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Letter

Mn-Catalyzed Electrooxidative Undirected C−H/P−H Cross-Coupling between Aromatics and Diphenyl Phosphine Oxides

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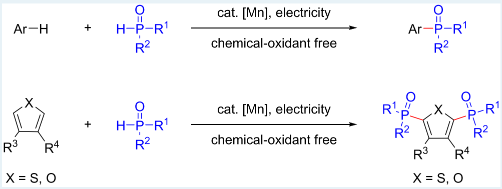
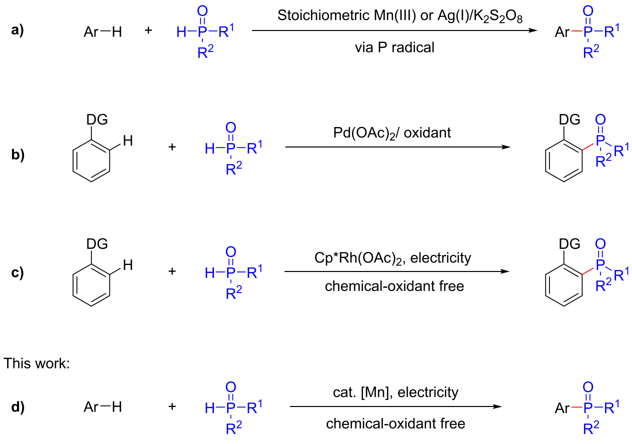
ABSTRACT: C−P bonds are widely found in a great many bioactive compounds and functional molecules. Transition-metal-catalyzed dehydrogenative C−H/P−H cross-coupling plays a crucial part in C−P bond formation since it requires no pretreatment of substrates. Herein, we reported a Mn-catalyzed electrochemical intermolecular dehydrogenative cross-coupling between aryl C−H and diphenyl phosphine oxides. In undivided cells, a series of phosphorylation or diphosphorylation products could be obtained separately by adjusting the proportion of substrates. A catalytic amount of inexpensive Mn(II) salt was used, and no external chemical oxidants were needed in this process. A kinetic isotope effect experiment suggested that the C−H activation was not the rate-determining step.



KEYWORDS: *transition-metal catalysis, C−P bond formation, electrochemistry, phosphorylation, hydrogen evolution*

The phosphorylation of aromatic compounds has drawn great attention from researchers in recent years since the C(sp2)−P bond widely exists in many bioactive compounds, pharmaceutical molecules, and functional materials.[1−11] Transition-metal-catalyzed cross-coupling of C−H/P−H is an important method to synthesize aryl phosphorus compounds,[12−15] and many achievements have been made via two strategies. In 2006, Zhang's group reported a $\mathrm{Mn}^{\mathrm{III}}$ promoted C−H phosphonation of thiazole and furan by using $\mathrm{Mn}^{\mathrm{III}}$ to generate the P radical.[16] Afterward, several reports have been published using a similar strategy.[17−19] In addition to the Mn-induced P radical method, Ag^{I}/peroxide, a classical radical reaction catalysis system, has also been utilized widely in C(sp2)−P bond formation reactions[20−23] (Scheme 1a). Additionally, a directed aryl C−H activation strategy could also be used in C−P bond formation. For example, Yu[24] and Murakami[25] reported Pd-catalyzed pyridine-directed benzene phosphorylation using benzoquinone and AgOAc, respectively, as oxidants (Scheme 1b). However, the above metioned methods usually require stoichiometric metal, chemical oxidant, or noble metal catalyst. In consideration of atom-economy and environment-friendliness, it would be desirable to develop an efficient approach to construct the C−P bond.

Scheme 1. Metal-Catalyzed Cross-Coupling between Aryl C−H and P−H



Electrochemistry has been a hot point in recent years because electricity was found to be an ideal alternative to chemical oxidants and reductants.[26−34] Combining transition-metal catalysis and electrolysis is a great idea to solve the atom-economical problem and expand the application of electrosynthesis.[35−39] Recently, many electrochemical transition-metal-catalyzed C−H functionalizations have been reported, including Co,[40−42] Cu,[43,44] Mn,[45,46] Pd,[47,48] and Ru.[49,50] By combining electrochemistry with traditional directed C−H activation to construct the C−P bond, Xu reported an electrooxidative directed Rh-catalyzed aryl C−H phosphorylation[51] (Scheme 1c). The strategy of metal-induced P radical is still waiting to be discovered via the electrochemical method. Herein, we introduce a Mn-catalyzed electrooxidative C−H phosphorylation between electron-rich aromatics and diphenyl phosphine oxide under a mild condition with low-cost

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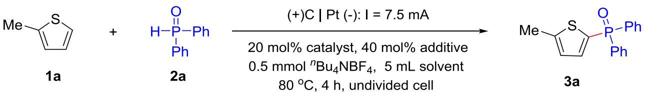
$Mn(OAc)_2{\cdot}4H_2O$ catalyst and no extra chemical oxidants (Scheme 1d).

The cross-coupling between 2-methyl-thiophene (**1a**) and diphenyl phosphine oxide (**2a**) was chosen as the model reaction. Using $^{n}Bu_4NBF_4$ as electrolyte and $Mn(OAc)_2{\cdot}4H_2O$ as catalyst, the target product (**3a**) could be obtained in 24% yield under 7.5 mA constant current for 4 h in acetic acid solvent (Table 1, entry 1). Other strong polar solvents such as acetonitrile and dimethylformamide were screened, but decreased yields were obtained (Table 1, entries 2 and 3). Then Mn^{II} and Mn^{III} salts with different coordination anion were tried; nonetheless, only $Mn(OAc)_3{\cdot}2H_2O$ had similar reactivity with $Mn(OAc)_2{\cdot}4H_2O$ (Table 1, entries 4 and 5). Besides Mn, other transition-metal catalysts such as Cu^{II} and Ag^{I} were examined, but both of them had bad reactivity for this transformation (Table 1, entries 6 and 7; see Supporting Information, Scheme S1 for the detailed catalyst screen). Interestingly, the addition of sodium acetate greatly increased the yield (Table 1, entry 8), which inspired us to screen different inorganic and organic bases (Table 1, entries 9−12). To our delight, an 81% yield was obtained with the addition of phenanthroline (Table 1, entry 13). After optimization, control experiments were conducted, and only a trace amount of product could be obtained without electrolysis (Table 1, entry 14), while no reaction took place without Mn catalyst either (Table 1, entry 15). In consideration of a high loading of catalyst, we made attempts to lower the amount of $Mn(OAc)_2{\cdot}4H_2O$ and recycle the catalyst and electrolyte (see Supporting Information, Scheme S2).

Table 1. Effects of Reaction Parameters[a]

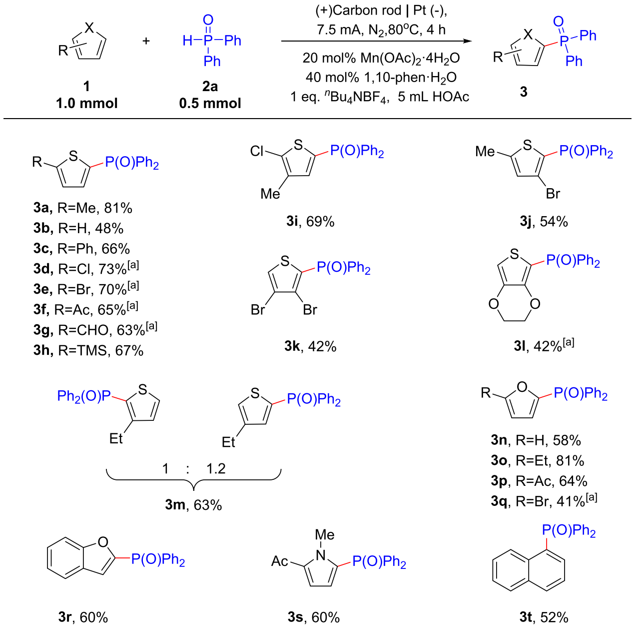


entry	catalyst	additive	solvent	yield[b]
1	$Mn(OAc)_2{\cdot}4H_2O$	none	HOAc	24%
2	$Mn(OAc)_2{\cdot}4H_2O$	none	MeCN	11%
3	$Mn(OAc)_2{\cdot}4H_2O$	none	DMF	8%
4	$MnBr_2{\cdot}4H_2O$	none	HOAc	trace
5	$Mn(OAc)_3{\cdot}2H_2O$	none	HOAc	25%
6	$Cu(OAc)_2$	none	HOAc	n.d.
7	AgOAc	none	HOAc	trace
8	$Mn(OAc)_2{\cdot}4H_2O$	NaOAc	HOAc	51%
9	$Mn(OAc)_2{\cdot}4H_2O$	Na_2CO_3	HOAc	54%
10	$Mn(OAc)_2{\cdot}4H_2O$	DBU	HOAc	56%
11	$Mn(OAc)_2{\cdot}4H_2O$	pyridine	HOAc	59%
12	$Mn(OAc)_2{\cdot}4H_2O$	2,2′-bypyridine	HOAc	75%
13	$Mn(OAc)_2{\cdot}4H_2O$	1,10-phen·H_2O	HOAc	81%
14[c]	$Mn(OAc)_2{\cdot}4H_2O$	1,10-phen·H_2O	HOAc	trace
15	none	1,10-phen·H_2O	HOAc	n.d.

[a] Reaction conditions: undivided cell, **1a** (1 mmol), **2a** (0.5 mmol), N_2. [b] Isolated yield. [c] Without electricity.

Then the scope of this Mn-catalyzed electrooxidative C(sp2)−H/P−H cross-coupling was explored under standard conditions (Scheme 2). First, thiophene and different *ortho*-substituted thiophenes were applied to this reaction (**3a**−**3h**). Thiophene only gave a medium yield (**3b**) while the difunctional byproduct was detected, and a good yield could be obtained with phenyl group (**3c**). Thiophenes bearing a halogen group and a strong electro-withdrawing acetyl or aldehyde group simply gave a medium yield; however, by increasing the amount of thiophene substrate and Mn catalyst, a good yield could be obtained for these substrates bearing electron-withdrawing groups (**3d**−**3g**). In addition, thiophene with a TMS group, which could be transferred into other functional groups, gave a rather good yield (**3h**). For disubstituted thiophenes, both 2-chloride-3-methylthiophene and 4-bromo-2-methylthiophene gave good yields (**3i** and **3j**); 3,4-dimethylthiophene had a moderate yield (**3k**), and 2,3-dihydrothieno[3,4-*b*][1,4]dioxine also had a medium yield by increasing the amount of the thiophene substrate and Mn catalyst (**3l**). When 3-ethylthiophene was applied as the substrate, both *ortho*-positions had reactivity, and two different phosphorylation products were obtained with the ratio of 1:1.2 according to NMR results (**3m**). In addition to thiophene, furan-type substrates also showed good reactivity in this reaction. Different sorts of furan were tried, and furan bearing no group, alkyl group, halogen group, and electro-withdrawing acetyl group obtained yields ranging from moderate to good (**3n**−**3q**). Benzofuran was tried, and 2-phosphorylation product was obtained with good yield (**3r**). However, N-heterocycles such as indole and pyrrole could not produce the corresponding products, which may be due to their active N−H and electron-rich character. By trial and error, we found that *N*-methyl-2-acetylpyrrole, which has a methyl protecting group for N−H and an acetyl group to lower electron density of pyrrole ring, could produce the target product with a good yield (**3s**). Besides heteroaromatics, a moderate amount of α-phosphorylation product was obtained by using naphthalene as substrate (**3t**).

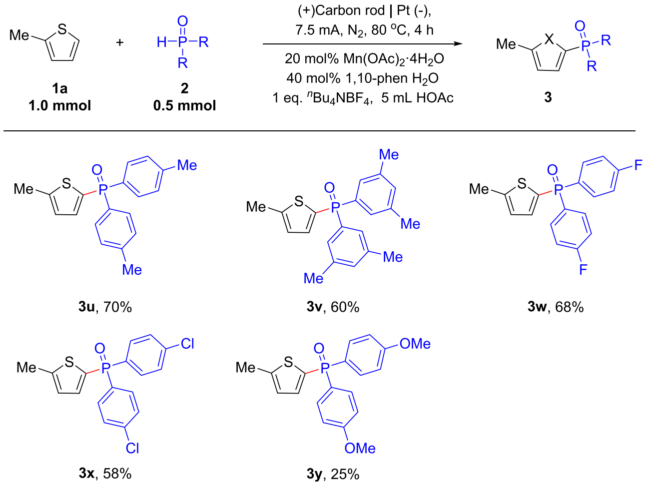
Scheme 2. Substrate Scope of Aromatics



[a] 1.5 mmol of aromatics and 30 mol % $Mn(OAc)_2{\cdot}4H_2O$ were used.

The scope of phosphine oxides was explored likewise under standard conditions (Scheme 3). Diphenyl phosphine oxides bearing diverse functional groups on benzene rings were synthesized and tested. A methyl group showed no harm to the reactivity, and both *para*-monomethyl substituted substrate and *meta*-dimethyl substituted substrate showed good yields (**3u** and **3v**). Halogen-substituted diphenyl phosphine oxides also exhibited good reactivity, and good yields could be

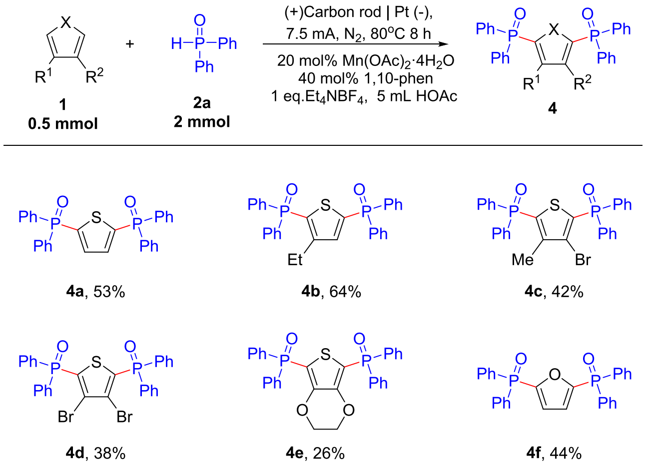
Scheme 3. Substrate Scope of Diphenyl Phosphine Oxides



obtained with fluorine and chlorine (**3w** and **3x**). However, an electron-donating methoxy group substituted substrate only gave a 25% yield (**3y**).

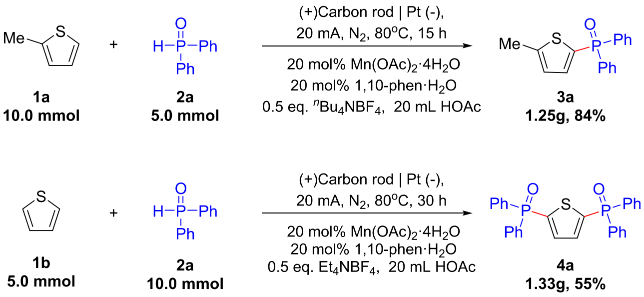
During the scope of the thiophene substrate, we found that thiophene and furan bearing two α-C-H had a difunctional byproduct. By increasing the amount of diphenyl phosphine oxide and prolonging the reaction time, *ortho*-diphosphorylated thiophene could be obtained with a 53% yield (Scheme 4, **4a**). 3-Ethylthiophene also had a good yield (**4b**), and for 3,4-disubstituted thiophenes, corresponding products could be obtained with moderate yields (**4c** to **4e**). Besides thiophene, difunctional furan could also be afforded with moderate yield using furan as the substrate (**4f**). It is worth mentioning that diphosphorylated structure such as **4a**, **4e**, and **4f** has been reported for the synthesis of optical active polymers,[52,53] and our convenient synthetic method for diphosphorylated skeleton could assist in the research.

Scheme 4. Double C−P Formation



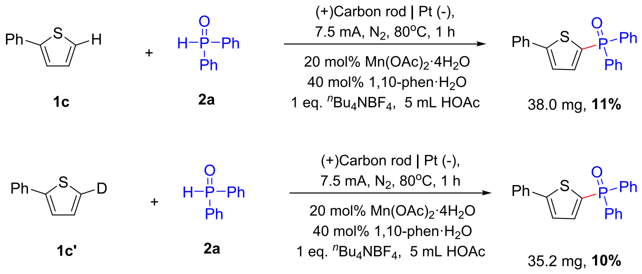
Then we evaluated the synthetic potential of this electrooxidative C−P bond formation by performing a 5 mmol-scale reaction. By using 20 mA current, 1.25 g of **3a** could be synthesized with an 84% yield, and 1.33 g of diphosphorylated product **4a** could also be synthesized with a 55% yield (Scheme 5). These amplification reaction results exhibited good potential application prospects of this electrooxidative C−H/P−H cross-coupling method.

Scheme 5. Gram-Scale Synthesis



To investigate the mechanism of Mn-catalyzed electrooxidative undirected C−H/P−H cross-coupling, a kinetic isotope effect experiment was conducted, and 2-phenylthiophene-5-d (**1c′**) was synthesized (Scheme 6). The ratio of reaction yield between **1c** and **1c′** was 1.1 under same reaction conditions (KIE = 1.1). This result indicated that C−H bond cleavage of thiophene might not be involved in the rate-determining step.

Scheme 6. Kinetic Isotope Effect Experiment



Furthermore, cyclic voltammetry experiments were conducted to study the redox potential of the substrates and catalyst (Figure 1). Oxidative peaks of 2-methylthiophene (**1a**) were obviously observed at 1.9 and 2.1 V, while diphenyl phosphine oxide (**2a**) exhibited no clear oxidative peak from

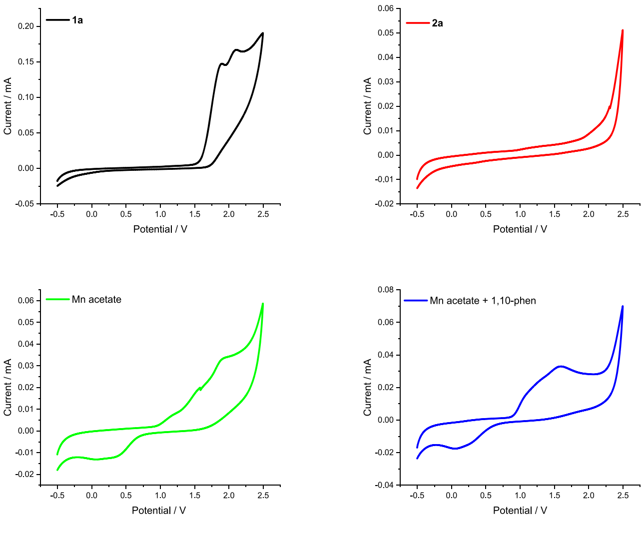
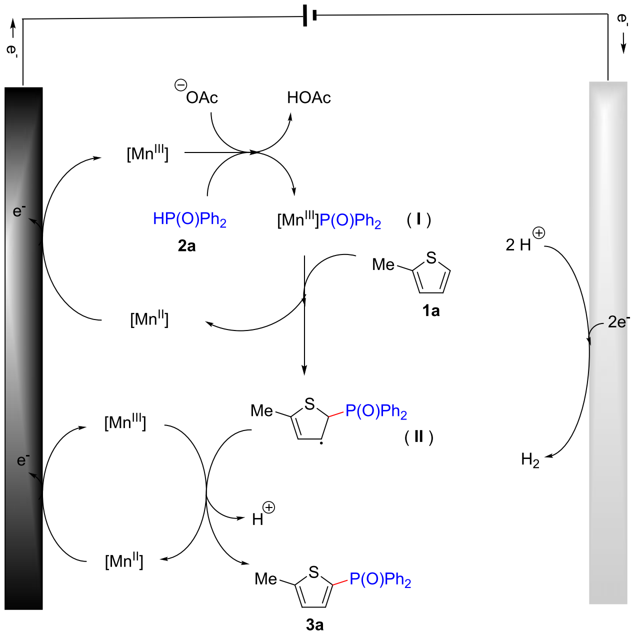


Figure 1. Cyclic voltammograms.

−0.5 V to 2.5 V. The oxidation of Mn^{II} could be detected from 1.0 to 2.0 V, but the oxidative current is slight and only a small peak at 1.9 V could be confirmed. However, when we mix Mn^{II} acetate and phenanthroline together, the oxidative current apparently amplified, and the oxidative peak could be found at 1.5 V. The additives we used in Table 1 were also tested, and the results implied that phenanthroline and bipyridine might affect the oxidation of Mn^{II} by coordination since NaOAc and pyridine had different CV results with them (see Supporting Information, Scheme S3). These results suggest that Mn^{II} catalyst might be oxidized prior to **1a** in the reaction system and the addition of 1,10-phenanthroline promoted the oxidation of Mn^{II}.

On the basis of the above-mentioned experiment results and previous reports,[16,46,54,55] we proposed a plausible mechanism for this Mn-catalyzed electrooxidative C−H/P−H cross-coupling reaction (Scheme 7). First, Mn^{II} coordinated by phenanthroline is oxidized to Mn^{III} on the carbon anode, which could be proved by the CV. Then Mn^{III}−$P(O)Ph_2$ complex (**I**) is formed from Mn^{III} and substrate **2a** with the abstraction of proton by acetate anion. Subsequently, the reaction between intermediate **I** and substrate **2a** affords the radical intermediate **II**, while Mn^{III} is reduced to Mn^{II}, which completes the Mn cycle. Finally, the allylic radical intermediate **II** is oxidized by Mn^{III}, and the following deprotonation gives the final product **3a**, while the proton is reduced on the Pt cathode to release hydrogen gas.

Scheme 7. Proposed Mechanism



In conclusion, we have developed a Mn-catalyzed electrooxidative dehydrogenative C−H/P−H cross-coupling between electron-rich aromatics and phosphine oxides under undivided electrolytic conditions. This electrochemical strategy employs a catalytic amount of inexpensive Mn(II) salt and avoids the use of chemical-oxidants, which affords a convenient and environmentally friendly pattern for the synthesis of the C(sp2)−P bond. Importantly, the good functional group tolerance, the brand new diphosphorylation method, and the excellent efficiency in gram-scale experiment reveal that this reaction has further potential in industrial production.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00549.

NMR data and characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor P. H. Dixneuf for his outstanding contribution on organometallic chemistry and catalyst.

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