smoothly with *H*-phosphonate to afford products **4k** in 58%

Table 2 Reaction of P(O)–H compounds with alkenes[a]





[a] Conditions: (1) alkene **1** (0.5 mmol), P–H **2** (1.0 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (1.5 mmol), CH_3COOH (3 mL), 8 h, 60 °C (oil bath temperature), under N_2; (2) alcoholysis: 1 M NaOH in CH_3OH, 1 hour, r.t. isolated yield.

yield. When 1-methyl-1-phenyl ethene was used, it reacted smoothly with **2a** resulting in product **4l** in 60% yield. Moreover, cyclic aromatic alkene also reacted smoothly with **2a**, leading to the desired product **4m** in 68% yield. The present reaction was also successfully applied to aliphatic alkenes, giving high conversions of alkenes, albeit in lower yields. The reaction of aliphatic alkenes gave a mixture containing β-alkenylphosphonates and β-hydroxyphosphonate. Thus, allylbenzene, 1-octene and 1-hexene reacted with diisopropyl *H*-phosphonate (**2a**)to afford the corresponding β-hydroxyphosphonate **4n**, **4o** and **4p** in 41%, 31% and 26% yield, respectively. 2-Vinylpyridine was also examined. Unfortunately, only trace amounts of desired product was detected.

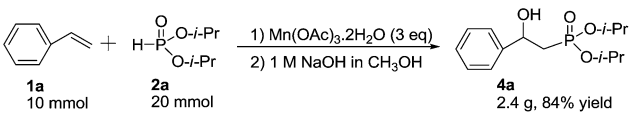
With regards to the *H*-phosphonates, it was also successfully applied to diethyl, dipropyl and dibutyl. All could be used as the substrates, generating the corresponding β-hydroxyphosphonates (**4q**–**4s**) in 73–82% yields. Dibenzyl *H*-phosphonate gave high conversion to β-acetoxyphosphonate. But only 46% yield of β-hydroxyphosphonate **4t** was obtained after metholysis because benzyl group was easily substituted by OH in the presence of NaOH. Difunctionalization of alkenes through treatment of diphenylphosphine oxide with alkenes led to the formation of product **4u**–**4w** in 67–78% yield which indicated that the reactivities of these P–H compounds are almost independent of the alkoxyl and alkyl moieties.

In order to demonstrate the practical application of this method, styrene (**1a**, 10 mmol) was employed in a gram-scale reaction with $(i\text{-PrO})_2$P(O)H (**2a**, 20 mmol) and delivered **4a** in 84% yield (Scheme 2).

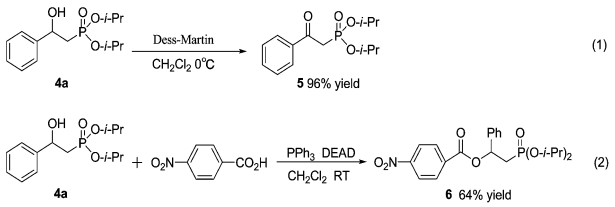
With the synthetic β-hydroxyphosphonates in hand, we next prepared β-ketophosphonate **5**, an important HWE precursor, in high yield using Dess–Martin reagent. β-Benzoxyphosphonate **6** could be easily obtained in good yield from β-hydroxyphosphonate *via* Mitsonobu reaction (Scheme 3).

No desired product was obtained when 2.0 equiv. of TEMPO was added in the reaction under the optimal conditions (Scheme 4). This result suggests that the radical was intercepted by TEMPO. *N*,*N*-diallyl-4-methylbenzenesulfonamide was examined, and substituted pyrrolidine was obtained. These results suggested that the reaction go through a radical pathway. Furthermore, 2-vinylpyridine and styrene with electron-withdrawing group on the benzene ring afford the corresponding product (**4i**, **4j**) in very low yields which indicates that the reaction might go through a cationic intermediate process. On the basis of this result, a mechanistic pathway for the manganese(III)-mediated radical oxidative phosphonation of alkenes with *H*-phosphonate is proposed in Scheme 5. The reaction of *H*-phosphonate **B** with Mn(III) salt generated phosphorous radicals **C** which then reacted with styrene **A** to produce **D**. Subsequently, cationic intermediate **E** was formed through single electron oxidation by Mn(III) from **D** which ultimately was attacked by AcOH (**F**) to afford **G**.

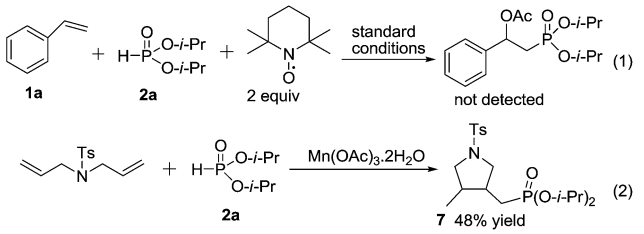
In conclusion, we have successfully developed a highly efficient and general method for the preparation of β-hydroxyphosphonates through $Mn(OAc)_3$-mediated radical oxidative phosphination of alkenes under relatively mild reaction conditions. This method is highly efficient and provides rapid access to a broad spectrum of β-hydroxyphosphonates in good to excellent yields. This reaction can be effectively scaled up and the product can be conveniently obtained in a one-pot process. Moreover, $Mn(OAc)_3$ can be easily prepared from $Mn(OAc)_2$ in laboratory. Further application of this method toward the synthesis of biologically active molecules is in progress.



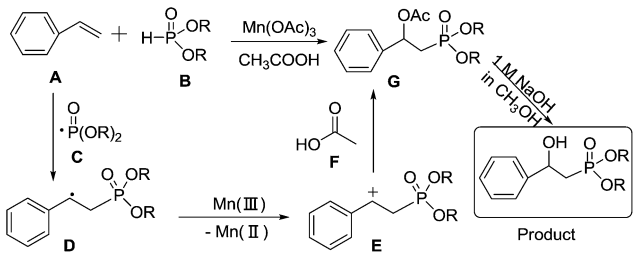
Scheme 2 Gram-scale preparation of **4a**.



Scheme 3 Application of β-hydroxyphosphonates.



Scheme 4 Experiment for mechanistic study.



Scheme 5 Possible reaction mechanism.

Acknowledgements

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