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Manganese(III)-mediated direct phosphonylation of arenes

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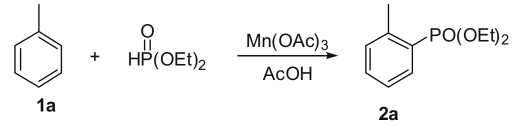
ABSTRACT

Manganese (III)-promoted direct phosphonylation of mono- and disubstituted arenes with dialkylphosphite afforded regioselective dialkylphosphonates in good yields. The reactions can apply to arenes bearing electron-donating groups and electron-withdrawing groups such as ester and nitrile.

Arylphosphonate compounds have broad applications in organic, medicinal, and agricultural chemistry.[1] The general methods for the preparation of arylphosphonates relay on the reactions of reactive functional groups such as displacement arylhalides[2] or phospho-Fries rearrangement.[3] Direct phosphonylations of C–H bonds promoted by *tert*-butyl peroxide, CAN, or $Na_2S_2O_8/AgNO_3$ have been reported.[4–6] However, these reactions are mainly for arenes bearing electron-donating groups and usually have low regioselectivities. The Ishii group recently reported a direct phosphonylation of arenes using $Mn(OAc)_2/Co(OAc)_2/O_2$ redox system and generated a mixture of regioisomers.[7] Reported in this Letter is a simple $Mn(OAc)_3{\cdot}H_2O$-promoted phosphonylation reaction system which has improved regieoselectivities.[8]

We recently reported $Mn(OAc)_3$-promoted direct phosphonylations of heteroarenes,[9] alkenes, and alkynes.[10] Since these reactions have demonstrated a good regioselectivity, we envisioned that they may be employed for reactions of arenes. In this project, the reaction of toluene and diethylphosphite was first carried out at 80 °C in the presence of $Mn(OAc)_3{\cdot}H_2O$ and using acetic acid as a solvent. A mixture of 2-, 3-, and 4-phosphonated products was obtained in 92% yield. The major isomer **2a** was isolated in 82% yield (Table 1, entry 1). The reaction was then conducted at a lower temperature of 60 °C in order to improve the regioselectivity. Under this condition, we found that **2a** was the major product in 90% isolated yield (entry 2). Decreasing temperature to 40 °C, no reaction was observed even after 24 h (entry 3). Reactions were also carried out at different ratios of Mn(III) to **1a** (entries 4–6).

Table 1
Phosphonylation of toluene[a]



Entry	Mn(III):**1a**	Temp (°C)	Time (h)	Yield[b] (%)
1	3:1	80	7	92[c]
2	3:1	60	7	90
3	3:1	40	24	No reaction
4	4:1	60	7	90
5	2:1	60	7	75
6	1:1	60	7	32

[a] Reaction conditions: toluene (3 mmol), diethylphosphite (6 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (9 mmol) under air.
[b] Overall yield of a mixture of 2-, 3-, and 4-tolylphosphonates.
[c] 2-Tolylphosphonate isolated in 82% yield.

Phosphonylations of dimethylated benzenes were explored (Table 2, entries 2–4).[11] Except *p*-xylene, both *m*- and *o*-xylenes gave two regioisomers. The reaction of tetrahydronaphthalene afforded **2e** as a major product (entry 5). The reaction of methoxybenzene gave 2- and 4-methoxybenzene phosphonates **2f** and **2f′** in a ratio of 82:18 (entry 6). The reaction of both 1,2- and 1,4-dimethoxybenzenes produced single products (entries 7 and 9), while that of 1,3-dimethoxybenzene gave **2h** and **2h′** in a ratio of 90:10 (entry 8). Reactions of methylene-1,3-dioxybenzene **1j** and ethylene-1,3-dioxybenzene **1k** produced single products **2j** and **2k**, respectively (entries 10 and 11). The regioisomer ratio was determined by isolated yields, and their structures were determined by $^3J_{HH}$ and $^3J_{PH}$ coupling constants of the ^1H NMR.

Phosphonylations of arenes bearing electron-withdrawing groups were also explored. Methylbenzoate mainly afforded *para*-phosphonated product **2l** (Table 3, entry 1). Dimethyl phthalate and dimethyl isophthalate afforded single phosphonated products **2m** and **2n** in 73% and 75% yields, respectively (entries 2 and 3). Reactions of both cyanobenzene and 1,3-dicyanobenzene produced a single product (entries 4 and 6). The reactions of carbonyl

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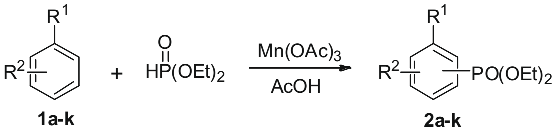
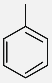
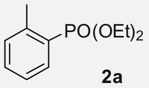
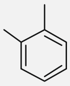
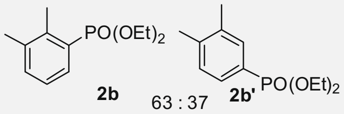
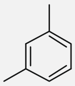
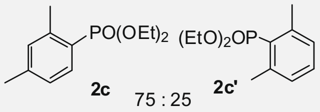
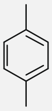
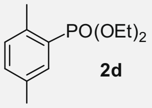
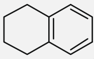
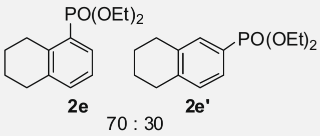
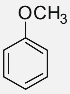
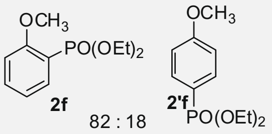
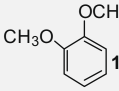
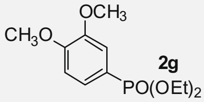
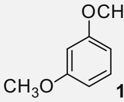
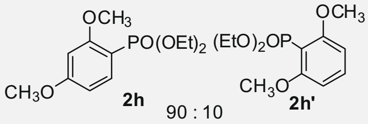
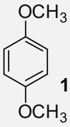
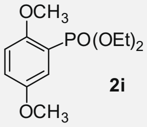
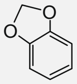
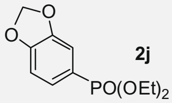
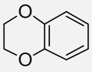
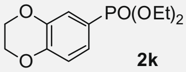
Table 2
Phosphonylation of arenes bearing electron-donating groups[a]



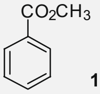
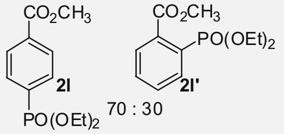
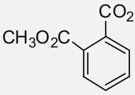
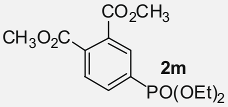
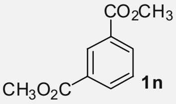
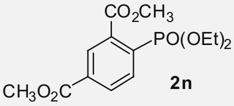
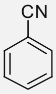
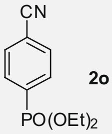
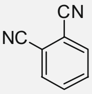
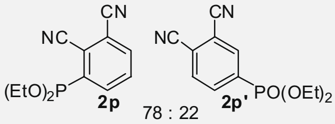
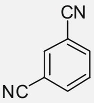
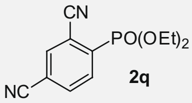
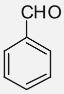
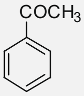
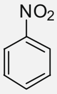
Entry	Substrate	Product	Yield (%)
1	 **1a**		90[b]
2	 **1b**	 **2b** 63 : 37 **2b'**	93[c]
3	 **1c**	 **2c** 75 : 25 **2c'**	91[c]
4	 **1d**		87
5	 **1e**	 **2e** 70 : 30 **2e'**	86[c]
6	 **1f**	 **2f** 82 : 18 **2'f**	90
7	 **1g**		95
8	 **1h**	 **2h** 90 : 10 **2h'**	91[c]
9	 **1i**		85
10	 **1j**		90
11	 **1k**		85

[a] Reaction conditions: arene (3 mmol), dialkylphosphite (6 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (9 mmol) in HOAc at 60 °C under air, 7 h for entries 1–5, 5 h for entries 6–11.
[b] Isolated from a mixture of 2-, 3-, and 4-tolyphosphonates.
[c] The ratio was determined by ^{1}H NMR.

substituted arenes such as benzaldehyde and acetophenone had low regioselectivities and yielded complex reaction mixtures (entries 7 and 8) presumably due to the competitive reaction of dialkyl phosphate with the carbonyl groups. The reaction of nitrobenzene gave no product because the electron-withdrawing effect of the nitro group is too strong which stop electrophilic phosphonyl radical addition process (entry 9).

Phosphonylations of arenes bearing both electron-donating and electron-withdrawing substituents were also conducted. The reaction of methyl 4-methoxybenzoate **1r** yielded single product **2r** in

Table 3
Phosphonylation of arenes bearing electron-withdrawing groups[a]

Entry	Substrate	Product	Yield (%)
1	 **1l**	 **2l** **2l'** 70 : 30	85
2	 **1m**	 **2m**	73
3	 **1n**	 **2n**	75
4	 **1o**	 **2o**	53[b]
5	 **1p**	 **2p** **2p'** 78 : 22	58
6	 **1q**	 **2q**	60
7		Complex mixture	
8		Complex mixture	
9		No reaction	

[a] Reaction conditions: arene (3 mmol), dialkylphosphite (6 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (9 mmol) in HOAc at 60 °C for 6 h under air.
[b] Isolated from a mixture of 2-, 3-, and 4-phosphonated cyanobenzenes.

92% yield (Table 4, entry 1), while 1-methoxy-4-acetylbenzene **1s** afforded a mixture of **2s** and **2s**′ in a ratio of 85:15 (entry 2). Both Methyl 4-methylbenzoate **1t** and 1-methyl-4-acetylbenzene **1u** gave two regioisomers (entries 3 and 4).

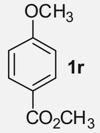
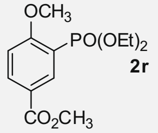
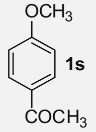
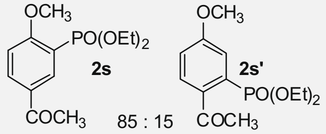
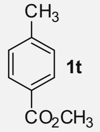
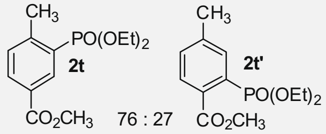
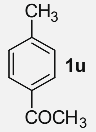
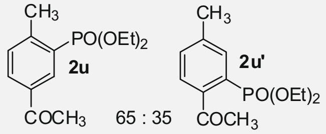
The results presented in Tables 2–4 indicate that $Mn(OAc)_3$-promoted direct phosphonylations have *ortho* and *para* regioselectivities for both electron-rich and electron-deficient arenes. A reaction mechanism is proposed in Scheme 1. For the reaction of a mono-substituted arene, phosphonyl radical **3** may attack *ortho*, *meta*, and *para* positions to form radicals **4**, **6**, and **9**. Since a aryl radical can be stabilized by an electron-donating group or a withdrawing group through the captodative effect,[12] so the formations of radicals **4** and **9** are favorable. The R group can be hyperconjugation groups such as $-CH_3$, electron-donating groups such as $-OCH_3$ and $-OCH_2O-$, or electron-withdrawing groups such as $-CN$ and $-CO_2CH_3$. After the phosphonyl radical addition, radicals **4** and **9** are then oxidized to cations followed by deprotonation to give **5** and **10** as the major products.

In order to evaluate the reactivity of different phosphorus reagents, reactions using diphenylphosphine oxide for phosphonylation of representative arenes were attempted (Table 5). Benzene, toluene, and methyl benzoate were found not reactive under the general reaction conditions (Table 5, entries 1–3). They each gave a complicated mixture containing regioisomers at reflux condition. Reactions of alkoxy benzene such as 1,2-dimethoxy-, 1,4-dimethoxy-, and methylene-1,3-dioxybenzenes gave phosphonylation products **2v**, **2w,** and **2x** in 40%, 45%, and 75% yields, respectively (entries 4–6). The yields are lower than that of diethyl phosphite.

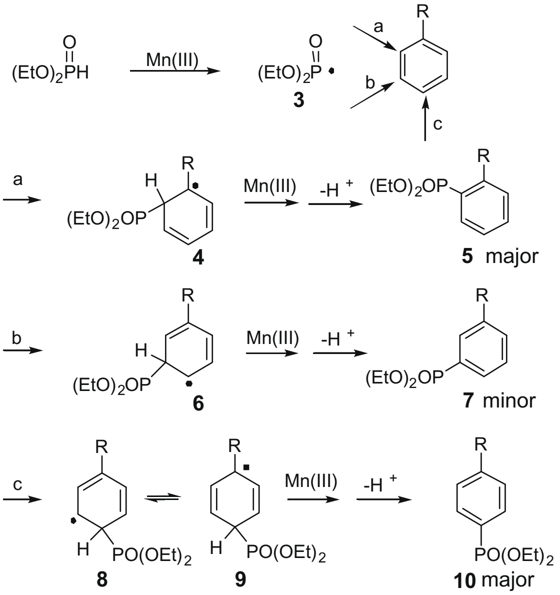
The method for direct phophonylation of arenes has been applied to the synthesis of ligands bearing phosphorus moiety, such as 3,3′-bis(OMe)-MeO-BIPHEP **11** (Scheme 2). The new method is straightforward and it can be carried out under milder conditions than those reported in literature.[13] The structure of compound **13** has been confirmed by X-ray crystal analysis (Fig. 1).

In summary, we have demonstrated that manganese (III) acetate can be used to promote the direct phosphonylation of substituted arenes with diethylphosphite or diphenylphosphine oxide. The reaction scope and regioselectivity for mono- and disubstituted arenes have been explored. The mono-substituted arenes afforded *para*- or *ortho*-phosphonylated compounds as the major products, whereas 1,2-dimethoxybenzene, dimethyl phthalate, 1,3-dicyanobenzene, and methyl 4-methoxybenzoate produced

Table 4
Phosphonylation of arenes bearing electron-donating and electron-withdrawing groups[a]

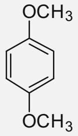
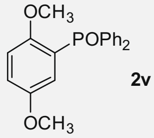
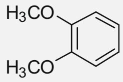
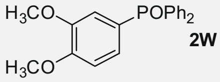
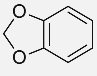
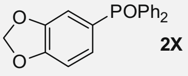
Entry	Substrate	Product	Yield (%)
1	 **1r**	 **2r**	92
2	 **1s**	 **2s** 85 : 15 **2s'**	90
3	 **1t**	 **2t** 76 : 27 **2t'**	80
4	 **1u**	 **2u** 65 : 35 **2u'**	86

[a] Reaction conditions: arene (3 mmol), dialkylphosphite (6 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (9 mmol) in HOAc at 60 °C for 6 h under air.

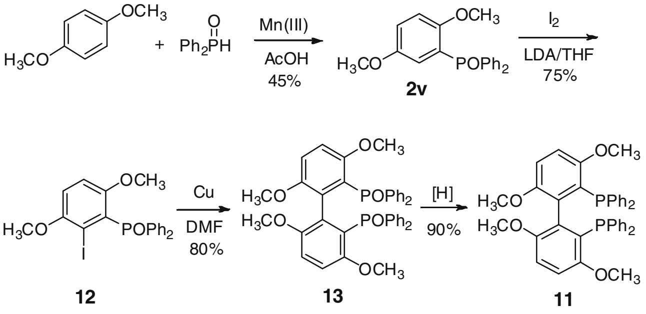


Scheme 1. Mechanism for regioselective phosphonylation.

Table 5
Phosphonylation with diphenylphosphine oxide[a]

Entry	Substrate	Product	Yield (%)
1	C_6H_6	No reaction	
2	$CH_3C_6H_5$	No reaction	
3	$C_6H_5CO_2Me$	No reaction	
4		 **2v**	45
5		 **2W**	40
6		 **2X**	75

[a] Reaction conditions: arene (3 mmol), diphenylphosphine oxide (6 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (9 mmol) in HOAc at 60 °C for 1 h under air.



Scheme 2. Synthesis of arylphosphonate ligand **11**.

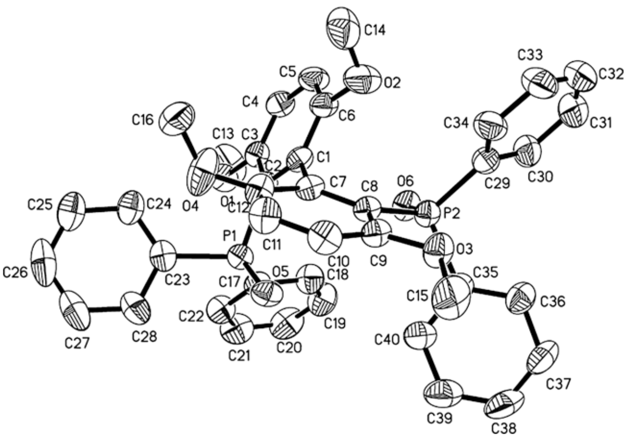


Figure. 1. X-ray crystal structure of compound **13**.

single phosphonated products. In addition to arenes bearing electron-donating groups, this reaction also works for some arenes bearing electron-withdrawing groups such as ester and nitrile, but it has a low regioselectivity for arenes bearing carbonyl groups, and is not reactive for nitrobenzene. The phosphonylation reaction has been successfully used to synthesize phosphorus ligand 3,3'-bis(OMe)-MeO-BIPH.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.029.

References and notes

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