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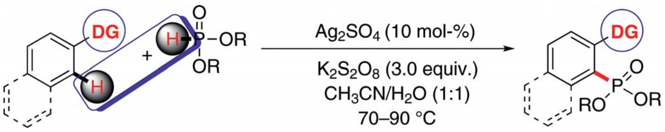

A highly regioselective phosphonation reaction has been developed by using *N*,*N*-dialkyl-substituted amides, *N*,*N*-dialkylsulfonamides, and nitro groups as directing groups (DGs); Ag_2SO_4 as a catalyst; and $K_2S_2O_8$ as a benign oxidant under mild reaction conditions. This method has a broad scope and offers facile construction of C–P bonds.

X. Mao, X. Ma, S. Zhang, H. Hu,
C. Zhu,* Y. Cheng* **1–5**

Silver-Catalyzed Highly Regioselective Phosphonation of Arenes Bearing Electron-Withdrawing Groups

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Silver-Catalyzed Highly Regioselective Phosphonation of Arenes Bearing Electron-Withdrawing Groups

Xuerong Mao,[a] Xiao Ma,[a] Shuwei Zhang,[a] Hongwen Hu,[a] Chengjian Zhu,*[a] and Yixiang Cheng*[a]

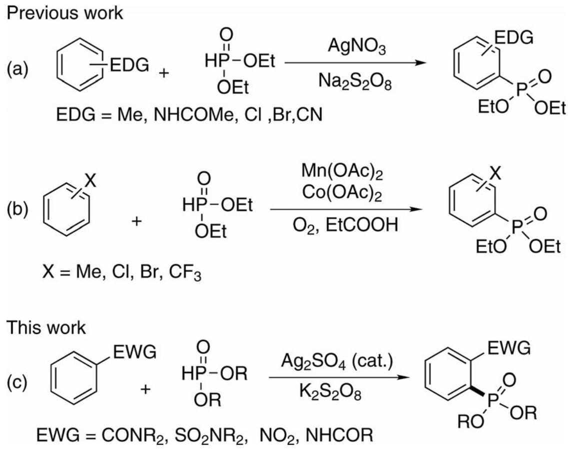
Keywords: Synthetic methods / Dehydrogenation / Cross-coupling / Phosphonation / Silver

A highly efficient, $Ag^I/K_2S_2O_8$-mediated regioselective phosphonation reaction has been developed by using electron-deficient directing groups. These phosphonation reactions were performed with *N*,*N*-dialkylbenzamides, *N*,*N*-dialkylbenzenesulfonamides, and nitrobenzene. This method has a broad substrate scope and offers facile construction of C–P bonds.

Introduction

Phosphorus compounds are very important intermediates in organic synthesis, medicinal chemistry, and photoelectric materials.[1] As aryl phosphonates and their derivatives are of great importance in chemistry, the synthesis of dialkyl arylphosphonates has drawn much attention, and some efficient methods have been established.[2] Among them, transition-metal-catalyzed coupling reactions serve as an efficient protocol for the construction of C–P bonds, for example, the Hirao reaction[3] and the transition-metal-catalyzed cross-coupling of diaryl and dialkyl phosphites with aryl halides, triflates, diazonium salts, tosylates, and so on.[4] However, these strategies require prefunctionalized reactants, which limit their applications. In recent years, cross-dehydrogenative-coupling (CDC) reactions have been extensively applied in the formation of C–C[5] and C–heteroatom bonds,[6] as C–H bonds are ubiquitous in organic molecules.[7] Our group recently reported an efficient oxidative phosphonation of sp^3 C–H bonds with various diarylphosphane oxides and dialkyl phosphites, which provides easy access to α-aminophosphonic compounds in high yields with a broad reaction scope.[8] Herein, we wish to report the phosphonation reaction of arenes.

In 1985, Effenberger reported the formation of C–P bonds by coupling arenes with diethyl phosphite by using $Na_2S_2O_8$ and $AgNO_3$, but only arenes bearing electron-donating groups (EDGs) were mainly suitable (Scheme 1, a).[9] In addition, Ishii's group realized the dehydrogenative synthesis of arylphosphonates under a redox system of $Mn(OAc)_2/Co(OAc)_2/O_2$ (Scheme 1, b).[10] In 2006, Zou and Zhang successfully developed noncatalytic cross-coupling reactions of heteroarenes with dialkyl phosphites by using $Mn(OAc)_3$ as an oxidant.[11] Notably, these transition-metal-catalyzed dehydrogenative phosphonation reactions of arenes were mainly focused on arenes bearing electron-donating groups. However, there is no report on the dehydrogenative cross-coupling reactions of dialkyl phosphites with arenes bearing strongly electron-deficient groups such as *N*-alkyl-substituted amides, *N*,*N*-dialkyl benzenesulfonamides and nitro groups. Therefore, the development of such a strategy is highly desirable. In this paper, we report the silver-catalyzed phosphonation of arenes bearing electron-withdrawing groups (EWGs, Scheme 1, c).



Scheme 1. Transition-metal-catalyzed phosphonylation reactions.

Results and Discussion

At the outset, *N*,*N*-diethylbenzamide (**1a**) and diethyl phosphite (**2a**) were selected as model substrates under the

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[a] Key Lab of Mesoscopic Chemistry of MOE, School of Chemistry and Chemical Engineering
Nanjing University, Nanjing 210093, China
E-mail: yxcheng@ nju.edu.cn
E-mail: cjzhu@nju.edu.cn
Homepage: http://hysz.nju.edu.cn/yxcheng/

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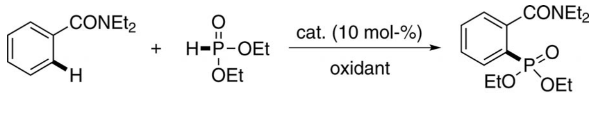
conditions of $Pd(OAc)_2$ (10 mol-%) and $K_2S_2O_8$ (3.0 equiv.) in CH_3CN at 90 °C.[6i] To our delight, we obtained diethyl (2-diethylcarbamoylphenyl)phosphonate (**3a**) in 15% yield (Table 1, entry 1). Encouraged by this result, we investigated the influence of the catalyst, oxidant, and solvent on this dehydrogenative cross-coupling reaction. A screening of the conditions is summarized in Table 1. If Ag^I compounds were chosen as catalysts, the yield of **3a** was greatly improved (Table 1, entries 4–7). Other metal salts such as CuI (Table 1, entry 2) and $FeCl_2$ (Table 1, entry 3) turned out to be much less active catalysts under the same conditions, and this indicates that Ag^I is the best catalyst in this reaction system. Subsequently, various oxidants, including *tert*-butyl hydroperoxide (TBHP), $PhI(OAc)_2$, and di-*tert*-butyl peroxide (DTBP; Table 1, entries 12–14), were also investigated, but expected product **3a** was not obtained, which thus demonstrates that $K_2S_2O_8$ plays a critical role in this C–P coupling reaction. Interestingly, **3a** could be obtained in a high yield of 81% by using Ag_2SO_4 (10 mol-%) and $K_2S_2O_8$ (3.0 equiv.) in CH_3CN/H_2O (1:1; Table 1, entry 8), and it was obtained in 47% yield in CH_2Cl_2/H_2O (1:1; Table 1, entry 15). Notably, **3a** was obtained in 64 and 81% yield if 5 and 20% Ag_2SO_4 was loaded (Table 1, entries 9 and 10). Moreover, the yield decreased if the reaction time were prolonged (24 h). Under $AgNO_3$ catalysis, **3a** was obtained in 76% yield in CH_2Cl_2/H_2O (1:1; Table 1, entry 16).[12] If $Mn(OAc)_2/Co(OAc)_2$ and $Mn(OAc)_3$ were used as catalysts, only a trace amount of product **3a** was detected (Table 1, entries 17 and 18). Therefore, the optimal reaction conditions for regioselective C–P bond formation are Ag_2SO_4 (10 mol-%), $K_2S_2O_8$ (3.0 equiv.) as the oxidant, and CH_3CN/H_2O (1:1) as the solvent at 90 °C.

To explore the reaction scope, *N*-alkyl-substituted aromatic amides (Scheme 2, **1a–f**) and aryl-substituted *N*,*N*-dimethylbenzamides (Scheme 2, **1g–j**) were chosen as substrates for phosphonation. As shown in Scheme 2, *N*-alkyl-substituted amides such as *N*-branched amides and cycloalkane-substituted amides were efficiently coupled to afford the expected products (Scheme 2, **3a–f**) in high yields (54–82%) under the standard conditions. As for aryl-substituted *N*,*N*-diethylbenzamides, electron-donating groups and most of the electron-withdrawing groups on the aromatic rings were compatible with the C–P coupling reaction. Moreover, aryl-substituted *N*,*N*-diethylbenzamides bearing electron-donating groups showed higher activity than those containing electron-deficient groups (i.e., **3g**). Interestingly, a moderate yield of 55% was provided by using *N*,*N*-diethyl-2-naphthamide as a substrate (Scheme 2, **3j**). Furthermore, replacement of chlorine with bromine as a substituent slightly enhanced the reactivity of the substrate in the phosphonation reaction; diethyl [5-chloro-2-(diethylcarbamoyl)phenyl]phosphonate (**3h**) and diethyl [5-bromo-2-(diethylcarbamoyl)phenyl]phosphonate (**3i**) were obtained in 61 and 64% yield, respectively. Beyond diethyl phosphonate (**2a**), phosphonates **3k–m** were also effective.

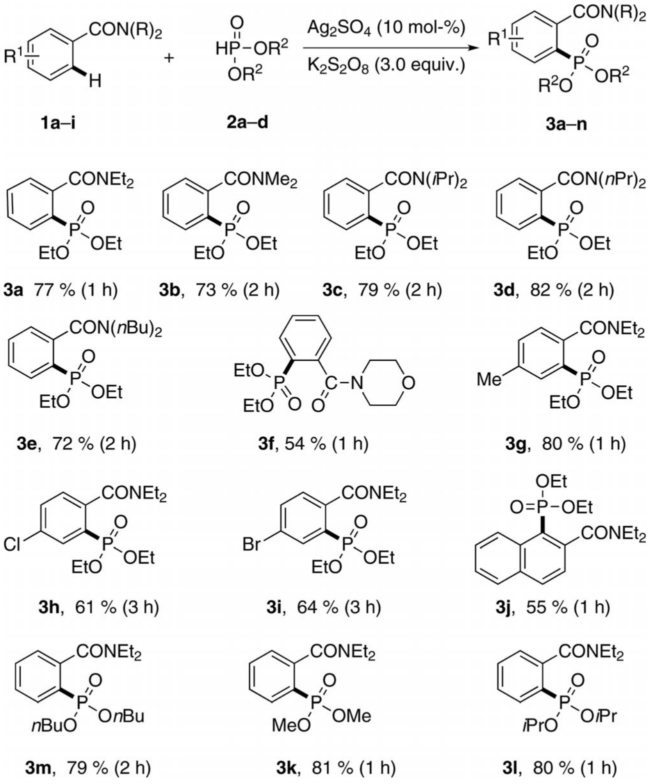
Table 1. Optimization of the phosphonation conditions.[a]



1a **2a** **3a**

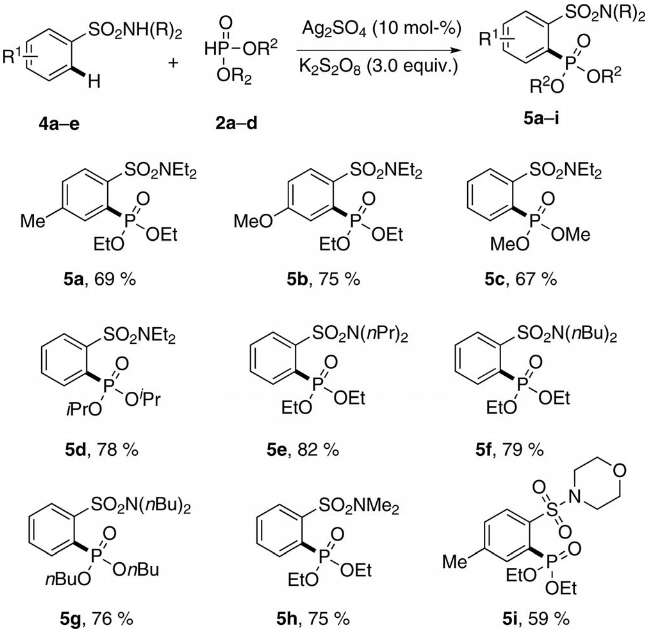
Entry	Catalyst	Oxidant	Solvent	Time [h]	Yield[b] [%]
1	$Pd(OAc)_2$	$K_2S_2O_8$	CH_3CN	10	15
2	CuI	$K_2S_2O_8$	CH_3CN	24	10
3	$FeCl_2$	$K_2S_2O_8$	CH_3CN	24	5
4	Ag_2SO_4	$K_2S_2O_8$	CH_3CN	24	41
5	Ag_2CO_3	$K_2S_2O_8$	CH_3CN	24	28
6	Ag_2O	$K_2S_2O_8$	CH_3CN	24	19
7	AgOAc	$K_2S_2O_8$	CH_3CN	24	32
8	Ag_2SO_4	$K_2S_2O_8$	CH_3CN/H_2O[c]	24	81
9[d]	Ag_2SO_4	$K_2S_2O_8$	CH_3CN/H_2O[c]	1	64
10[e]	Ag_2SO_4	$K_2S_2O_8$	CH_3CN/H_2O[c]	1	81
11[f]	Ag_2SO_4	$K_2S_2O_8$	CH_3CN/H_2O[c]	10	73
12	Ag_2SO_4	TBHP	CH_3CN/H_2O[c]	4	trace
13	Ag_2SO_4	$PhI(OAc)_2$	CH_3CN/H_2O[c]	4	trace
14	Ag_2SO_4	DTBP	CH_3CN/H_2O[c]	4	trace
15	Ag_2SO_4	$K_2S_2O_8$	CH_3CN/H_2O[c]	24	47
16	$AgNO_3$	$K_2S_2O_8$	CH_2Cl_2/H_2O[c]	1	76
17	$Mn(OAc)_3$[g]	–	HOAc	24	trace
18	$Mn(OAc)_2$	Co(OAc)	HOAc	24	trace

[a] The reaction was carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (10 mol-%), and oxidant (0.3 mmol) in solvent (2 mL) at 90 °C in air. [b] Yield of **3a**. [c] v/v = 1:1. [d] Catalyst loading: 5 mol-%. [e] Catalyst loading: 20 mol-%. [f] Under catalyst (10 mol-%) for 24 h. [g] 3.0 equiv.



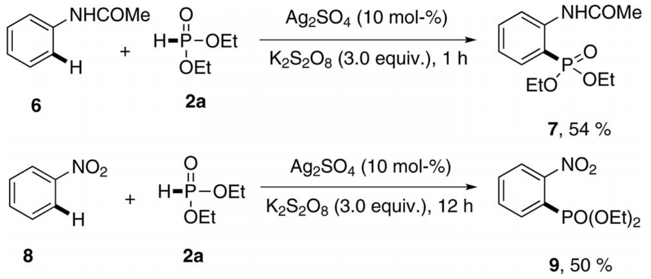
Scheme 2. The scope of the *P*-arylation reaction. Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), Ag_2SO_4 (10 mol-%), $K_2S_2O_8$ (3.0 equiv. relative to **1**), CH_3CN (1 mL), H_2O (1 mL), in air, 90 °C.

We also investigated the scope of the C–P coupling reaction by changing the directing groups and substrates. Whereas the *N*,*N*-dialkylsulfonamide was varied as the directing group, the reaction time for each substrate was set to 2 h by using Ag_2SO_4 (10 mol-%) and $K_2S_2O_8$ (3.0 equiv.) in CH_3CN/H_2O (1:1) in air at 90 °C. As shown in Scheme 3, *N*,*N*-dialkylbenzenesulfonamides **4** also successfully underwent the CDC reactions with dialkyl phosphites, and highly regioselective C–P bond formation was achieved in moderate to good yields (Scheme 3; **5a**–**i**, 59–82%).



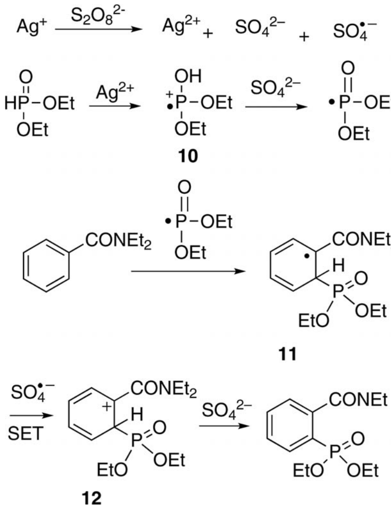
Scheme 3. Phosphonation of *N*,*N*-dialkyarenesulfonamides. Reaction conditions: **4** (0.1 mmol), **2** (0.3 mmol), Ag_2SO_4 (10 mol-%), $K_2S_2O_8$ (3.0 equiv.), CH_3CN (1 mL), H_2O (1 mL), in air, 90 °C, 2 h.

Recognizing that the scope of the phosphonation reaction was not just limited to these two types of substrates, we also performed the CDC of diethyl phosphonate with *N*-phenylacetamide and nitrobenzene. Under identical reaction conditions, both *N*-phenylacetamide and nitrobenzene reacted with diethyl phosphonate to provide the corresponding phosphonation product in moderate yield (Scheme 4).



Scheme 4. The scope of the phosphonation reactions. Reaction conditions: **6** or **8** (0.1 mmol), **2a** (0.3 mmol), Ag_2SO_4 (10 mol-%), $K_2S_2O_8$ (3.0 equiv. relative to **6** or **8**), CH_3CN (1 mL), H_2O (1 mL), in air, 90 °C.

The proposed mechanism for regioselective C–P bond formation is shown in Scheme 5. The reaction rate and yield dramatically decreased under our standard coupling conditions if a radical scavenger [i.e., (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl, (TEMPO)] was added to the *N*,*N*-diethylbenzamide and diethyl phosphonate system, which is indicative of a free-radical process. According to some previous reports and our experimental results, we herein propose that the Ag^I salt and the persulfate anion forms unstable Ag^{II}, which further reacts with diethyl phosphite to afford intermediate cation radical **10**. Then, **10** may lead to a free phosphonyl radical after losing a proton. It is important that electrophilic addition to *N*,*N*-diethylbenzamide leads to intermediate **11**. Upon considering that the aryl radical can be stabilized by a withdrawing group through the captodative effect, the formation of radical **11** is favorable.[13] Subsequently, **11** is converted into **12** by a single-electron transfer (SET), followed by deprotonation to yield **3a**.



Scheme 5. Proposed mechanism of the phosphonation reaction.

Conclusions

In summary, we developed a highly regioselective Ag^I-catalyzed cross-dehydrogenative-coupling reaction for the direct phosphonation of arenes bearing an electron-withdrawing group. A series of coupling products could be synthesized with inexpensive Ag_2SO_4 as the catalyst and $K_2S_2O_8$ as the oxidant. This method has a broad scope and offers facile construction of C–P bonds.

Experimental Section

General Procedure: A solution of the dialkyl phosphite (0.30 mmol), tertiary amide (0.10 mmol), catalyst (10 mol-%), and oxidant (0.3 mmol) in solvent (2.0 mL) was heated at 70–90 °C. After completion of the reaction, the mixture was poured into water and extracted with EtOAc (3 × 8 mL). After the solvent was removed, the residue was purified by flash column chromatography on silica gel or by preparative TLC on GF 254 to afford the desired product.

Supporting Information (see footnote on the first page of this article): General information, optimization of the reaction conditions, general procedure for the phosphonation of amides, characterization data, and copies of the ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra.

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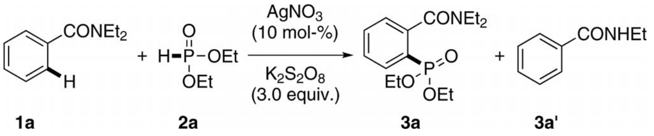
[12] At first, *N,N*-diethylbenzamide (**1a**) and diethyl phosphite (**2a**) were selected as model substrates in the presence of AgNO$_3$ (10 mol-%) with K$_2$S$_2$O$_8$ (3.0 equiv.) as the oxidant in CH$_3$CN/H$_2$O in air at 90 °C. Upon completion of the phosphonation reaction of the amide with diethyl phosphite, we found that AgNO$_3$ was not the best catalyst for the system. The following is the reaction:



When Ag$_2$SO$_4$ was used to replace AgNO$_3$ as the catalyst under the same conditions, we obtained **3a** as the sole product.

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