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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)/O_2 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)/$K_2S_2O_8$-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% $AgNTf_2$ as the catalyst, 3.0 equiv. of $K_2S_2O_8$ 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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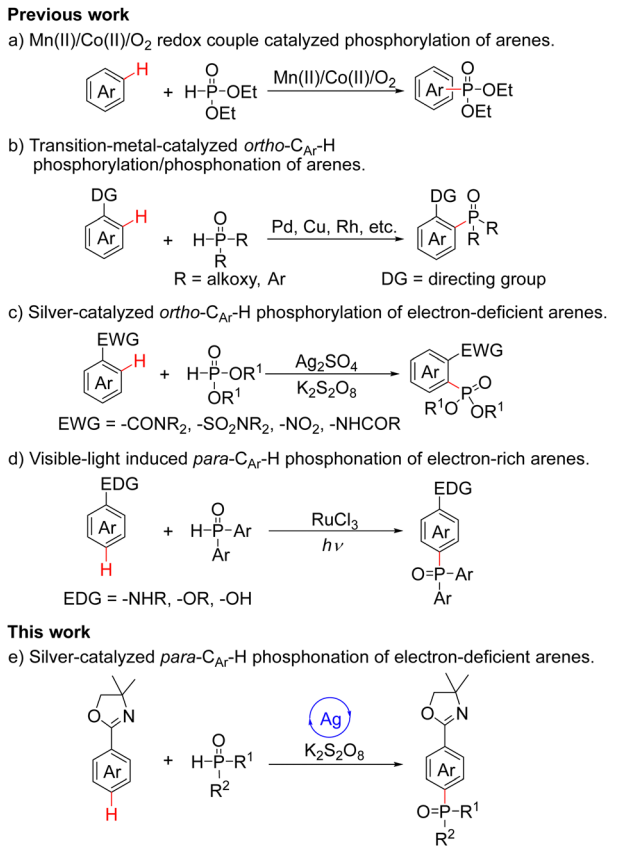
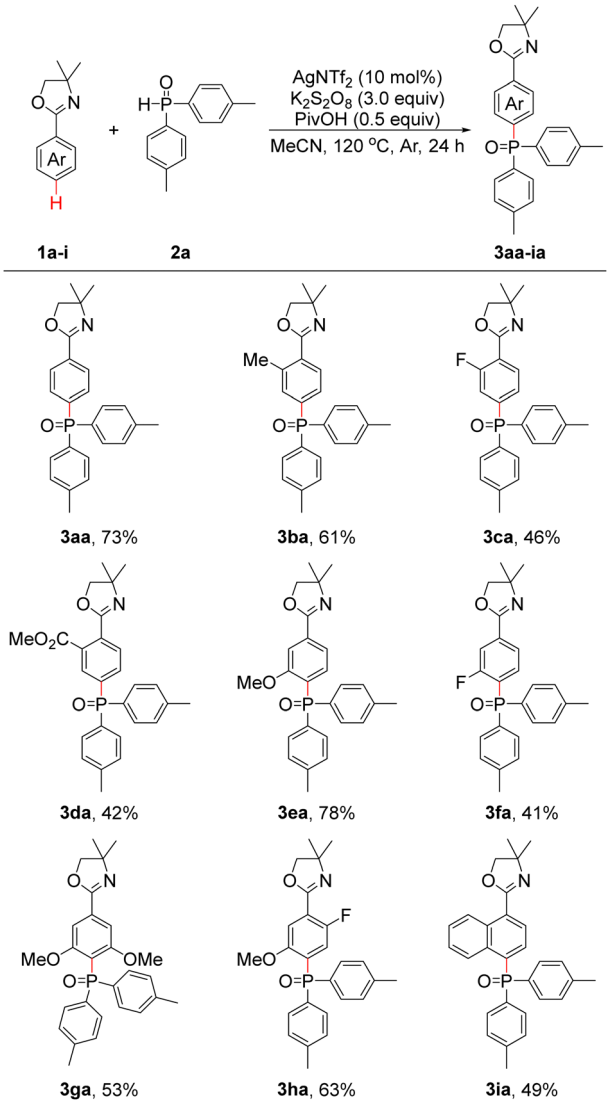


Scheme 1 Previous (a–d) and this (e) work on transition-metal-catalyzed C–H phosphorylation/phosphonation of arenes.

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 CO_2Me 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**) 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 1 Scope of 2-aryloxazolines[a,b]



[a] Reaction conditions: **1a–i** (0.2 mmol), **2a** (0.6 mmol), $AgNTf_2$ (10 mol%), $K_2S_2O_8$ (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**.

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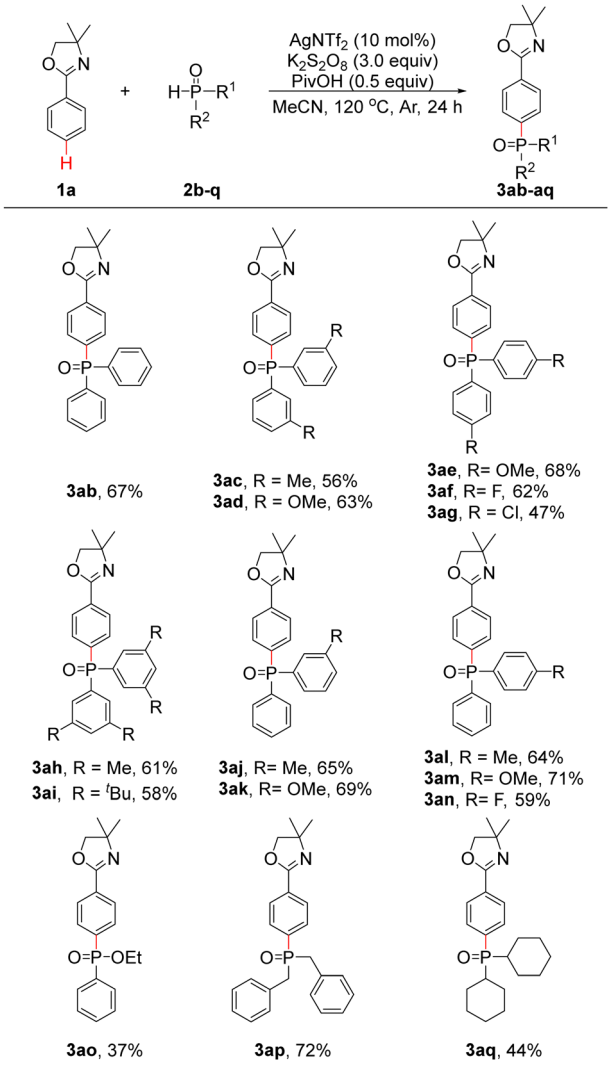
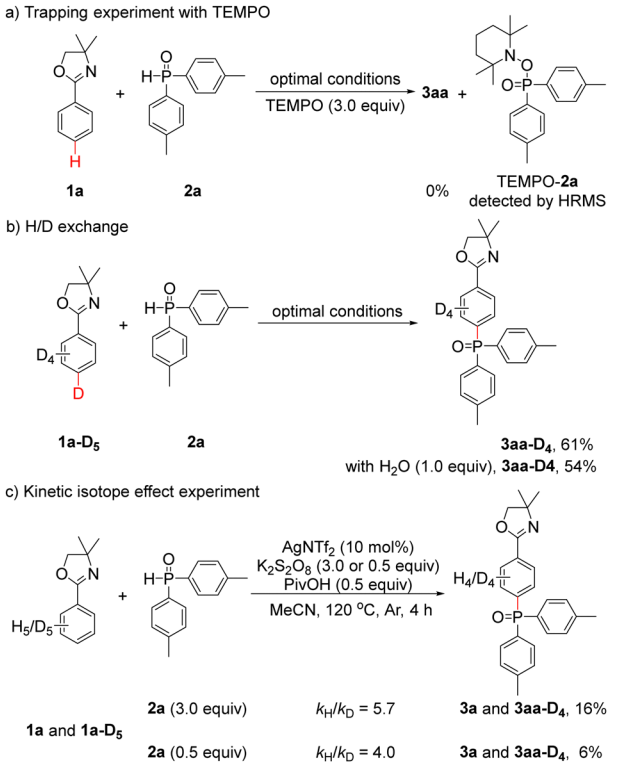
Table 2 Scope of phosphine oxides[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), **2b–q** (0.6 mmol), $AgNTf_2$ (10 mol%), $K_2S_2O_8$ (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**.



Scheme 2 Preliminary mechanistic studies.

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-tetramethylpiperidinooxy (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-D$_5$** was employed under optimal conditions, pure **3aa-D$_4$** (Fig. S2, ESI†) was obtained in 61% yield. In addition, pure **3aa-D$_4$** (Fig. S3, ESI†) could also be isolated in 54% yield with an additional 1.0 equiv. of H_2O. These results indicated that no D/H scrambling occurred on the phenyl ring of **3aa-D$_4$** 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 oxazolinium 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 ($S_2O_8^{2-}$) to give the key P-centered radical **B** together with a hydrogen sulfate anion (HSO_4^-) and a sulfate radical anion ($SO_4^{\bullet-}$) (Scheme 3, *path a*).[16] Alternatively, **2** can exist in rapid equilibrium with the corresponding tautomeric isomer **2′**.[17] The Ag^{2+} 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 $S_2O_8^{2-}$ to regenerate Ag^{2+} together with a sulfate dianion (SO_4^{2-}) and a $SO_4^{\bullet-}$ (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 $SO_4^{\bullet-}$ to give intermediate **D**. Finally, the *para*-phosphonation product **3** is obtained by

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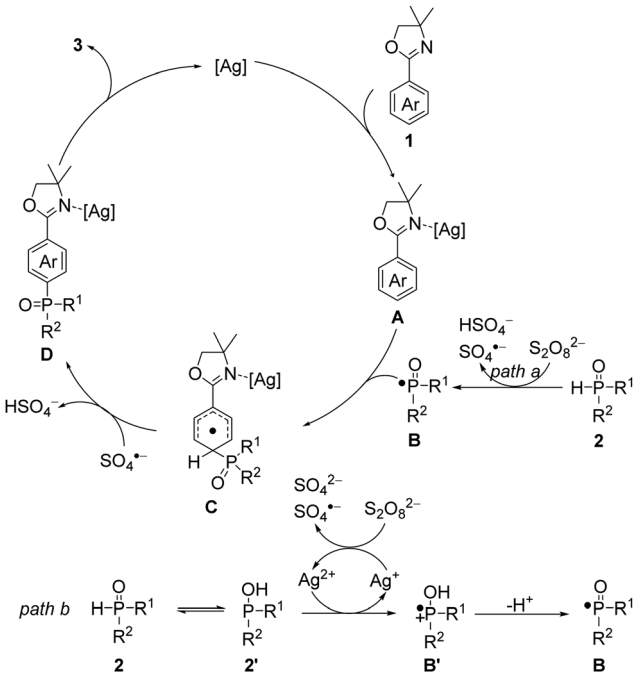
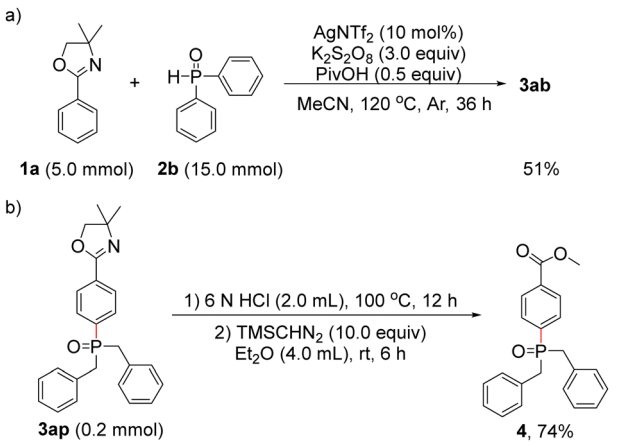


Scheme 3 Proposed mechanism.



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 $K_2S_2O_8$ 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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