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Silver-promoted cascade radical cyclization of γ,δ-unsaturated oxime esters with P(O)H compounds: synthesis of phosphorylated pyrrolines†

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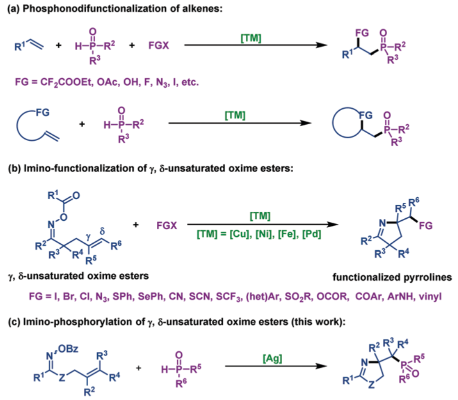
A cascade radical cyclization was realized for the first silver-promoted imino-phosphorylation of γ,δ-unsaturated oxime esters, which provided a step-economical and redox-neutral route to access a variety of phosphorylated pyrrolines in good to excellent yields. Moreover, a new bulky trivalent phosphine ligand with a pyrroline motif was obtained through a deoxidation process.

Organophosphorus compounds[1] have attracted considerable interest in recent years due to their wide applications in coordination chemistry,[2] organic synthesis,[3] materials science,[4] agrochemistry[5] and medicinal chemistry.[6] Moreover, they can serve as chiral ligands and organocatalysts in asymmetric catalysis.[7] In light of their importance, numerous efficient C–P bond-forming methodologies have been developed for the construction of phosphorus compounds.[8] Traditionally, alkyl phosphorus compounds are formed *via* substitution reactions of $R_2P(O)Cl$ with reactive organometallic nucleophiles. But the poor functional group compatibility, relatively harsh conditions and toxic reagents have limited their applications.[9] In recent years, a more clean and versatile alternative preparation of alkyl phosphorus compounds has been the radical addition of H-phophonate or diarylphosphine oxide to alkenes. This strategy allows the rapid incorporation of P(O)RR′ and a second functionality in a single synthetic operation, which significantly increases the step economy and diversity of molecules (Scheme 1a).[10]

Functionalized pyrrolines are valuable structural motifs in numerous bioactive molecules,[11] and can be facilely obtained *via* cascade cyclization of γ,δ-unsaturated oxime esters under the catalysis of transition metals.[12–23] In recent years, Narasaka,[12] Zhu,[13] Bower,[14] Zhu,[15] Leonori,[16] Ohe,[17] Selander,[18] Yu,[19] Tong,[20] Wang,[21] Liang[22] and our group[23] realized imino-functionalization of γ,δ-unsaturated oxime esters, furnishing a variety of functionalized pyrrolines (Scheme 1b). Although the field of transition-metal-catalyzed/mediated imino-functionalization of alkenes, such as imino-halogenation, imino-trifluoromethylthiolation and imino-azidation, has been widely developed, to the best of our knowledge, the imino-phosphorylation process has remained unexplored. As a continuation of our interest in imino-functionalization of γ,δ-unsaturated oxime esters to construct various functionalized pyrrolines,[23] we report the first example of a silver-promoted cascade radical cyclization of γ,δ-unsaturated oxime for the synthesis of phosphorylated pyrrolines (Scheme 1c).



Scheme 1 Project background and design for imino-phosphorylation of alkenes to construct C(sp^3)–P bonds.

We initiated our studies with the screening of reaction conditions by reacting γ,δ-unsaturated oxime ester **1a** with diethyl H-phosphonate **2a** under various reaction parameters. The combination of **1a** (1.0 equiv.), **2a** (2.0 equiv.), $AgNO_3$ (50 mol%) and K_2CO_3 (2.0 equiv.) in MeCN at 100 °C under a N_2 atmosphere for 12 h was found to be optimal, and phosphorylated pyrroline **3aa** was obtained in as high as 96% isolated yield (Table 1, entry 1). The desired product **3aa** was not detected in the absence of $AgNO_3$, which demonstrated that a silver salt was essential for this transformation (Table 1, entry 2). Other silver salts, such as Ag_2CO_3, AgOAc and $AgSbF_6$, were found to

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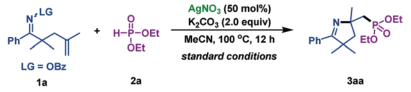
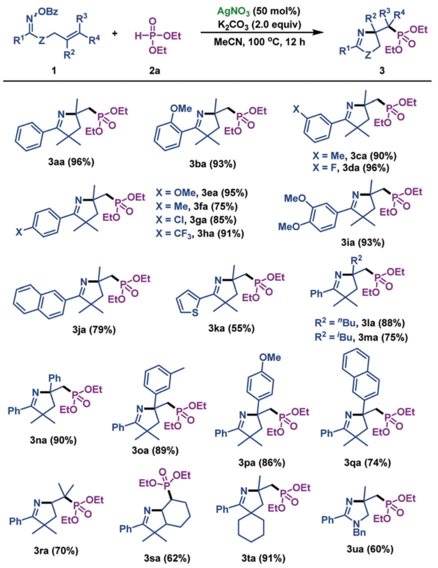
Table 1 Optimization of the reaction conditions^a



Entry	Variation from the standard conditions	**3aa**^{b}
1	None	96%
2	Without AgNO$_3$	ND^c
3	Ag$_2$CO$_3$ instead of AgNO$_3$	15%
4	AgOAc instead of AgNO$_3$	$<$5%
5	AgSbF$_6$ instead of AgNO$_3$	$<$5%
6	Cu(OAc)$_2$ instead of AgNO$_3$	$<$5%
7	30 mol% AgNO$_3$ was used	56%
8	70 °C	44%
9	Toluene as solvent	38%
10	DMF as solvent	20%
11	K$_3$PO$_4$ as base	$<$ 5%
12	LG = OAc	86%
13	LG = OCO(4-CF$_3$-C$_6$H$_4$)	95%
14	1.0 equiv. of **2a**	88%
15	5.0 mmol scale	92%

^{a} All reactions were performed with 0.2 mmol of **1a**, 0.4 mmol of **2a**, 0.1 mmol of catalyst and 0.4 mmol of base in 3.0 mL of the indicated solvent under a nitrogen atmosphere for 12 h. ^{b} Isolated yield. ^{c} ND = not detected.

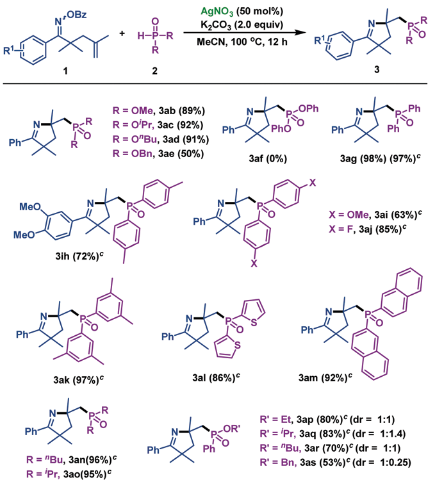


Scheme 2 Variation of γ,δ-unsaturated oxime esters **1**.^{a,b} ^{a}Reaction conditions: the reactions were carried out with **1** (0.2 mmol), **2a** (0.4 mmol), AgNO$_3$ (0.1 mmol), K$_2$CO$_3$ (0.4 mmol) in MeCN (3.0 mL) under a nitrogen atmosphere for 12 h. ^{b}Isolated yield.

be less efficient than AgNO$_3$ (Table 1, entries 3–5). Replacing the silver salt with a copper salt in our case, however, severely decreased the product yield (Table 1, entry 6). The amount of AgNO$_3$ was found to be the important factor for reaction performance since the use of 30 mol% AgNO$_3$ drastically reduced the yield of **3aa** to 56% (Table 1, entry 7). Decreasing the temperature to 70 °C caused the yield to descend to 44% (Table 1, entry 8). In addition, different solvent systems and bases were tested, and the results showed that other solvents and bases did not offer better results (Table 1, entries 9–11). To examine the effect of the leaving group, other derivatives were investigated as starting materials. Less activated and more stable *O*-acyl oxime afforded a lower yield of 86% (Table 1, entry 12). Although the use of *O*-4-trifluoromethylbenzoyl oxime led to a similar yield, from the viewpoint of atom economy and cost, **1a** was used for further studies (Table 1, entry 13). When the loading of **2a** was reduced to 1.0 equiv., lower yield was observed (Table 1, entry 14). Notably, this transformation could be scaled up to 5.0 mmol scale and no significant changes in yield were noted. The desired product **3aa** was obtained in 92% yield (Table 1, entry 15).

With an optimized set of conditions in hand, we turned our attention to exploring the substrate scope of γ,δ-unsaturated oxime esters. As shown in Scheme 2, aryl-substituted oxime esters with different electronic properties at the *ortho*, *meta*, and *para* positions performed well in the reaction, which included methoxyl, methyl, fluoro, chloro, and trifluoromethyl, affording phosphorylated pyrrolines **3ba–3ia** in 75–96% yields. Naphthyl-substituted oxime ester **1j** showed a positive result, providing **3ja** in 79% yield. Gratifyingly, γ,δ-unsaturated oxime ester containing a thienyl moiety was also compatible with this reaction (**1k**), while **3ka** was obtained in 55% yield. Alkene units bearing different substitution patterns at R^2 were investigated, such as butyl, isobutyl, phenyl, substituted phenyl and naphthyl, and the corresponding products **3la–3qa** were obtained in 74–90% yields. Notably, compared to previous reports for the functionalization of 1,1-disubstituted olefinic γ,δ-unsaturated oxime esters, our protocol was efficient for trisubstituted alkenes, and the desired products **3ra** and **3sa** were furnished in 70% and 62% yields, respectively. When **1t**, with cyclohexyl at the α position, was used as the substrate, **3ta** was obtained in 91% yield. Moreover, we were pleased to find that an amidooxime **1u** was also a suitable substrate, which could be transformed into the phosphorylated imidazoline derivative **3ua** in 60% yield.

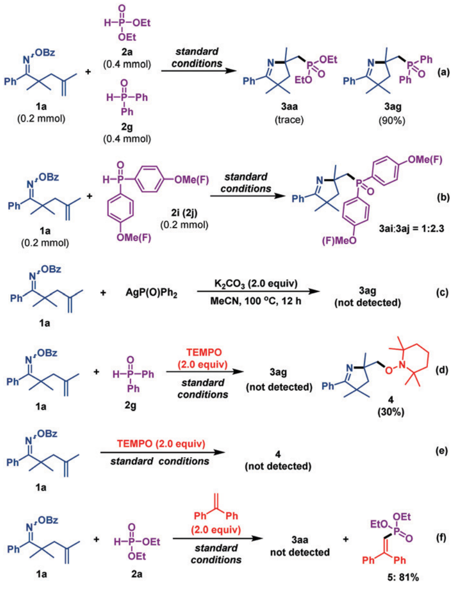
Various phosphinoyl radical precursors **2** were then explored by using the reaction with γ,δ-unsaturated oxime esters **1**. As shown in Scheme 3, dimethyl, diisopropyl, dibutyl and dibenzylphosphites reacted well with **1a** to give the products **3ab–3ae** in good yields. However, the reaction was found to be sluggish with diphenylphosphite (**3af**). It is worth noting that switching the H-phosphonates to diphenylphosphine oxides, led to the corresponding phosphorylation product **3ag** in 98% yield. But we found that **3ag** was very difficult to purify *via* column chromatography due to its similar polarity to unreacted HP(O)Ph$_2$. To our delight, when the loading of HP(O)Ph$_2$ was reduced to 1.0 equiv., a similar yield was observed, and the problem of purification was well resolved. Therefore, the scope of diarylphosphine oxides was also investigated. Diarylphosphine oxides with different electronic properties reacted smoothly with γ,δ-unsaturated oxime esters to deliver the desired products **3ih** and **3ai–3ak** in good yields (63–97%). Notably, di(thiophen-2-yl)phosphine oxide **2l** and di(naphthalen-2-yl)phosphine oxide **2m** were suitable for the reaction to afford the corresponding products in excellent yields. Interestingly, dialkylphosphine oxides **2n** and **2o** could react with **1a** to afford **3an** and **3ao** in 96% and 95% yields, respectively. In addition, the current protocol is not restricted to symmetric phosphine oxides. Unsymmetric phosphine oxides



Scheme 3 Variation of phosphonates and phosphine oxides **2**.[a,b] [a]Reaction conditions: the reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol), $AgNO_3$ (0.1 mmol), and K_2CO_3 (0.4 mmol) in MeCN (3.0 mL) under a nitrogen atmosphere for 12 h. [b]Isolated yield. [c]**2** (0.2 mmol).

2p–2s were also proved to be suitable substrates for this transformation (see **3ap–3as**).

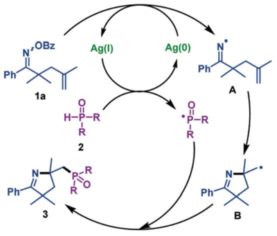
To understand the details of this transformation, several control experiments were performed. Intermolecular competition experiments between $HP(O)(OEt)_2$ and $HP(O)Ph_2$ were attempted and the result indicated that $HP(O)Ph_2$ displayed a higher reactivity[10c] (Scheme 4a). In addition, a competition experiment between electronically distinct diarylphosphine oxides was also examined, and the NMR analysis of this product mixture revealed a preference for more electron-withdrawing diphenylphosphine oxide (**3ai** : **3aj** = 1 : 2.3) (Scheme 4b). When the $AgP(O)Ph_2$ complex was carried out in a stoichiometric fashion, no conversion of **1a** was observed, which demonstrated that the $AgP(O)Ph_2$ complex was not an active intermediate in our reaction (Scheme 4c). When **1a** and $HP(O)Ph_2$ were used as substrates in the presence of 2.0 equiv. of TEMPO (radical scavengers), the trapping product **4** was obtained in 30% yield, which indicated the plausibility of a carbon centered radical intermediate, presumably forming a 5-*exo*-trig cyclization of the iminyl radical (Scheme 4d). Notably, TEMPO adduct **4** was not observed in the absence of $HP(O)Ph_2$ (Scheme 4e). This result illustrates that $HP(O)Ph_2$ first reacts with Ag(I) and forms a phosphinoyl radical and Ag(0). Subsequently, an iminyl radical is likely initiated through *in situ* generated Ag(0) species. Thus, the iminyl radical intermediate cannot be formed in the absence of $HP(O)Ph_2$. To further confirm the existence of a phosphinoyl radical, an additional experiment with relatively low reactivity $HP(O)(OEt)_2$ as a phosphinoyl radical precursor and 1,1-diphenylethylene (DPE) as a radical trap was conducted, and the coupling product **5** was isolated in 81% yield, which demonstrated that a phosphinoyl radical might be involved in the reaction (Scheme 4f).



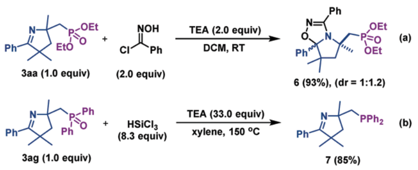
Scheme 4 Control experiments.

On the basis of the above experiments and previous reports, a plausible mechanism is drawn in Scheme 5. Initially, a phosphinoyl radical and iminyl radical intermediate **A** were initiated from **2** and **1a** with the assistance of $AgNO_3$. Then **A** undergoes an intramolecular 5-*exo*-trig radical cyclization to generate a C-centered radical intermediate **B.** Finally, the desired product **3** was obtained *via* the coupling of alkyl radical **B** and the phosphonyl radical.

To further showcase the reactivity of our prepared phosphorylated pyrrolines, a few synthetic transformations were conducted. Biologically relevant phosphorylated 1,2,4-oxadiazoline **6** was obtained in 93% yield (dr = 1 : 1.2) by [3+2] cycloaddition of **3aa** and *N*-hydroxybenzimidoyl chloride (Scheme 6a). It is important to note that the resulting phosphine oxide product **3ag** could undergo deoxidation reaction smoothly. In the presence of trichlorosilane and triethylamine at 150 °C in xylene for 48 h, the corresponding trivalent phosphine product **7** was obtained in 85% yield, which might be used as a phosphine ligand in transition-metal-catalyzed synthetic transformations (Scheme 6b). This strategy offers a novel method to construct new bulky phosphine ligands with a pyrroline motif.



Scheme 5 Proposed mechanism.



Scheme 6 Transformations of phosphorylated pyrrolines.

In summary, we have developed the first silver-promoted imino-phosphorylation of γ,δ-unsaturated oxime esters *via* a cascade radical cyclization, which allows for the efficient and straightforward construction of various phosphine-containing pyrrolines in good to excellent yields under oxidant-free conditions. Moreover, this reaction could be easily performed on a gram scale and the resulting phosphorylated pyrrolines were useful for further transformations. Most importantly, this strategy offers a novel method to construct new bulky trivalent phosphine ligands with a pyrroline motif, which was difficult to synthesize using other methods. Further investigations on the scope of imino-functionalization of γ,δ-unsaturated oxime esters are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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