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Silver(I)-catalyzed highly *para*-selective phosphonation of 2-aryloxazolines†

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A silver-catalyzed phosphonation of 2-aryloxazolines has been accomplished. This protocol provides highly regioselective access to *para*-phosphonation products with good functional group tolerance and moderate to good yields via cross-dehydrogenation coupling. Mechanistic studies have shown that *para*-phosphonation products are obtained via a radical pathway. Furthermore, the directing oxazoline group in the *para*-phosphonation products is removable and can be converted to benzoic esters.

Benzoic acid derivatives are widely used in drugs and agrochemicals.¹ Hence, their chemical modifications have potential applications. In the past few decades, transition-metal-catalyzed C–H bond activation has attracted extensive attention from chemists because of its high efficiency, atom economy and good functional group tolerance.² In this regard, modifications of benzoic acid derivatives utilizing C–H activation have been significantly developed.³ Remote C–H activation of benzoic acid derivatives is relatively rare compared to *ortho*-C–H functionalization. To achieve remote C–H functionalization of benzoic acid derivatives, more complex auxiliary groups need to be utilized and tend to result in regioisomeric mixtures.⁴ Thus, it is urgent to develop new methodologies for the *para*-functionalization of benzoic acid derivatives using easily available directing groups. The conversion of benzoic acids to 2-aryloxazolines is a commonly used method.

On the other hand, phosphorus-containing compounds exhibit a wide range of applications in pharmaceuticals, materials

and catalysis.⁵ In recent decades, transition-metal-catalyzed C–H functionalization to construct C–P bonds has been used as an important methodology for the synthesis of organophosphorus compounds.⁶ In 2006, Ishii and coworkers published the Mn(II)/Co(II)/O₂ redox-couple catalyzed phosphorylation of arenes; although providing a simple approach to the preparation of organophosphorus compounds, the site-selectivity was relatively poor (Scheme 1a).⁷ For good selectivity, functional group-directed C–H activation protocols are particularly valuable. In 2013, the Yu group reported *ortho*-phosphorylation of arenes via heterocycle-directed *ortho*-palladation (Scheme 1b).⁸ Subsequently, the Chen and Yu groups described a process for the *ortho*-phosphorylation of arenes using an inexpensive copper catalyst (Scheme 1b).⁹ Since phosphorus reagents strongly coordinate with metals, a slow release of phosphorus reagents is required to ensure that the reaction proceeds smoothly. In 2019, the Wen, Zhang and Xu groups demonstrated a costly rhodium-catalyzed methodology to achieve *ortho*-phosphonation of electron-rich arylamine derivatives, and the use of oxidants was avoided because of the employed electrochemical oxidation (Scheme 1b).¹⁰ In 2013, the Zhu and Cheng groups realized the Ag(I)/K₂S₂O₈-mediated *ortho*-phosphorylation of electron-deficient arenes via a radical pathway (Scheme 1c).¹¹ In 2020, the Liang group reported the visible-light-induced *para*-C_{Ar}-H phosphonation reactions with electron-rich arenes by cross-dehydrogenation coupling (CDC) (Scheme 1d).¹² As part of our continuing interest in remote C–H functionalization,¹³ herein we disclose the silver-catalyzed highly *para*-phosphonation of electron-deficient 2-aryloxazolines (Scheme 1e).

In our initial investigation, we chose 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (**1a**) and di-*p*-tolylphosphine oxide (**2a**) as model substrates to screen the reaction conditions (see Table S1 in the ESI† for details). After extensive screenings, the optimal conditions were established as follows: with 10 mol% AgNTf₂ as the catalyst, 3.0 equiv. of K₂S₂O₈ as the oxidant, 0.5 equiv. of pivalic acid (PivOH) as the additive and MeCN as the solvent, the reaction of **1a** and **2a** (3.0 equiv.) performed best at 120 °C for 24 h under an argon atmosphere to give **3aa** in 73% yield.

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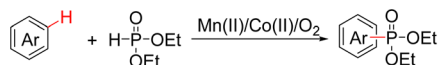
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† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data, ¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR and HRMS of compounds **3** and **4**. See DOI: <https://doi.org/10.1039/d3cc06241d>

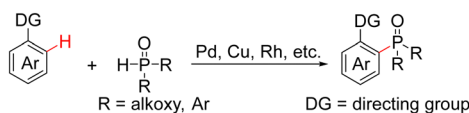


Previous work

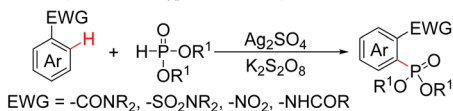
a) Mn(II)/Co(II)/O₂ redox couple catalyzed phosphorylation of arenes.



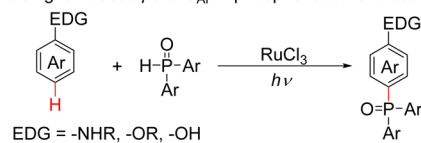
b) Transition-metal-catalyzed *ortho*-C_{Ar}-H phosphorylation/phosphonation of arenes.



c) Silver-catalyzed *ortho*-C_{Ar}-H phosphorylation of electron-deficient arenes.

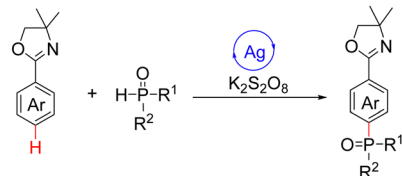


d) Visible-light induced *para*-C_{Ar}-H phosphonation of electron-rich arenes.



This work

e) Silver-catalyzed *para*-C_{Ar}-H phosphorylation of electron-deficient arenes.

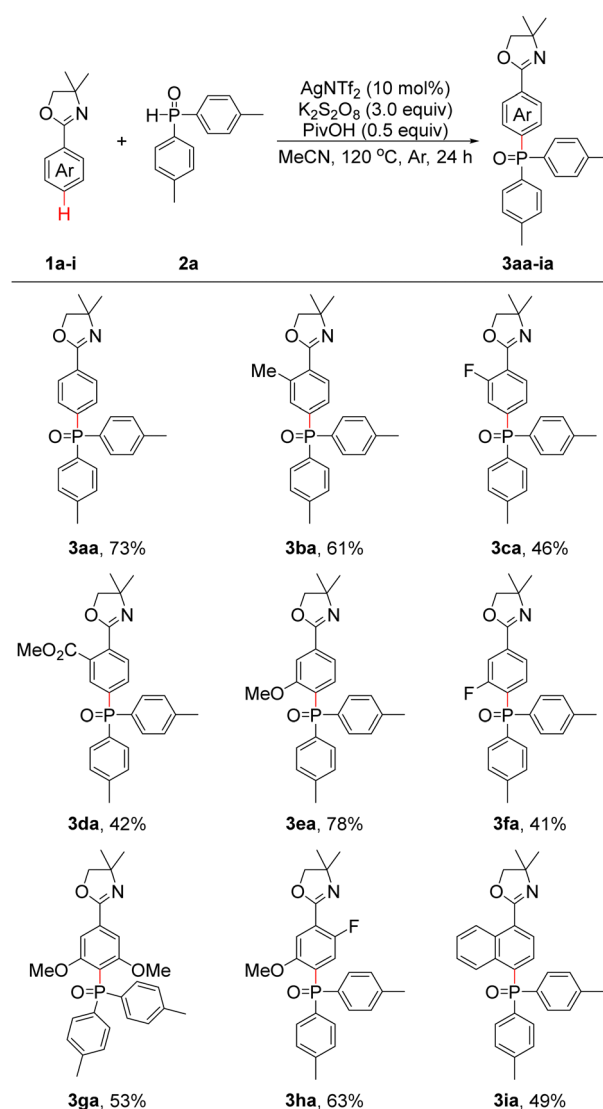


Scheme 1 Previous (a–d) and this (e) work on transition-metal-catalyzed C–H phosphorylation/phosphonation of arenes.

With the optimal conditions in hand, we then investigated the scope and functional group tolerance of 2-aryloxazolines **1**. As shown in Table 1, the reactions of **1a–i** with **2a** proceeded smoothly to afford *para*-phosphonation products **3aa–ia** in moderate to good yields. First, **1a**, which had an unsubstituted phenyl group, afforded **3aa** in 73% yield under optimal conditions. Substrate **1b** with an *ortho*-substituted Me group was able to provide **3ba** in 61% yield. Substrates **1c–d** with the *ortho*-substituted F and CO₂Me groups could deliver **3ca** and **3da** in 46% and 42% yields, respectively. Substrates **1e–f** with the *meta*-substituted OMe and F groups also proceeded smoothly to afford **3ea–fa** in 41–78% yields. To our delight, when 3,5-dimethoxy-substituted substrate **1g** was employed, **3ga** was isolated in 53% yield. In addition, 2-(2-fluoro-5-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (**1h**) could also react with **2a**, and **3ha** was obtained in 63% yield. These findings also provided a novel strategy for synthesizing multisubstituted arenes. For 4,4-dimethyl-2-(naphthalen-1-yl)-4,5-dihydrooxazole (**1i**), **3ia** could be produced in a yield of 49%.

To further explore the generalizability of the substrates, the reactions of **1a** with a series of diarylphosphine oxides (**2b–n**), ethyl phenylphosphinate (**2o**) and dialkylphosphine oxides (**2p** and **2q**) were investigated under optimal conditions. As shown in Table 2, diphenylphosphine oxide (**2b**) was found to be suitable under our optimal conditions, and **3ab** was obtained in 67% yield. When bis(*m*-tolyl)phosphine oxide (**2c**)

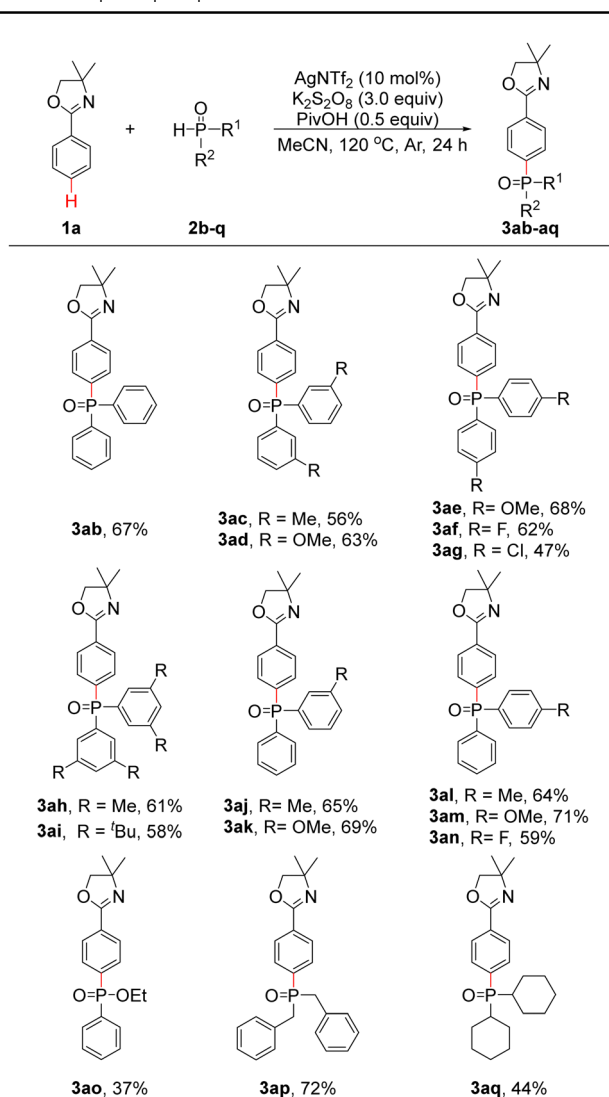
Table 1 Scope of 2-aryloxazolines^{a, b}



^a Reaction conditions: **1a–i** (0.2 mmol), **2a** (0.6 mmol), AgNTf₂ (10 mol%), K₂S₂O₈ (0.6 mmol), PivOH (0.1 mmol), MeCN (1.0 mL) at 120 °C for 24 h under an argon atmosphere. ^b Isolated yields based on **1a–i**.

and bis(*m*-methoxyphenyl)phosphine oxide (**2d**) were employed, **3ac** and **3ad** were obtained in 56% and 63% yields, respectively. If bis(*p*-methoxyphenyl)phosphine oxide (**2e**) was used, **3ae** was obtained in 68% yield. Bis(*p*-fluorophenyl)phosphine oxide (**2f**) and bis(*p*-chlorophenyl)phosphine oxide (**2g**) proceeded well to produce **3af** and **3ag** in 62% and 47% yields, respectively. Delightedly, when bis(3,5-dimethylphenyl)phosphine oxide (**2h**) and bis(3,5-di-*tert*-butylphenyl)phosphine oxide (**2i**) were applied, **3ah** and **3ai** were generated in 61% and 58% yields, respectively. Subsequently, phenyl(tolyl)phosphine oxides (**2j** and **2l**), phenyl(methoxyphenyl)phosphine oxides (**2k** and **2m**) and phenyl(*p*-fluorophenyl)phosphine oxide (**2n**) were also applicable under optimal conditions, and **3aj–an** could be obtained in 59–71% yields. As a result, the synthesis of phosphine oxide products with three different aryl groups is made possible.



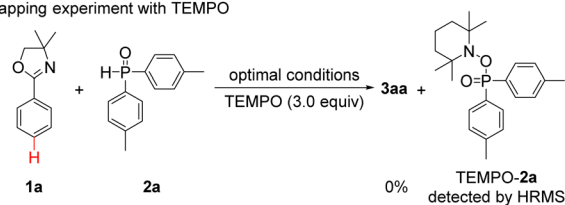
Table 2 Scope of phosphine oxides^{a, b}

^a Reaction conditions: **1a** (0.2 mmol), **2b-q** (0.6 mmol), AgNTf₂ (10 mol%), K₂S₂O₈ (0.6 mmol), PivOH (0.1 mmol), MeCN (1.0 mL) at 120 °C for 24 h under an argon atmosphere. ^b Isolated yields based on **1a**.

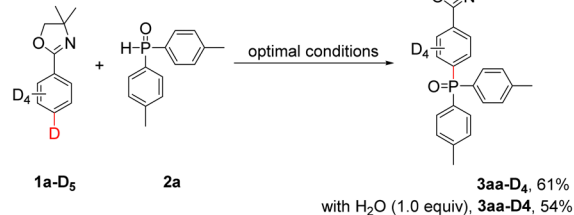
To our delight, when **2o** was investigated, **3ao** was generated in 37% yield. Products **3ap** and **3aq** could be isolated in 72% and 44% yields, respectively, when dibenzylphosphine oxide (**2p**) and dicyclohexylphosphine oxide (**2q**) were applied. Unfortunately, other substrates such as di(thiophen-2-yl)phosphine oxide and diethyl phosphonate failed to provide the desired products.

To gain insight into the reaction mechanism, additional experiments were conducted. First, **3aa** could not be obtained when 3.0 equiv. of the radical scavenger 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was added under optimal conditions, and the TEMPO-**2a** adduct could be detected by high resolution mass spectrometry (HRMS) (Scheme 2a and Fig. S1, ESI[†]). This result showed that a radical pathway may be involved in the reaction. Second, when **1a-D₅** was employed under optimal conditions, pure **3aa-D₄** (Fig. S2, ESI[†]) was obtained in 61% yield. In addition, pure

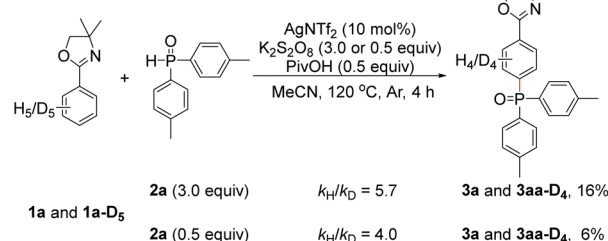
a) Trapping experiment with TEMPO



b) H/D exchange



c) Kinetic isotope effect experiment

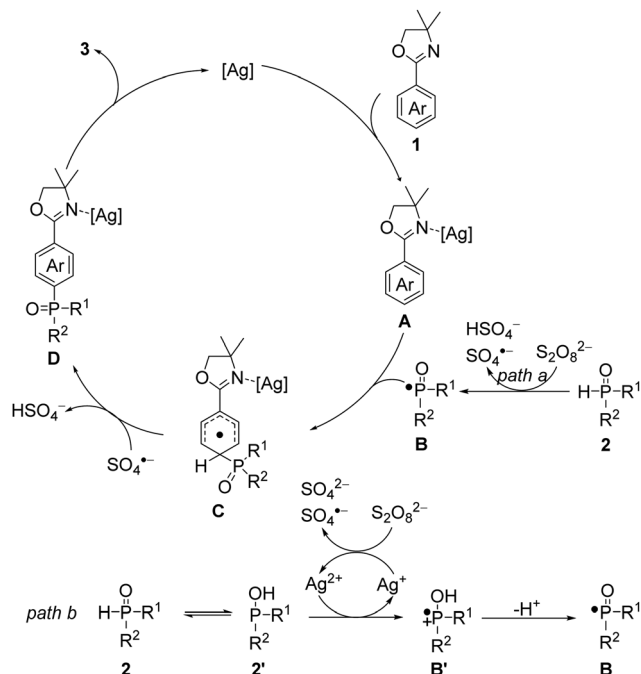


Scheme 2 Preliminary mechanistic studies.

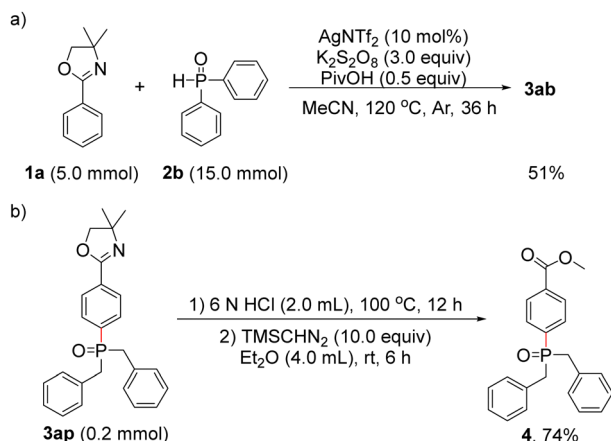
3aa-D₄ (Fig. S3, ESI[†]) could also be isolated in 54% yield with an additional 1.0 equiv. of H₂O. These results indicated that no D/H scrambling occurred on the phenyl ring of **3aa-D₄** and implied that no *ortho* C-H activation process took place (Scheme 2b). Third, an intermolecular kinetic isotope effect (KIE) experiment was performed, and the k_H/k_D value was determined to be 5.7 (Fig. S4, ESI[†]); when **2a** was reduced to 0.5 equiv., the k_H/k_D value was 4.0 (Fig. S5, ESI[†]), suggesting that C-H cleavage may be involved in the rate-determining step (Scheme 2c).

Based on the above findings of mechanistic studies and previous reports, a plausible reaction mechanism is shown in Scheme 3.^{11,14-18} First, 2-aryloxazoline **1** interacts with the silver catalyst to form the intermediate **A**.¹⁴ Similar oxazolium ion can also be generated in the presence of PivOH and participates in subsequent steps as the intermediate **A**.¹⁵ Meanwhile, phosphine oxide **2** is directly oxidized by the persulfate dianion (S₂O₈²⁻) to give the key P-centered radical **B** together with a hydrogen sulfate anion (HSO₄⁻) and a sulfate radical anion (SO₄^{•-}) (Scheme 3, *path a*).¹⁶ Alternatively, **2** can exist in rapid equilibrium with the corresponding tautomeric isomer **2'**.¹⁷ The Ag²⁺ salt can oxidize **2'** to afford a Ag⁺ species and cation radical **B'**, which may lead to the P-centered radical **B** after losing a proton; and the formed Ag⁺ salt can be oxidized by a S₂O₈²⁻ to regenerate Ag²⁺ together with a sulfate dianion (SO₄²⁻) and a SO₄^{•-} (Scheme 3, *path b*).^{11,18} Radical **B** then regioselectively undergoes a radical addition to the *para* position of **A** to give the intermediate **C**, which is subsequently oxidized and deprotonated by SO₄^{•-} to give intermediate **D**. Finally, the *para*-phosphonation product **3** is obtained by





Scheme 3 Proposed mechanism.

Scheme 4 (a) Gram-scale synthesis of **3ab**. (b) Further synthetic transformation of **3ap**.

removal of the silver catalyst to complete the catalytic cycle. The oxidant K₂S₂O₈ was mandatory and could promote the *para*-phosphonation alone, albeit in a low yield of 13% (Table S1, entries 22 and 23, ESI[†]). The beneficial effects of the silver salt (Table S1, entry 24, ESI[†]) and PivOH (Table S1, entry 25, ESI[†]) might originate from the activation of **1** by the formation of **A** and oxazolinium ion, respectively. Furthermore, the silver salt can also be employed as an oxidant to generate **B**.

To demonstrate the synthetic utility and importance of the present protocol, the reaction of **1a** with **2b** was carried out at the 5.0-mmol scale, and the *para*-phosphonation product **3ab** was isolated in 51% yield (Scheme 4a). We chose **3ap** as an example for further transformation, its oxazoline group could

be easily hydrolysed under acidic conditions, providing the *para*-phosphonated benzoic acid derivative **4** in 74% yield (Scheme 4b).¹⁹

In summary, a precise and efficient approach for the silver-catalyzed *para*-selective phosphonation of 2-aryloxazolines *via* cross-dehydrogenation coupling has been demonstrated. This protocol is able to provide highly regioselective *para*-phosphonation products and tolerates a wide range of functional groups. Furthermore, the directing oxazoline group in the products is removable and can be easily hydrolysed to give *para*-phosphonated benzoic esters. Preliminary mechanistic studies support that the *para*-phosphonation products are generated *via* a radical pathway. It is anticipated that the present protocol will also be valuable in pharmaceutical and materials science.

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Conflicts of interest

There are no conflicts to declare.

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