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Manganese-Catalyzed and Promoted Reactions of *H*-Phosphinate Esters

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Abstract: *H*-Phosphinates react with alkenes and alkynes using catalytic manganese(II) acetate. Under stoichiometric conditions with manganese(III) acetate or with catalytic manganese(II) acetate + excess manganese(II) oxide various reactions like arylation or cyclization through radical oxidative arylation can take place. Whereas the chemistry of manganese is already well developed for the functionalization of *H*-phosphonates, the present methodology provides an unprecedented access to functionalized phosphinates in acceptable to good yields.

Keywords: *H*-phosphinates; manganese; phosphorus; phosphorus heterocycles; radical reactions

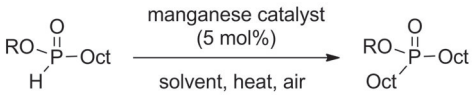
Manganese-catalyzed or promoted free-radical reactions have become a staple of organic synthesis.[1] Besides their low toxicity, manganese compounds are inexpensive over a broad range of oxidation states. Ishii and co-workers pioneered the reactions of *H*-phosphonate diesters for elegant P–C bond formation.[2] More recently, the direct arylation of *H*-phosphonate diesters has been investigated rather intensely.[3] However, and to the best of our knowledge, similar reactions with *H*-phosphinates have not been studied previously.

Continuing with our laboratory's interest in *H*-phosphinate reactivity in both free radical and metal-catalyzed processes,[4] we started exploring the reactions of *H*-phosphinates using manganese(II or III) acetate with various unsaturated partners. Herein, we are reporting our preliminary findings. The reaction of *H*-phosphinates with alkenes and alkynes to form disubstituted phosphinates is in general a difficult process even under free radical conditions, especially with alkyl *H*-phosphinate esters.[5,6] Since our methodologies can provide many different *H*-phosphinates,[4] we thought that Ishii's reaction should be studied on these substrates. In the Ishii process,[2] $(RO)_2P(O)H$ is used under neat conditions and in excess (3 equivalents), which is quite wasteful although those compounds are inexpensive. For a practical reaction, decreasing this to stoichiometric (or as nearly stoichiometric as possible) conditions would be much more desirable, especially if more valuable *H*-phosphinates $R^1P(O)(OR)H$ are to be employed.

We started this investigation by looking at relatively challenging[5] octyl-*H*-phosphinate esters OctP(O)(OR)H as the model compounds. Table 1 shows the results. The reactions are conducted in air since a nitrogen atmosphere does not lead to acceptable conversions. Under oxidative conditions, it is clear that a competitive pathway leading to OctP(O)(OR)-OH will be operating (responsible for most of the lost mass). This is likely the reason why Ishii's conditions used an excess of the $(RO)_2P(O)H$ reagent.[2] On the other hand, using an excess of alkene/alkyne will increase oligomerization especially under neat conditions. Moderate to high isolated yields were obtained under a variety of conditions, including neat or in solution (cyclohexane or DMSO).

Reaction of the ethyl ester produced the disubstituted product in 71% yield (entry 1). However, the same reaction at room temperature did not give any product after 48 h. Similarly, no product formed in the absence of catalyst. With the butyl ester, various manganese catalysts could be employed, but generally larger amounts of 1-octene gave slightly better results (for example: entry 4 *versus* entry 2). Reactions in solution also furnished reasonably good results, but with a 1.2:1 molar ratio, neat conditions were slightly better. Interestingly, the Jacobsen salen catalyst could be employed provided sodium acetate is added, presumably to form the catalytically active Mn(III) species (entry 10). Using an excess of *H*-phosphinate gave a higher yield than using an excess of 1-octene (entry 10b *versus* entry 10a). Because reagent ratios closer to one are desirable, reactions with a slight

Table 1. Reaction conditions.[a]



Entry	R (equiv.)	Equiv. of 1-octene	Manganese catalyst	Solvent	Isolated Yield [%]
1	Et (1)	2.5	$Mn(OAc)_2$	neat	71
2	Bu (1)	1	$Mn(OAc)_2$	neat	52
3	Bu (1)	1.5	$Mn(O_2C_8H_{15})_2$[b]	neat	64
4	Bu (1)	2.5	$Mn(OAc)_2$	neat	81
5	Bu (1)	2.5	$Mn(OAc)_3{\cdot}2H_2O$	neat	85
6	Bu (1)	2.5	$Mn(OAc)_2$	C_6H_{12}	74
7	Bu (1)	2.5	$Mn(OAc)_2$	AcOH	nr
8	Bu (1)	2.5	$Mn(OAc)_2$	DMSO	71
9	Bu (1)	2.5	$Mn(O_2C_8H_{15})_2$[b]	DMSO	78
10a	Bu (1)	2.5	(*R*,*R*)- Jacobsen	neat	60
10b	Bu (2)	1	NaOAc (20 mol%)		83
11	Et (1.2)	1	$Mn(OAc)_2$	neat	77
12	Bu (1.2)	1	$Mn(O_2C_8H_{15})_2$	neat	75
13	Bu (1.2)	1	$Mn(OAc)_2$	neat	89
14	Cy (1.2)	1	$Mn(OAc)_2$	DMSO	97[c]

[a] All reactions were conducted in air at 100 °C, except for those in cyclohexane (reflux). All reaction times were 3 h, except for those with DMSO (18 h). In general, octene dimerization was less than 5%, so simple extraction gave the products >95% pure.
[b] Manganese(II) 2-ethylhexanoate.
[c] Only 42% isolated yield after 3 h.

excess of *H*-phosphinate were conducted (entries 11–14). Results were generally comparable (slightly lower or higher) to other stoichiometries under neat conditions, but clearly superior in DMSO with the cyclohexyl ester (entry 14).

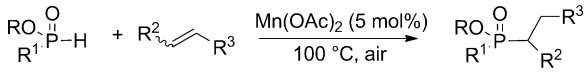
In a competition experiment under the conditions of Table 1 entry 11, but also adding $(EtO)_2P(O)H$ (1.2 equiv.), a 2.8:1 phosphinate/phosphonate product ratio was obtained, showing that the octyl-*H*-phosphinate is more reactive. Similarly, diethyl *H*-phosphonate (1.2 equiv.) alone gave only a 42% isolated yield of diethyl octylphosphonate, reinforcing the idea that excess reagent is necessary in Ishii's hydrophosphonylation reaction. Finally, when entry 14 was repeated in the absence of 1-octene, cyclohexyl octylphosphonate monoester was obtained in 82% isolated yield.

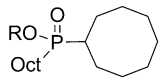
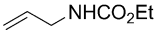
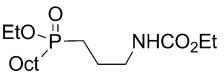
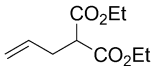
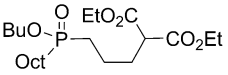
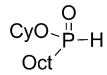
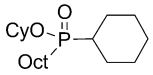
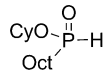
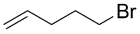
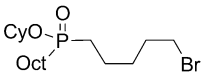
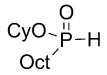
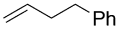
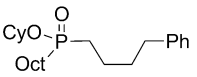
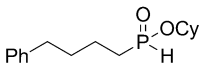
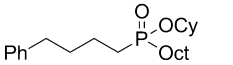
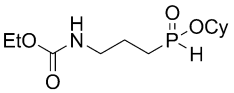
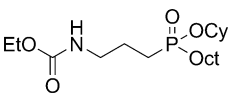
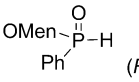
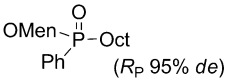
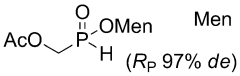
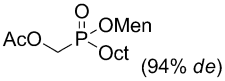
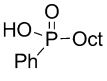
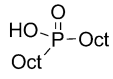
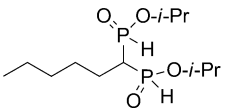
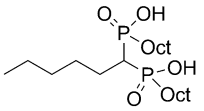
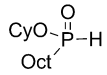
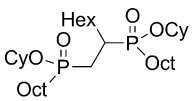
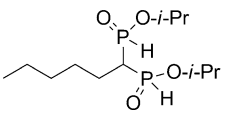
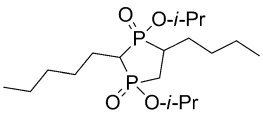
Once the conditions had been explored, the scope with various *H*-phosphinate/alkene combinations could be investigated (Table 2). Isolated yields ranged from 46 to 90% with alkenes. With cyclooctene some variations in yields were observed depending on the ester chosen (entry 1). Other alkenes reacted successfully with various cyclohexyl *H*-phosphinate esters (entries 4–8) typically in yields around 50%. Interestingly, *P*-stereogenic menthyl *H*-phosphinates[7] reacted with excellent stereoselectivity to produce the corresponding disubstituted products (entries 9 and 10). The absolute configuration of the product in entry 9 was established as R_P proving that the reaction takes place with retention of configuration. Entry 10 constitutes the first example of hydrophosphinylation with *P*-stereogenic *H*-phosphinate that is not substituted with an aryl group.[6a] In this case the absolute configuration was not established, but is likely to be R_P based on entry 9. As discussed previously, aryl-substituted *H*-phosphinates have special reactivity.[6,8] In fact, the reaction of menthyl phenyl-*H*-phosphinate with 1-octene using our Et_3B/air system[9] instead of $Mn(OAc)_2$ gave the product in entry 9 in 73% isolated yield and 95% *de*.

The reaction is not limited to *H*-phosphinate esters[10] as acids also react successfully (entries 11 and 12). A 1,1-bis-*H*-phosphinate ester[11] could be employed (entry 13) and the corresponding acid was obtained after hydrolysis. Finally, the reaction with 1-alkynes was briefly investigated (entries 14 and 15). With an excess of *H*-phosphinate the corresponding 1,2-bis-phosphinate was obtained (entry 14). Heterocyclization was also achieved in entry 15.

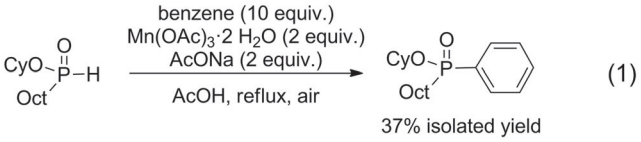
We then turned our attention to Mn(III)-promoted reactions based on various literature precedents with *H*-phosphonates. The direct intermolecular arylation of cyclohexyl octyl-*H*-phosphinate ester gave the corresponsing cyclohexyl octyl-phenylphosphinate in 37% yield [Eq (1)].

Table 2. Scope of the manganese-catalyzed hydrophosphinylation reaction.[a]



Entry	*H*-Phosphinate	R	Alkene	Solvent	Time [h]	Product	Isolated Yield [%]
1a 1b 1c		Et Bu Cy	cyclooctene	none	3 3 18		65 58 53
2		Et		none	3		55
3		Bu		none	3		72
4		Cy	cyclohexene	none	18		73
5		Cy		none	18		54
6		Cy		none	18		46
7a 7b		Cy	1-octene	none DMSO	18		52 89
8		Cy	1-octene	DMSO	24		48
9	 (R_P 95% *de*)	Men	1-octene	none	16	 (R_P 95% *de*)	79[b]
10	 (R_P 97% *de*)	Men	1-octene	DMSO	16	 (94% *de*)	55
11		H	1-octene	DMSO	24		87
12		H	1-octene	DMSO	24		90
13		*i*-Pr	1-octene (3 equiv.)	neat	18		69[c]
14		Cy	1-octyne (0.5 equiv.)	none	18		51
15		*i*-Pr	1-hexyne (1 equiv.)	DMSO	18		40

[a] Product purity >95%. All products are new compounds with the exception of entries 9, 11 and 12.
[b] Retention of configuration.
[c] After hydrolysis (conc. aqueous HCl, toluene, reflux, 18 h).



(1)

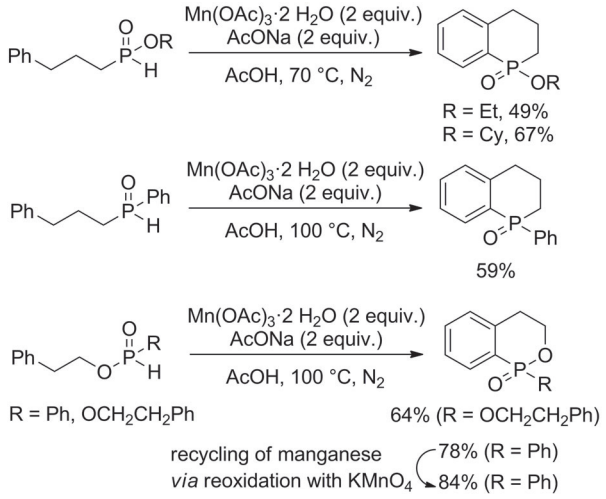
Whereas the yield is mediocre, it is comparable to the 48% yield that was reported with benzene (1 equiv.), $(EtO)_2P(O)H$ (2 equiv.), $AgNO_3$ (20 mol%), and $Na_2S_2O_8$ (5 equiv.).[3b]

On the other hand, *H*-phosphinates offer possibilities for heterocyclization *via* intramolecular arylation. This was briefly investigated and the results are shown in Scheme 1.

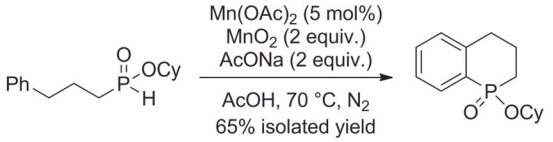
3-Phenylpropyl-*H*-phosphinate esters were cyclized using 2 equivalents of $Mn(OAc)_3$/AcONa. The ethyl ester gave a lower yield (49%) presumably because some cleavage takes place in acetic acid, than the more resistant cyclohexyl ester (67%).

The reaction was not limited to *H*-phosphinates as shown by the successful cyclization of a related secondary phosphine oxide (59%) and an *H*-phosphonate diester (64%). Similarly, phenethyl phenyl-*H*-phosphinate ester was cyclized in excellent yield (78%). After this run, the manganese was recovered and converted back to $Mn(OAc)_3$ using $KMnO_4$.[12] A subsequent reaction with the regenerated $Mn(OAc)_3$ gave the same product in 84% yield.

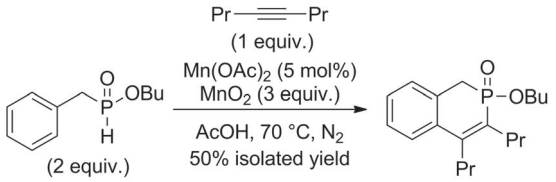
Further work in this exciting area will be conducted and disclosed in the corresponding full paper. Clearly, this heterocyclization method is competitive with alternative approaches such as metal-catalyzed cross-coupling since the starting materials are readily available and the cost remains low. It should be noted that attempts at using manganese(II) or (III) catalytically



Scheme 1. $Mn(OAc)_3$-promoted heterocyclization *via* intramolecular radical arylation. All yields are isolated. Reaction conditions are unoptimized.



Scheme 2. $Mn(OAc)_2$-catalyzed/MnO_2-promoted heterocyclization *via* intramolecular radical arylation. Reaction conditions are unoptimized.



Scheme 3. $Mn(OAc)_2$-catalyzed/MnO_2-promoted alkyne-arene annulation.

were unsuccessful. However, we found the $Mn(OAc)_2$ (5 mol%)/MnO_2 (2 equiv.) combination to be an inexpensive replacement to Mn(III) (Scheme 2). While the generality of this new system still needs to be probed, MnO_2 alone gave low conversion. An additional example of the MnO_2-promoted reaction is shown in Scheme 3 for an alkyne-arene annulation.[13]

In conclusion, the present methodology provides a simple and inexpensive way to prepare either symmetrically or differentially disubstituted phosphinates in moderate to good yields. Furthermore, manganese-promoted reactions can also be used to achieve direct arylation, or heterocyclization. Since the manganese can be recycled through $KMnO_4$ oxidation as demonstrated in one example, the process should be practically useful. Perhaps more importantly, a new set of conditions employed $Mn(OAc)_2/MnO_2$, which is cheaper than the related silver(I)/$K_2S_2O_8$ system. This work will be the subject of a full account describing developments, and optimizations in the near future, as well as an expanded investigation of the heterocyclization reaction.

Experimental Section

General Methods

All starting materials were purchased from commercial sources and used as received. ^1H NMR spectra were recorded on a 300 MHz Varian INOVA spectrometer or 400 MHz Bruker Avance spectrometer. Chemical shifts for ^1H NMR spectra (in parts per million) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with deuterated chloroform. ^{13}C NMR spectra were recorded at 75 or 101 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ ($\delta = 77.0$ ppm). ^{31}P NMR spectra

were recorded at 121 or 162 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid ($\delta = 0.0$ ppm). Flash chromatography experiments were carried out on Silica Gel premium R_f grade (40–75 μm). Ethyl acetate/hexane mixtures were used as the eluent for chromatographic purifications.TLC plates were visualized by UV, iodine or immersion in permanganate potassium (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aqueous NaOH and 300 mL of water) followed by heating. High resolution mass spectra (HR-MS) were obtained either by direct probe (EI/CI) and analyzed by magnetic sector, or by electrospray using a TOF analyzer.

General Procedure for Manganese-Catalyzed Addition of Alkenes or Alkynes to *H*-Phosphinates

To a selected *H*-phosphinate (1.2 mmol, 1.2 equiv.) either neat or in DMSO (0.2 M, 5 mL) was added an alkene (1 mmol, 1 equiv.) and $Mn(OAc)_2$ (9 mg, 0.05 mmol, 5 mol%). The reaction mixture was stirred for 20 h at 100 °C with the condenser open to the air. Ethyl acetate (~20 mL) and an aqueous solution of $Na_2S_2O_4$ at 0.5 M in brine (~40 mL) were added, partitioned and the two layers were separated. The organic layer was washed with saturated $NaHCO_3$/brine (~40 mL) and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product. Generally, the compound was ≥95% pure; however, column chromatography was used if further purification of the product was needed.

General Procedure for $Mn(OAc)_3$-Promoted Arylation of *H*-Phosphinates

To a solution of cyclohexyl octyl-*H*-phosphinate (260 mg, 1 mmol, 1 equiv.) in a mixture of acetic acid and benzene (2.5 mL:2.5 mL) was added $Mn(OAc)_3 \cdot 2H_2O$ (536 mg, 2 mmol, 2 equiv.) and sodium acetate (164 mg, 2 mmol, 2 equiv.). The suspension was stirred for 24 h at 100 °C under N_2. 100 mL of ethyl acetate were added and the suspension was filtered to remove the manganese. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.5 M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 6:4).

General Procedure for $Mn(OAc)_2/MnO_2$-Promoted Intramolecular Arylation of *H*-Phosphinates

To a solution of cyclohexyl 3-phenylpropyl-*H*-phosphinate (133 mg, 0.5 mmol, 1 equiv.) in acetic acid (2.5 mL) was added $Mn(OAc)_2$ (4.3 mg, 0.025 mmol, 5 mol%), MnO_2 (85% activated, 102 mg, 1 mmol, 2 equiv.) and sodium acetate (82 mg, 1 mmol, 2 equiv.). The suspension was stirred for 12 h at 70 °C under N_2. Ethyl acetate (40 mL) and 0.1 M aqueous solution of $Na_2S_2O_4$ saturated with NaCl (20 mL) were added. The mixture was stirred for 5 min and the suspension was filtered over Celite®. The organic layer was washed with aqueous solutions of $Na_2S_2O_4$ 0.1 M saturated with NaCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9:1 to 6:4) to afford the product as colorless oil; yield: 86 mg (65%).

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