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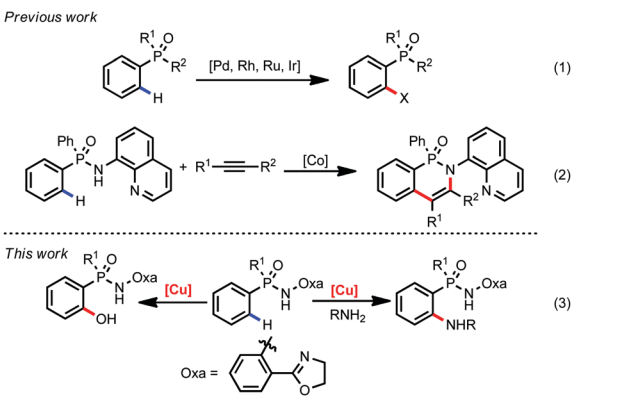
Copper mediated C(sp^2)–H amination and hydroxylation of phosphinamides†

Shang-Zheng Sun, ‡[a] Ming Shang,‡[b] Hui Xu,[c] Tai-Jin Cheng,[c] Ming-Hong Li[c] and Hui-Xiong Dai *[c]

Copper mediated C(sp^2)–H amination and hydroxylation of arylphosphinic acid are accomplished by adopting phosphinamide as the directing group. This method is distinguished by its wide substrate scope and excellent functional group tolerance, thus allowing for the rapid preparation of organophosphorus compounds in organic synthesis.

Organophosphorus compounds represent an important and fundamental class of molecules due to their extensive application in medicinal chemistry, organic materials and catalysis.[1] Traditionally, their preparation or modification needs tedious manipulation and usually suffers from a limited substrate scope.[2] In recent years, transition metal catalyzed C–H functionalization reactions have become a useful tool in organic synthesis.[3] In this regard, a directing group (DG) is often required to locate the metal catalyst to proximate C–H bonds. To date, DGs based on the carbonyl group such as carboxyl acids, amides, and ketones have been frequently used in C–H functionalization reactions.[4] However, examples employing P-containing functional groups as DGs are relatively rare, which extremely limits their utility in rapid preparation of important organophosphorus compounds.[5] In 2013, Kim and co-worker introduced benzyl and phenoxyl phosphonic acids as DGs for Pd-catalyzed oxidative Heck reaction.[6] Since then, Pd, Rh, Ru, and Ir-catalyzed C–H transformations such as oxidative annulation, arylation, and amination in phosphorus compounds have been reported in succession (eqn (1), Scheme 1).[7] However, the high price and toxicity of these precious metals limit their further industrial applications. Compared with precious metals, the first-row transition metals such as Fe, Co, Ni, and Cu are earth abundant and low toxic.[8] Recently, Daugulis and co-workers first employed arylphosphinic acid aminoquinoline amides as the substrates for cobalt catalyzed C–H annulation with alkynes and alkenes (eqn (2), Scheme 1).[9] To the best of our knowledge, there are no examples of copper catalyzed C–H functionalization for arylphosphinic acid. Herein, we disclose a copper-mediated amination and hydroxylation of phosphinamide C(sp^2)–H bonds (eqn (3), Scheme 1).

Recently, we developed an efficient amide-tethered oxazoline bidentate auxiliary for copper-mediated C–H amination, trifluoromethylation, alkynylation, hydroxylation, arylation, and thiolation of arenes and heteroarenes.[10] Inspired by these results, we were curious whether the oxazoline-containing bidentate auxiliary could facilitate the C(sp^2)–H functionalization of arylphosphinic amide. Though arylphosphinic amide containing oxazoline has a similar coordination model to its benzoic amide analogues, the relative acidity of the N–H bond and subtle changes of the molecular structure blurred this idea. Considering the importance of the N,P-bidentate ligand in homogenous catalysis,[11] we first chose $Cu(OAc)_2$-mediated ortho C–H amidation as our target reaction. Gratifyingly, amidation occurred smoothly on diphenylphosphinic



Scheme 1 C–H functionalization of organophosphorus compounds.

[a] *Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, Shanghai, 200444, China*
[b] *Department of Chemistry, The Scripps Research Institute, 10550N. Torrey Pines Road, La Jolla, California 92037, USA*
[c] *Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai, 201203, China. E-mail: hxdai@simm.ac.cn*

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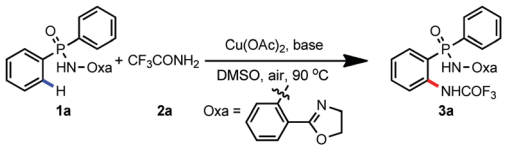
‡ These authors contributed equally to this work.

Table 1 Optimization of amination reaction conditions[a]



Entry	Base	Solvent	Temp. (°C)	Yield[b] (%)
1	Na_2CO_3	DMSO	90	69
2	K_2CO_3	DMSO	90	66
3	Li_2CO_3	DMSO	90	21
4	Cs_2CO_3	DMSO	90	25
5	NaOAc	DMSO	90	41
6	KOAc	DMSO	90	54
7	Na_2CO_3	DMF	90	15
8	Na_2CO_3	DMA	90	10
9	Na_2CO_3	NMP	90	20
10	Na_2CO_3	MeCN	90	n.r.
11	Na_2CO_3	DMSO	60	43
12	Na_2CO_3	DMSO	80	66
13	Na_2CO_3	DMSO	100	84
14	Na_2CO_3	DMSO	110	82
15[c]	**Na_2CO_3**	**DMSO**	**100**	**88 (76)**[d]
16[c]	Na_2CO_3	DMSO	100	12[e], 30[f]

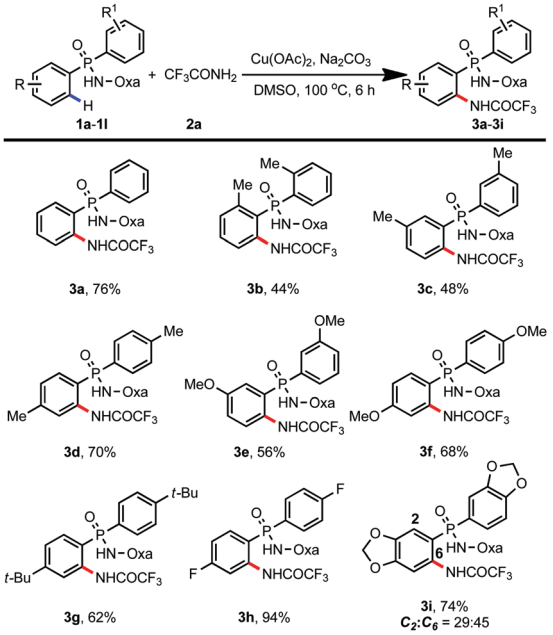
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (0.1 mmol), base (0.2 mmol), solvent (1.0 mL), temp., air, 6 h. [b] The yield was determined by ^1H NMR analysis of a crude reaction mixture using CH_2Br_2 as an internal standard. [c] Na_2CO_3 (0.25 mmol). [d] Isolated yield. [e] 20 mol% $Cu(OAc)_2$. [f] N_2 atmosphere.

amide **1a** with exclusive *ortho*-selectivity (Table 1, entry 1). Subsequently, we screened a variety of bases including K_2CO_3, Li_2CO_3, Cs_2CO_3, NaOAc, and KOAc, and found that Na_2CO_3 was the optimal choice (Table 1, entries 2–6). The yields dramatically decreased when DMSO was replaced with other polar solvents, such as DMF, DMA, NMP and MeCN (Table 1, entries 7–10). The yield could be improved to 84% by increasing the reaction temperature to 100 °C (Table 1, entries 11–14). Finally, a small improvement was observed by enhancing the loading of Na_2CO_3 to 2.5 equivalents, affording the amidated product in 88% yield (Table 1, entry 15). When we decreased the loading of $Cu(OAc)_2$ to 20 mol%, only 12% yield of product **3a** was obtained. The yield decreased to 30% when the reaction was carried out under a N_2 atmosphere, indicating that air was crucial for the reaction.

Having identified the optimal conditions for C–H amidation, we next explored the substrate scope (Table 2). To our delight, a variety of phosphinic amides with electron-donating methyl-, methoxy-, and *tert*-butyl substituents could be amidated smoothly, giving the corresponding products in moderate to good yields (**3a–3g**, 44–76%). To our surprise, only 21% yield of the amidation product was obtained when 8-aminoquinoline was used as the directing group (ESI†). Moreover, electron-deficient phosphinamide **1h** was also compatible with the reaction, providing the amidation product **3h** in 94% yield. For benzodioxole derived phosphinamide **1i**, two regioisomers were formed, with the less sterically hindered C6-position-amidated product as the major one (**3i**, 74%).

In addition to trifluoroacetamide, a wide range of sulfonamides and (hetero)anilines were also compatible with this transformation (Table 3). For example, amidation proceeded smoothly with sulfonamides bearing both electron-donating

Table 2 The scope of phosphinamides for C–H amination[ab]

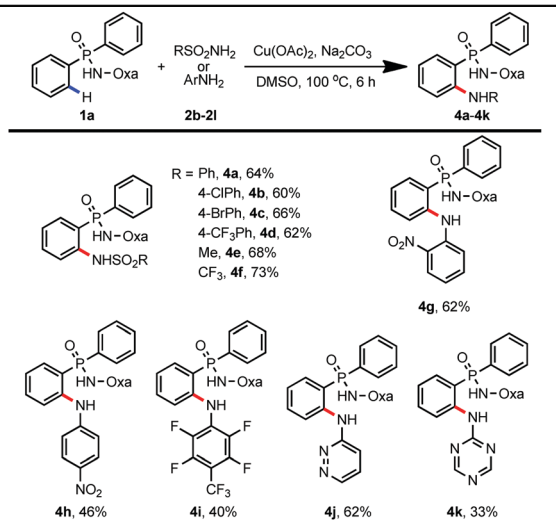


[a] Reaction conditions: **1a–1i** (0.1 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (0.1 mmol), Na_2CO_3 (0.25 mmol), DMSO (1 mL), 100 °C, air, 6 h. [b] Isolated yield.

and electron-withdrawing groups (**4a–4f**, 60–73%). To our surprise, electron-deficient anilines and heteroanilines could also serve as amine donors, providing a useful method for the preparation of organophosphorus compounds which have potential applications in homogenous catalysis and medicinal chemistry (**4g–4k**, 33–62%).[11,12]

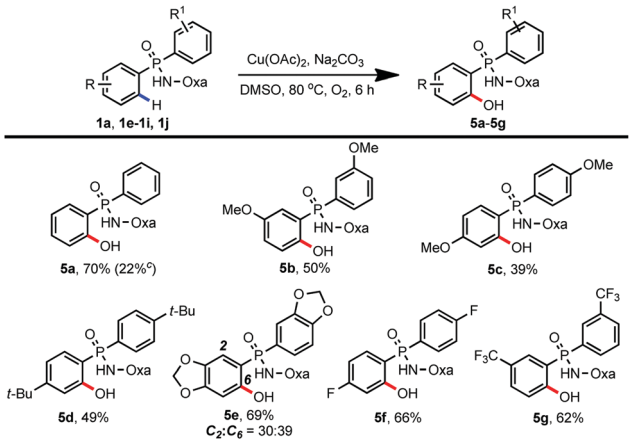
With the success of achieving C–H amidation and amination of phosphinamides, we wondered whether this protocol could be compatible with C–H hydroxylation reaction as well.[13] To our delight, we could introduce a free hydroxyl group into a

Table 3 Scope of amine coupling partners[ab]



[a] Reaction conditions: **1a** (0.1 mmol), **2b–2l** (0.2 mmol), $Cu(OAc)_2$ (0.1 mmol), Na_2CO_3 (0.25 mmol), DMSO (1 mL), 100 °C, air, 6 h. [b] Isolated yield.

Table 4 Scope of phosphinamides for C–H hydroxylation[a,b]



[a] Reaction conditions: **1** (0.1 mmol), $Cu(OAc)_2$ (0.1 mmol), Na_2CO_3 (0.1 mmol), DMSO (1 mL), 80 °C, O_2, 6 h. [b] Isolated yield. [c] N_2 atmosphere.

variety of phosphinamides by adopting our previous reaction conditions.[10f] As shown in Table 4, regardless of the electronic properties of the substituents, substrates bearing both electron-donating and electron-withdrawing groups were well tolerated, giving the desired hydroxylated products in moderate to good yields (**5a–5g**, 39–70%). In accordance with previous work, the yield of **5a** decreased to 22% when the reaction was carried out under a N_2 atmosphere.[10f]

Finally, the removal of this amide-oxazoline directing group was demonstrated by treating product **4a** with 2 N KOH/EtOH at 80 °C, releasing the corresponding amino-phosphinic acid **6** in 75% yield with 93% recovery of the directing group (Scheme 2).

In conclusion, we developed a Cu-promoted C–H amination and hydroxylation for phosphinamide compounds. Unlike previously reported copper-catalyzed or copper-mediated C–H functionalization, in this study we developed phosphinamide as a new directing group. The technique showed a broad scope and excellent functional group tolerance, providing a new strategy for the preparation of various amino- and hydroxyl-contained arylphosphinic compounds in organic synthesis.

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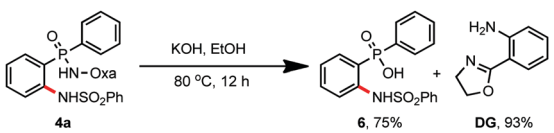

Scheme 2 Removal of the directing group.

Conflicts of interest

The authors declare no conflict of interest.

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