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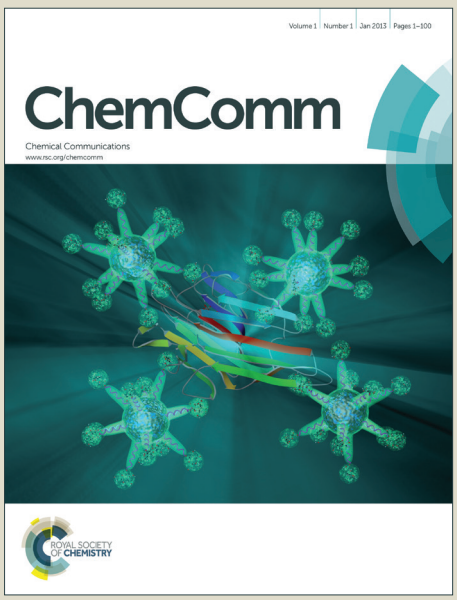

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Copper-Catalyzed Radical Cascade Cyclization for the Synthesis of Phosphorated Indolines

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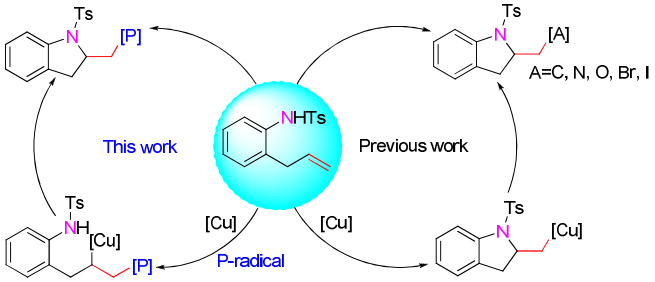
A novel and convenient approach to the synthesis of various phosphorated indolines via copper-catalyzed radical cascade cyclization reaction has been developed. The reaction employs cheap copper as the catalyst and $K_2S_2O_8$ as the oxidant under mild conditions. Various alkenes and P-radical precursors are compatible with this transformation. Preliminary mechanistic studies reveal that the addition of P-radical may initiate the reaction, and then oxidative cyclization may be achieved to afford the desired product.

The nitrogen heterocyclic components have found abundant applications as structural motifs in pharmaceutically active compounds and natural products.[1] Consequently, many endeavors have been focused on the development of efficient approaches to afford these heterocycles.[2] Transition-metal catalyzed/promoted difunctionalization of derivative 2-allylaniline represents one of the most direct and atom-economical approaches,[3] including aminooxygenation,[4] aminohalogenation,[5] diamination[6] and carboaminations.[7] However, its application in the synthesis of phosphorated indolines by aminophosphination *via* radical cascade cyclization has never been demonstrated. As expected products contain the vicinal amine and phosphorus segment, phosphorated indolines are ubiquitous in pharmaceuticals,[8] common catalysts[9] and popular ligands.[10] Therefore, successfully achieve the amino-phosphorus difunctionalization of alkenes to synthesize phosphorated indolines in one operation is highly desirable in organic synthesis, because potentially difficult work-up and isolation steps can be avoided and the generation of chemical waste is minimized.

In the past decades, there are a number of powerful methods that address C–P bond construction.[11-12] Thereinto, adding the P-centered radicals to alkenes or alkynes is well precedented.[13] However, examples that involve in the aminophosphination of alkenes or alkynes in one pot via a cascade sequence remain elusive and rudimentary.[14] Very recently, our group has disclosed the novel silver-catalyzed oxidative arylphosphination of alkenes.[15] On the basis of these works, we hypothesize that the addition of the P-radical to 2-allylaniline could trigger the oxidative cyclization to afford the corresponding phosphorated indolines. Herein, we describe the first example of copper-catalyzed amino-phosphorus difunctionalization *via* cascade cyclization that exhibits several features. 1) cheap copper catalyst and $K_2S_2O_8$ oxidant are employed without any base under mild conditions; 2) compared with previous cases,[3c, 4b, 5d, 6g, 7i] this reaction may be initiated from the addition of P-radical, and then oxidative cyclization may be achieved to access the desired product (Scheme 1).

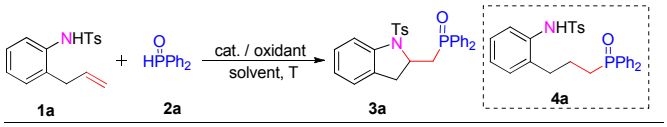


Scheme 1. Copper-Catalyzed Radical Cascade Cyclization

At the outset of this investigation, we chose the *N*-Ts-2-allylaniline (**1a**) and $HP(O)Ph_2$ (**2a**) as the model substrates and various silver and copper catalysts in different solvents at different temperatures were tested. Regrettably, only the addition product (**4a**) was obtained. In light of these factors, we hypothesized that silver or copper salts might promote the addition of P-radical to alkene, and then maybe need the appropriate oxidant to enhance the eletrophilicity of copper species which will activate the N-H bond leading to complete the cyclization. So we used $AgNO_3$ as an oxidant to screen different copper catalysts (50 mol %). To our delight, when $Cu(ClO_4)_2 \cdot 6H_2O$ was used as the catalyst, the desired product (**3a**) was obtained in 16% yield (Table 1, entry 1; SI Table S1). Motivated by this result, we further optimized the reaction

conditions. Various silver oxidants, the loading of $Cu(ClO_4)_2 \cdot 6H_2O$, different catalysts, temperatures and solvents were investigated respectively (Table 1, entries 2-8; SI Tables S2-6). Screening of different radical initiators showed that P-centered radicals were also generated from cheaper peroxides such as $K_2S_2O_8$, $Na_2S_2O_8$ and ^{t}BuOOH (Table 1, entries 9-11; SI Table S7).[16] After several trials, the most appropriate oxidant was identified as $K_2S_2O_8$ (Table 1, entry 12; SI Table S8). After a large number of attempts, we decreased the amount of $Cu(ClO_4)_2 \cdot 6H_2O$ to 20 mol % by adding $HP(O)Ph_2$ slowly with a syringe pump (Table 1, entry 13; SI Table S9). Finally, the optimized reaction conditions are as follows: $Cu(ClO_4)_2 \cdot 6H_2O$ (20 mol %) as catalyst, $K_2S_2O_8$ (3.0 equiv) as oxidants in CH_3CN at 35 °C for 6 h.

Table 1. Selected Reaction Conditions Optimization[a]

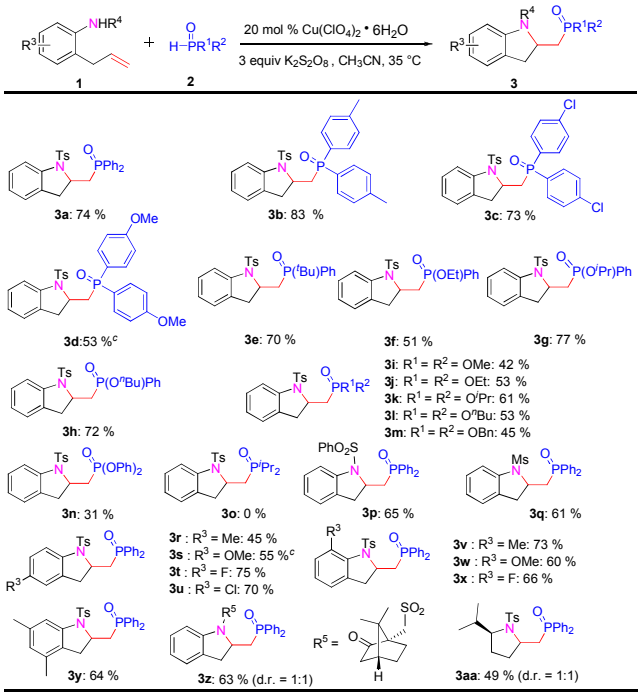


entry	cat. (mol %)	oxidant (equiv)	T (°C)	yield of **3a** (%)[b]
1	$Cu(ClO_4)_2 \cdot 6H_2O$ (50)	$AgNO_3$ (1.0)	80	16
2	$Cu(OAc)_2$ (50)	$AgNO_3$ (1.0)	80	trace
3	$Cu(OTf)_2$ (50)	$AgNO_3$ (1.0)	80	trace
4	$Cu(ClO_4)_2 \cdot 6H_2O$ (50)	AgOTf (1.0)	80	10
5	$Cu(ClO_4)_2 \cdot 6H_2O$ (50)	Ag_3PO_4 (1.0)	80	37
6	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	Ag_3PO_4 (1.0)	80	65
7	$Cu(OTf)_2$ (200)	Ag_3PO_4 (1.0)	80	60
8	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	Ag_3PO_4 (1.0)	65	68
9	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	$K_2S_2O_8$ (1.0)	65	48
10	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	$Na_2S_2O_8$ (1.0)	65	41
11	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	^{t}BuOOH (1.0)	65	43
12	$Cu(ClO_4)_2 \cdot 6H_2O$ (200)	$K_2S_2O_8$ (3.0)	65	73[c]
13	$Cu(ClO_4)_2 \cdot 6H_2O$ (20)	$K_2S_2O_8$ (3.0)	35	74[d]
14	$Cu(ClO_4)_2 \cdot 6H_2O$ (15)	$K_2S_2O_8$ (3.0)	35	60[d]

[a]All reactions were carried out in the presence of 0.2 mmol of **1a** and 0.3 mmol of **2a** in 2.0 mL different solvents under Ar atmosphere; [b]Yield of isolated product. [c]**2a** (0.8 mmol) was used. [d]**2a** (0.8 mmol) in solvent (2 mL) was added dropwise *via* an automatic syringe to the mixture of **1a** (0.2 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$, $K_2S_2O_8$ (0.6 mmol) in solvent (2 mL) in 6 hours at 35 °C.

With the optimized conditions in hand, we investigated the substrate scope as shown in Table 2. Firstly, we evaluated a series of phosphinoyl radicals. Diverse diphenylphosphine oxides, *tert*-butylphenylphosphine oxide and alkyl phenylphosphinates served as suitable P-radical precursors for this transformation, and the desired products were isolated in good yields (**3a-3h**). Moreover, reactions could also proceed well by using dialkyl *H*-phosphates and afford the corresponding products in moderate yields (**3i-3n**). However, under the same conditions, diisopropylphosphine oxide failed to provide the desired product (**3o**). Subsequently, an investigation into different *N*-protecting groups showed that sulfonyl groups provided corresponding products in good yields (**3p-3q**), but Boc, Ac, and Bz protecting groups did not work at all. Finally, variously substituted *N*-Ts-2-allylanilines bearing different functional groups on different positions could still afford desired products in good yields (**3r-3y**). In addition, we introduced stereogenic centers at the α-position of the nitrogen atom or the *N*-protecting group, but expected products were obtained only in moderate yields with low d.r. values (**3z-3aa**). We also have examined disubstituted alkenes. Disappointingly, only addition products were obtained.

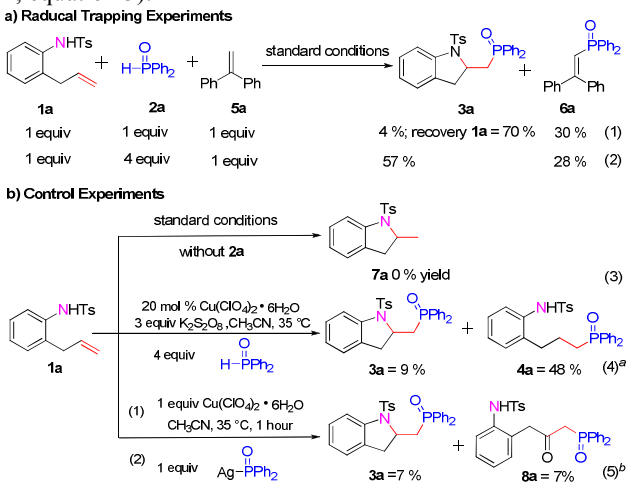
Table 2. Substrates Scope[a, b]



[a]**2** (0.8 mmol) in CH_3CN (2 mL) was added dropwise *via* an automatic syringe to the mixture of **1** (0.2 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.04 mmol), $K_2S_2O_8$ (0.6 mmol) in CH_3CN (2 mL) in 6 hour at 35 °C. [b]Yield of isolated product. [c]Reaction was carried out in the presence of **1** (0.2 mmol), **2** (0.8 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mmol), $K_2S_2O_8$ (0.6 mmol) in CH_3CN (2 mL) in 6 hour at 65 °C.

In order to gain insight into the catalytic procedure, we carried out a series of control experiments. As illustrated in Scheme 2, the process was partially suppressed in the presence of 1.0 equiv of 1, 1-diphenylethylene as a radical scavenger and a trapped compound **6a** was isolated, thus suggesting that the formation of the phosphinoyl radical (**2A**) was the key step in this transformation and 1, 1-diphenylethylene was superior to **1a** in the addition of the phosphinoyl radical (**2A**) (Scheme 2, equations 1 vs. 2). When **1a** was investigated under standard conditions without **2a**, the cyclization product **7a** was not detected. This result illustrates that the addition of the phosphinoyl radical triggered cyclization (Scheme 2, equation 3). Furthermore, when **1a** was added dropwise *via* an automatic syringe to the mixture of **2a**, $Cu(ClO_4)_2 \cdot 6H_2O$, $K_2S_2O_8$ in solvent, **4a** was the major product and the desired product **3a** was obtained in 9 % yield. Thus, we concluded that the crucial step was the oxidative addition in the presence of excess Cu catalyst to obtain complex **4A** (Scheme 2, equation 4). Additionally, the reaction could also proceed through a stoichiometric $[Ph_2P(O)Ag]$ complex in order to afford the

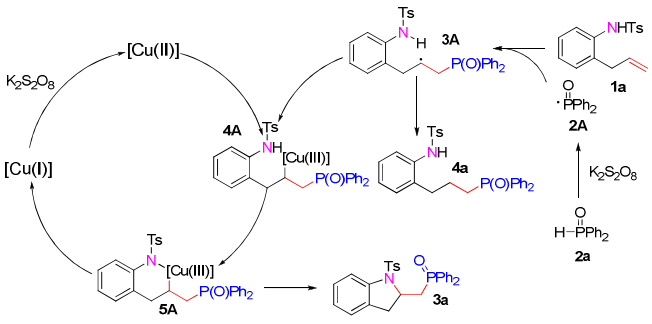
corresponding product as well as the byproduct **8a**[14j] (Scheme 2, equation 5).



[a]**1a** (0.2 mmol) in CH_3CN (2 mL) was added dropwise *via* an automatic syringe to the mixture of **2a** (0.8 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (0.04 mmol), $K_2S_2O_8$ (0.6 mmol) in CH_3CN (2 mL) in 6 hour at 35 °C. [b]**1a** (0.2 mmol) was stirred in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$ (0.2 mmol) and $Ph_2(O)PAg$ (0.2 mmol) was added after 1 hour.

Scheme 2. Experiments for Mechanistic Studies

According to previous reports on the phosphinoyl radicals,[14g, 17,] we proposed a tentative mechanism. First, a phosphinoyl radical **2A** is generated from diphenylphosphine oxide **2a** promoted by $K_2S_2O_8$,[16a] and then the addition of **2A** to alkene **1a** affords alkyl radical **3A**. The byproduct **4a** might be generated from **3A**. Alternatively, **3A** also might undergo oxidative addition providing copper (III) complex **4A**.[14j, 18] Next the intermediate **5A** is obtained *via* intramolecular Ullmann-type reaction,[19] followed by reductive elimination to release the product **3a** along with copper (I). Finally, in the presence of $K_2S_2O_8$, the copper (I) is oxidized to copper (II) to complete the catalytic cycle (Scheme 3). And we also depicted a competitive alternate mechanism (SI Scheme S1).



Scheme 3. Plausible Mechanistic Pathway

In summary, we have demonstrated a novel and convenient approach to the synthesis of various phosphorated indolines by copper-catalyzed amino-phosphorus difunctionalization *via* cascade cyclization. The reaction employs cheap copper as catalyst and $K_2S_2O_8$ as an oxidant under mild condition.

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