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Copper-Mediated Hydroxylation of Arenes and Heteroarenes Directed by a Removable Bidentate Auxiliary

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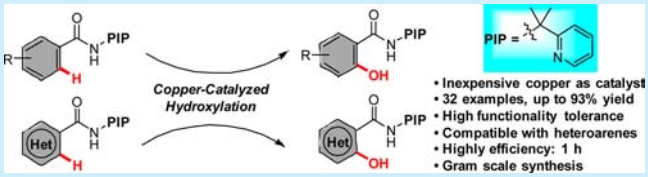
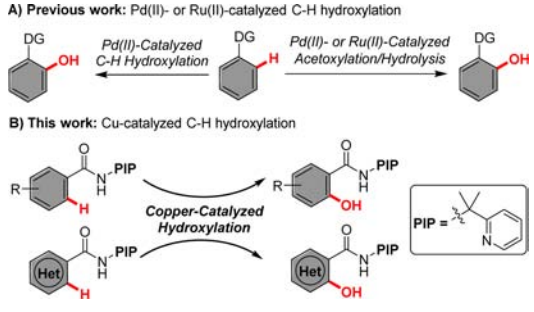
Supporting Information

ABSTRACT: A copper-mediated C−H hydroxylation of arenes and heteroarenes using our newly developed PIP directing group has been developed. This procedure is scalable and compatible with a wide range of functional groups and heteroarenes, providing an operationally simple protocol for the synthesis of *o*-hydroxybenzamides. The hydroxylation of nicotinamides gave 4-oxo-1,4-dihydropyridine-3-carboxamides selectively. Preliminary mechanistic studies implicate that a basic ligand-enabled, irreversible, rate-determining CMD step is most likely involved in this process.



Functionalized phenols are an important structural motif in nature and have extensive application in pharmaceuticals, agrochemicals, and material science.[1] Besides, they are also versatile synthetic intermediates and asymmetric catalysis in organic synthesis. Therefore, the direct hydroxylation of arenes to phenols has been the topic of extensive research interests, and tremendous progress has been made on the direct C−H hydroxylation reactions catalyzed by the expensive, second-row transition metals, such as palladium and ruthenium.[2−6] In 1990, the seminal work by Fujiwara reported a $Pd(OAc)_2$-catalyzed hydroxylation of arenes with molecular oxygen; however, this protocol suffered from low efficiency, poor selectivity, and harsh reaction conditions.[3] In 2009, Yu described a novel Pd-catalyzed hydroxylation of arenes directed by a carboxyl group.[4] Jiao reported a novel $PdCl_2$ and NHPI cocatalyzed C−H hydroxylation of 2-phenylpyridines.[5] More recently, the synthesis of hydroxylated arenes via *in situ* hydrolysis of the acetoxylated products generated from Pd- or Ru-catalyzed C−H acetoxylation were disclosed by several groups (Scheme 1A).[6] Despite this success, the direct hydroxylation of arenes catalyzed by less expensive copper catalysts is still very rare.[7] Herein, we report a copper-mediated C−H hydroxylation of arenes and heteroarenes directed by a removable bidenate directing group. The reaction possesses several favorable attributes, including a broad substrate scope, high efficiency, and compatibility with heteroarenes (Scheme 1B).

Scheme 1. Transition-Metal-Catalyzed C−H Hydroxylation



Over the past decade, copper-catalyzed oxidative C−H functionalization has gained significant attention owing to the abundance, inexpensiveness, and versatile reactivity of copper catalysts.[8,9,11−13] In 2006, Yu and Chatani independently reported the Cu-mediated C−H functionalization of 2-arylpyridines.[7a,9] Recently, the 8-aminoquinoline-derived bidentate auxiliary, which was first developed by Daugulis,[10] has been used in copper-catalyzed direct C−H amination, arylation, and phenoxylation.[12] We also developed a removable bidentate directing group derived from 2-(pyridine-2-yl)isopropylamine (PIP-amine).[14] This directing group has shown superior reactivity in the functionalization of C−H bonds. Meanwhile, Stahl and co-workers have shown both macrocyclic amine and 8-aminoquinoline benzamide ligands facilitate the oxidative functionalization of arene C−H bonds.[15] Inspired by these precedents, we reasoned that a copper-catalyzed hydroxylation of arene C−H bonds assisted by the PIP directing group might be achieved for the following reasons: (1) the bidentate PIP auxiliary can facilitate the C−H bond activation and cyclometalation process; (2) the C,N,N-pincer type ligand can stabilize the high valent Cu(III) intermediate; and (3) the C,N,N-pincer type Cu(III) intermediate may also facilitate C−O reductive elimination.

To examine this hypothesis, we commenced our studies by the reaction of benzamide **1a** in the presence of $Cu(OAc)_2$ and Ag_2CO_3 as the catalyst system in DMF at 100 °C, and to our

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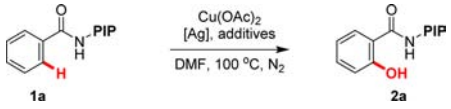
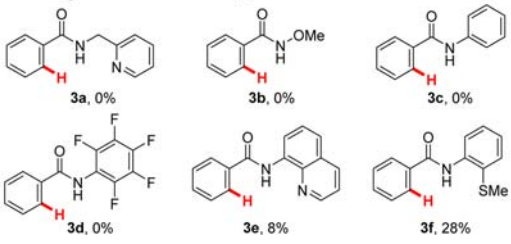
delight, the desired hydroxylated product **2a** was obtained in 51% yield (Table 1, entry 1). Various silver salts, such as AgOAc and

Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	[Ag]	additive (equiv)	time (h)	yield (%)[b]
1	Ag_2CO_3	$NaHCO_3$ (1)	12	51
2	AgOAc	$NaHCO_3$ (1)	12	31
3	AgOTf	$NaHCO_3$ (1)	12	Trace
4	Ag_2CO_3	$KHCO_3$ (1)	12	12
5	Ag_2CO_3	KOAc (1)	12	35
6	Ag_2CO_3	$PhCO_2Li$ (1)	12	63
7	Ag_2CO_3	$PhCO_2Na$ (1)	12	35
8	Ag_2CO_3	TBAB (1)	12	58[c]
9	Ag_2CO_3	TBAB (2)	12	79[c]
10	Ag_2CO_3	TBAB (3)	12	77[c]
11	**Ag_2CO_3**	**TBAI (2)**	**1**	**90**
12[d]	Ag_2CO_3	TBAI (2)	1	75[c]



[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), [Ag] (0.4 mmol) and additive in DMF (2 mL) at 100 °C. [b]Isolated yield. [c]^{1}H NMR yield using CH_2Br_2 as the internal standard. [d]90 °C.

AgOTf, were tested, and Ag_2CO_3 proved to be particularly effective (entries 2 and 3). We then investigated different inorganic salts as additives and observed that $PhCO_2Li$ was the most efficient, affording **2a** in 63% yield (entries 4−7). Through extensive optimization of the additives, we were pleased to find that the reaction can proceed to completion within 1 h at 100 °C in the presence of 2 equiv of tetrabutylammonium iodide (TBAI) with high yield (entry 11, 90% yield). The hydroxylation structure was confirmed by X-ray analysis of compound **2a** (Supplementary Figure S1).

We then investigated the effect of the directing group on the efficiency of the hydroxylation reaction. No reaction occurred when the amide **3a** was used as the substrate, indicating the presence of the *gem*-dimethyl substitution is crucial for the reaction to proceed. The weakly coordinating *N*-arylamide **3d** and *N*-methoxyamide **3b**, which have been widely applied in Pd-catalyzed C−H functionalization reactions of carboxylic acids, also failed under the optimized conditions. The 8-aminoquiloline and 2-thiomethylaniline directing group was less effective in this case (**3e**, 8% yield and **3f**, 28% yield, respectively).

With these optimal reaction conditions in hand, we then explored the scope of this C−H hydroxylation process. As shown in Figure 1, this protocol was compatible with a wide range of functional groups, such as alkyl, trifluoromethyl, methoxy, chloro, fluoro, cyano, nitro, bromo, and acetylamino. *o*-Methylbenzamide **1d** gave reduced yield due to the steric effect of the *ortho*-substituent, which obstructs the formation of the putative palladacycle intermediate (**2d**, 37%). Curiously, when *m*-methylbenzamide **1c** was subjected to the hydroxylation reaction, a mixture of **2ca** and **2cb** was obtained with hydroxylation of less hindered C−H bond happening predominantly (**2ca**, 19% and **2cb**, 57%). The strongly electron-deficient functional groups, such as cyano and nitro, were also tolerated (**2m** and **2n**). Notably, bromo-substituted benzamide **1o** was also effective, which could be used as versatile handles for further transformations.

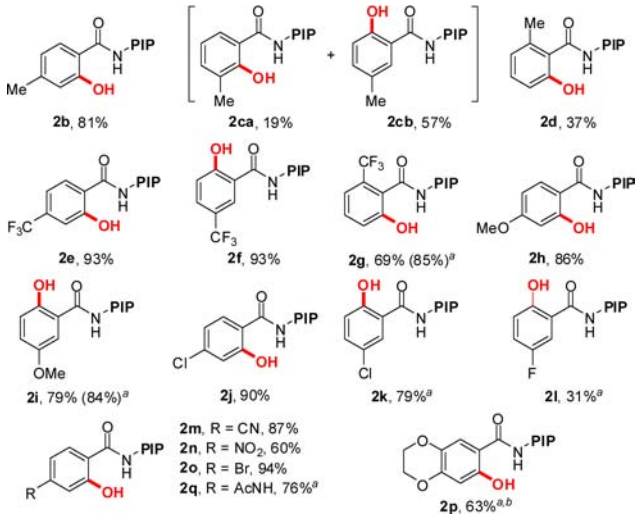


Figure 1. Substrate scope of arenes. Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), Ag_2CO_3 (0.4 mmol) and TBAI (0.4 mmol) in DMF (2 mL) at 100 °C for 1 h. Isolated yields. Notes: [a]12 h. [b]2 mmol.

Due to the importance of heteroarenes in pharmaceuticals and material science, we are particularly interested in the synthesis of divergent heteroarenes via the direct C−H functionalization strategy.[16] To our delight, a wide range of biologically important heterocycles were suitable for this conversion (Figure 2). The hydroxylation of nicotinamides bearing various substitutents reacted regioselectively at the C-4 position, even when the sterically bulky 5-methylnicotinamide **4d** was employed as substrate. These results indicated that C(4)−H bond is more

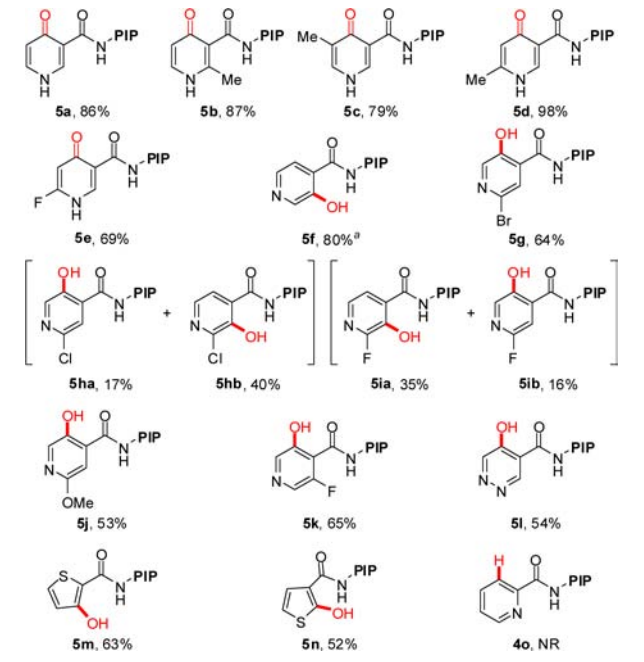


Figure 2. Substrate scope of heteroarenes. Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), Ag_2CO_3 (0.4 mmol) and TBAI (0.4 mmol) in DMF (2 mL) at 100 °C for 1 h. Isolated yields. Notes: [a]12 h.

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reactive than the C(2)−H ones in this reaction system. Interestingly, NMR spectra of **5a**−**5e** showed that these compounds had carbonyl signals around 178 ppm, and ^{1}H NMR signals of the active hydrogen were extremely downfield, indicating that the exact structure of **5a**−**5e** should be their 4-oxo-1,4-dihydropyridine isomers. This was undoubtedly confirmed by X-ray analysis of compounds **5a** and **5c** (Supplementary Figure S2). Isonicotinamides **4f**−**4k** were also tolerated and proceeded smoothly to give the desired products in good yields. A mixture of isomers was obtained when 2-chloro and 2-fluoroisonicotinamide **4h** and **4i** were used as substrates. Besides, heterocycles such as pyridazine and thiophene also survived under the reaction conditions (**5l**−**5n**). However, no desired hydroxylation product was observed when picolinamide **4o** was subjected to the standard conditions, since piconamide **4o** could coordinate with copper as a N,N,N-pincer-type ligand.

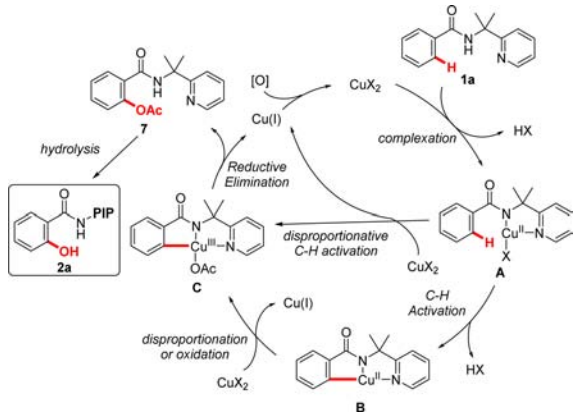
To highlight the synthetic utility of this procedure, a 5 mmol scale reaction was conducted using benzamide **1a** as substrate, and the reaction proceeded smoothly to give the corresponding hydroxylation product **2a** in excellent yield (91%, 1.17 g). Furthermore, removal of the PIP directing group from the *o*-hydroxylcarboxamide **2a** was achieved under acidic conditions, and salicylic acid **6** was obtained in 61% yield (Scheme 2).

Scheme 2. Large Scale Synthesis and Removal of the Directing Group

To gain more insights into the mechanism of the C−H hydroxylation reactions, a series of experiments were conducted. First, the addition of radical scavengers, such as 1,4-dinitrobenzene, TEMPO, or 1,1-diphenylethylene, had no significant influence on the reaction, which rules out the possibility of a radical mechanism (Supplementary Scheme S1a). Next, the intermolecular kinetic isotope effect (KIE) was determined to be 5.3, indicating that C−H bond cleavage of **1a** is the rate-determining step of the catalytic cycle (Supplementary Scheme S1b). When the reaction was performed in D_2O or AcOD, no deuterium incorporation in both starting material and product **2a** was observed, suggesting that C−H activation step is irreversible (Supplementary Scheme S1c). Finally, *o*-acetoxyl benzamide **7** could be converted to **2a** under the reaction conditions (Supplementary Scheme S1d). This result suggested that the reaction might go through a $Cu(OAc)_2$-mediated acetoxylation followed by a rapid hydrolysis.

On the basis of these observations and earlier precedents, a putative reaction pathway as proposed in Scheme 3 is possible. First, the complexation of benzamide **1a** with copper using the *N,N*-bidentate directing group yields a Cu(II)-complex **A**. A basic ligand (acetate or carbonate)-enabled, rate-determining concerted-metalation-deprotonation (CMD) C−H activation then affords the Cu(II)-aryl species **B**. The C,N,N-pincer type Cu(III)-aryl intermediate **C** was produced by disproportionation or oxidation. Subsequent reductive elimination leads to the acetoxylation product **7** together with the formation of a Cu(I) species. The catalytic cycle is closed by the reoxidation of Cu(I) to Cu(II) by silver salt. The acetoxylation product **7** is transformed to **2a** via a rapid hydrolysis.[7a] Alternatively, a disproportionative C−H activation from Cu(II)-complex **A** to

Scheme 3. Plausible Reaction Mechanism



the C,N,N-pincer type Cu(III)-aryl intermediate **C** in one elementary step is also possible as established by Ribas and Stahl.[15] Although the exact role of silver is unclear at this point, on the basis of our own preliminary studies and earlier precedent,[12d,e] we rationalize that Ag_2CO_3 might not only act as oxidant but also could react with $Cu(OAc)_2$ to generate the $[LCu^{II}(\kappa^2\text{-}CO_3)]^-$ (Cu^{II}-complex **A** in Scheme 3, where X = κ^2-CO_3, L = deprotonated **1a**) as indicated by Stahl.[12d,17]

In conclusion, we have developed an effective copper-mediated hydroxylation of arenes and heteroarenes directed by a removable bidentate auxiliary. Advantages of our protocol include a broad substrate scope, high functional group tolerance, compatibility with heteroarenes, simplicity of operation, and the use of inexpensive copper catalyst. Preliminary mechanistic studies suggest that a basic ligand-enabled, irreversible, rate-determining CMD step is most likely involved in this process.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for all new compounds, and X-ray for **2a**, **5a**, and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) XPS analysis of the oxidation state of copper after the reaction indicated that there were no significant differences with and without silver (Supplementary Figures S4 and S5).

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