OL Organic Letters

pubs.acs.org/OrgLett Letter

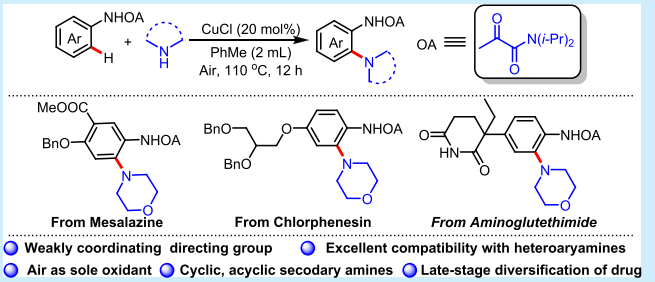
Copper-Catalyzed Oxalamide-Directed *ortho*-C−H Amination of Anilines with Alkylamines

Peng Wu, Wei Huang, Tai-Jin Cheng, Hai-Xia Lin, Hui Xu, and Hui-Xiong Dai*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01632 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A copper-catalyzed oxalamide-directed *ortho*-C−H amination of anilines has been developed by using 1 atm of air as the sole oxidant. The protocol shows excellent functional group tolerance, and some heterocyclic amines including indole, benzothiophene, benzothiazole, quinoline, isoquinoline, and quinoxaline could be compatible in the reaction. The late-stage diversification of medicinal drugs demonstrates the synthetic utility of this protocol.



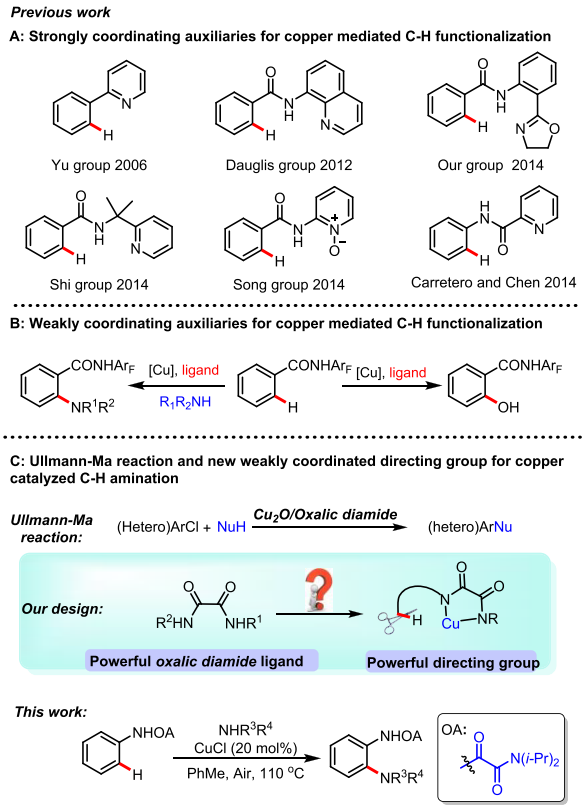
Over the past decade, transition-metal-catalyzed, such as Ru-, Rh-, Pd-, and Ir-catalyzed, C−H functionalization has emerged as a novel synthetic tool in organic synthesis.[1] Compared with these precious metals, Cu salts are earth-abundant and have low toxicity. Recently, directing-group-assisted copper-mediated C−H functionalization has become a hot research field (Scheme 1A).[2] In 2006, Yu and coworkers reported the first directed copper-catalyzed C−H functionalization of 2-phenylpyridine and proposed the single electron transfer (SET) pathway mediated by a Cu(II) intermediate.[3] However, the nonremovability of the pyridyl group limits the further application in organic synthesis. An elegant work about the copper-promoted *ortho*-C−H sulfenylation of benzoic acid derivatives by using 8-aminoquinoline as the removable directing group was developed by the Daugulis in 2012.[4] Subsequently, they and other research groups exploited this directing group to achieve biaryl coupling,[5] amination,[6] fluorination,[7] etherification,[8] and so on. Later on, we developed amide-tethered oxazoline as the directing group to realize Cu-catalyzed or -mediated C−H amination, trifluoromethylation, alkynylation, hydroxylation, arylation, and thiolation.[9] Meanwhile, Chen and Carretero independently developed the copper-catalyzed picolinamide-directed *ortho*-C−H amination of anilines with good functional group tolerance.[10] However, it was not sufficiently active for acyclic amines, and a stoichiometric amount of the expensive $PhI(OAc)_2$ was required as an oxidant. Furthermore, Shi and Song, respectively, developed the 2-(pyridin-2-yl)-isopropylamine (PIP)-directing group and the 2-aminopyridine 1-oxide directing group for copper-catalyzed or -mediated C−H functionalization.[11]

Despite undisputable advances, copper-mediated C−H functionalization reactions inevitably rely on strongly coordinating directing groups due to the low reactivity of the copper catalyst. Strong coordination can form a more stable metallacycle and thus cause less reactivity in the subsequent C−H functionalization step. As a consequence, adding a stoichiometric copper catalyst is required. In contrast, weak coordination could kinetically facilitate the functionalization step by forming the less thermodynamically stable metallacycle and thus could theoretically achieve the catalytic cycle of the copper catalyst.[12] In 2017, we demonstrated that the use of a weakly coordinating monodentate directing group in combination with an oxazoline ligand could achieve the copper-promoted C−H amination and hydroxylation (Scheme 1B).[13] The downside is that the reaction system requires stoichiometric amounts of Cu(I) and Cu(II) to obtain the moderate yields. Therefore, how to realize C−H functionalization effectively by using weakly coordinated directing groups remains a challenge.

Recently, Ma and coworkers elegantly developed the oxalic diamide as an efficient ligand in the copper-catalyzed Ullmann−Goldberg-type coupling reactions of the less reactive (hetero)aryl chloride with the nucleophilic reagent.[14] The oxalic diamide ligand was so efficient that only 0.01 mol % of Cu_2O and ligand could catalyze the cross-coupling of (hetero)aryl iodides with primary amines in good yields.[14d] Inspired by these works, we hypothesized that we could convert this powerful Cu/oxalamide catalytic system into Cu-catalyzed oxalamide-directed C−H functionalization (Scheme 1C). Herein we report a copper-catalyzed *ortho*-C−H

Received: May 13, 2020

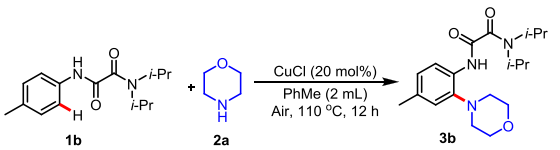
Scheme 1. Directing Groups for Copper-Catalyzed or -Mediated C−H Functionalization



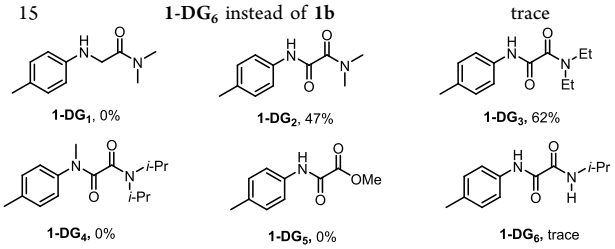
amination of aniline by using oxamide as a weakly coordinating directing group.

We commenced our studies by choosing N^1,N^1-diisopropyl-N^2-(*p*-tolyl) oxalamide **1b** and morpholine **2a** as the model substrates. The optimized reaction conditions for the copper-catalyzed *ortho*-C−H amination of anilines are shown in Table 1. A series of control experiments were carried out to better understand this reaction. As expected, removing Cu from the reaction mixture resulted in no detectable formation of amination product **3b** (entry 2). The yield was slightly reduced when we lowered the loading of CuCl to 10 mol % (entry 3). Toluene was the optimal solvent, and the yields significantly decreased when THF or DMSO was used (entries 4 and 5). No desired product was observed when $PhI(OAc)_2$ was added as the oxidant (entry 6). As expected, the yield decreased to trace under the N_2 atmosphere, which showed that air was indispensable to oxidize Cu(I) to Cu(II) (entry 7). Moreover, when the reaction was carried out under the O_2 atmosphere, the result was consistent with that under air (entry 8). Decreasing the temperature to 80 °C resulted in lower conversion (entry 9). No reaction occurred when the amino acid skeleton was used instead of oxalamide, presumably due to the flexibility of the amino acid skeleton (entry 10). We further modulated the substituents on the amide nitrogen and found that the diisopropyl-substituted substrate showed the best results (entries 11 and 12). The *N*-methylaniline substrate was totally unreactive, indicating that the covalent bond formed with copper was essential for the reaction (entry 13). In addition, ester is not stable enough due to the aminolysis with alkylamine (entry 14). Although **1-DG$_6$** could form a five-membered bis-dentate complex with Cu(II), no desired product was observed (entry 15).

Table 1. Optimization of the Reaction Conditions[a,b,c]



entry	variations from the standard conditions	yield (%) of **3b**
1	none	72 (70)[c]
2	no Cu	0
3	CuCl (10 mol %)	56
4	DMSO instead of PhMe	trace
5	THF instead of PhMe	6
6	$PhI(OAc)_2$ (2 equiv)	0[d]
7	at N_2 atmosphere	trace
8	at O_2 atmosphere	71
9	at 80 °C	29
10	**1-DG$_1$** instead of **1b**	0
11	**1-DG$_2$** instead of **1b**	47
12	**1-DG$_3$** instead of **1b**	62
13	**1-DG$_4$** instead of **1b**	0
14	**1-DG$_5$** instead of **1b**	0
15	**1-DG$_6$** instead of **1b**	trace

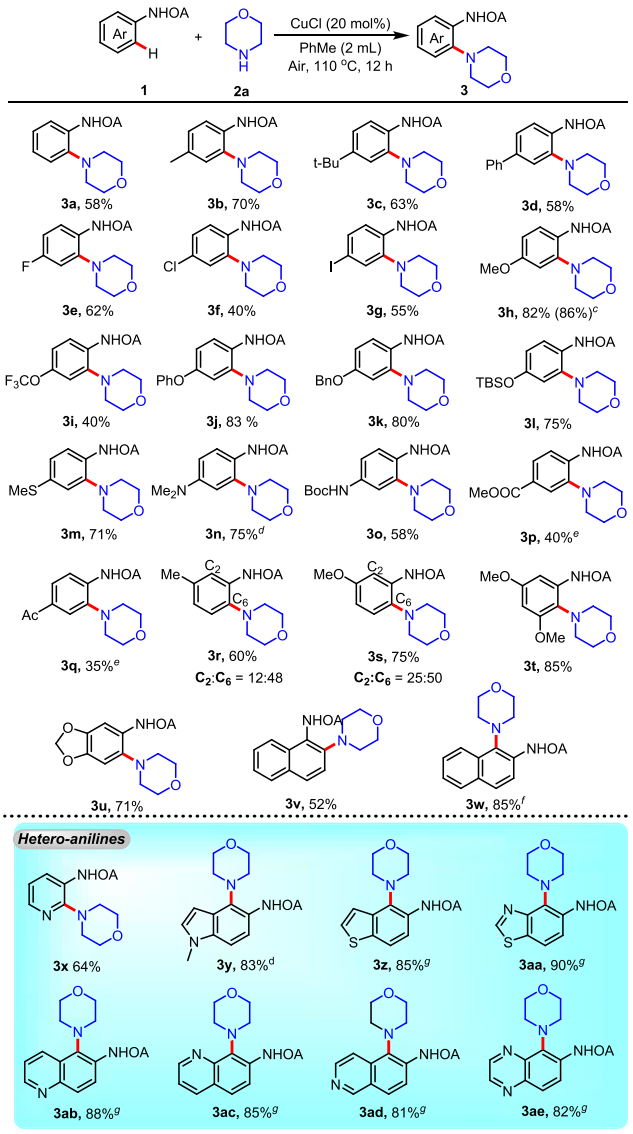


[a]Reaction conditions: **1b** (0.1 mmol), **2a** (0.2 mmol), CuCl (20 mol %), PhMe (2.0 mL), air, 110 °C, 12 h. [b]^{1}H NMR yields were determined by using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield. [d]N_2 atmosphere.

With the optimal conditions in hand, we proceeded to explore the substrate scope with the corresponding anilines. As shown in Scheme 2, electron-donating substrates showed better reactivity than electron-withdrawing substrates. Weak electron-donating groups, such as *t*-Bu, Ph, CF_3O, and NHBoc at the para position were well tolerated (**1a**, **1b**, **1c**, **1d**, **1i**, **1o**), giving the desired products in 40−70% yields. A variety of electron-rich groups such as MeO, PhO, BnO, TBSO, and MeS groups (**1h**, **1j**, **1k**, **1l**, **1m**) at the same position provided good yields. Substitutes including fluoro, chloro, and very sensitive iodo substitutions could be well tolerated, leaving a functional handle for further elaboration (**3e**−**g**). When we increased the catalyst loading of CuCl to 1 equiv, electron-withdrawing ester and keto substitutions were found to be tolerable (**3p**, **3q**). *N*,*N*-Dimethyl-1,4-phenylenediamine (**1n**) and 2-naphthylamine (**1w**) gave poor yields under the standard conditions, and most of starting materials were decomposed due to the amine exchange with morpholine **2a**. Luckily, when we reduced the temperature to 90 and 80 °C, both of them showed high reactivity, giving the corresponding products in 75 and 85% yields respectively (**3n**, **3w**). *meta*-Methyl- and methoxy-substituted anilines furnished moderate to good yields, with the less sterically hindered six-position-aminated product as the major product (**3r**, **3s**). 1-Naphthylamine (**1v**) gave a much lower yield than 2-naphthylamine (**1w**), probably due to the steric hindrance. Multisubstituted substrates such as 3,5-dimethoxy and 3,4-(methylenedioxy)

https://dx.doi.org/10.1021/acs.orglett.0c01632
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of Aromatic Anilines[a,b]



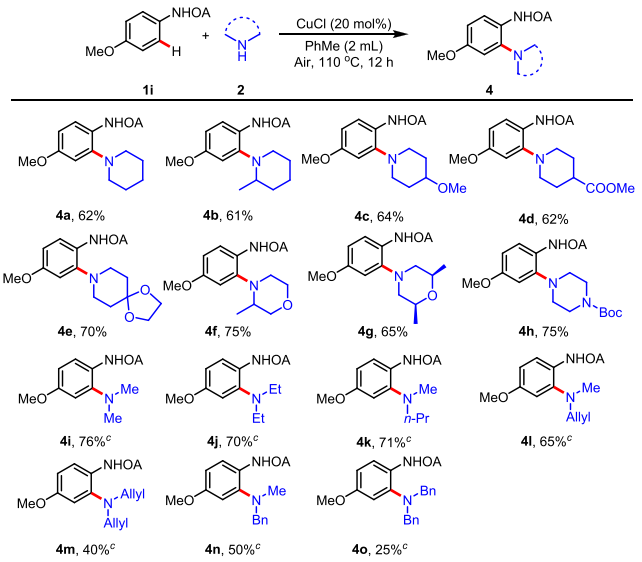
[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), CuCl (20 mol %). PhMe (2 mL), air, 110 °C, 12 h. [b]Isolated yield. [c]1 mmol scale. [d]90 °C. [e]CuCl (100 mol %). [f]80 °C. [g]100 °C, 3 h.

anilines gave excellent yields (**3t**, **3u**). Remarkably, this protocol could be well applied to heterocyclic amines (**1x**–**ae**). Substrates containing pyridine (**1x**), indole (**1y**), and quinoline (**1ab**, **1ac**) provided moderated yields. To our delight, this protocol could be extended to substrates containing benzothiophene, benzothiazole, isoquinoline, and quinoxaline, which had not been reported in previous work,[10] providing the desired products in excellent yields (**3z**, **3aa**, **3ad**, **3ae**).

Next, we began to explore the scope of alkylamines. As shown in Scheme 3, regardless of steric hindrance, amines such as piperazine, piperidine, and morpholine were well compatible in the reaction (**4a**–**h**). In addition, the reaction gave better results for acyclic amines than that with picolinic amide-embodied substrates,[10] providing the amination products in moderate to good yields (**4i**–**o**).

To demonstrate the synthetic utility of this protocol, we applied this protocol to the late-stage diversification of

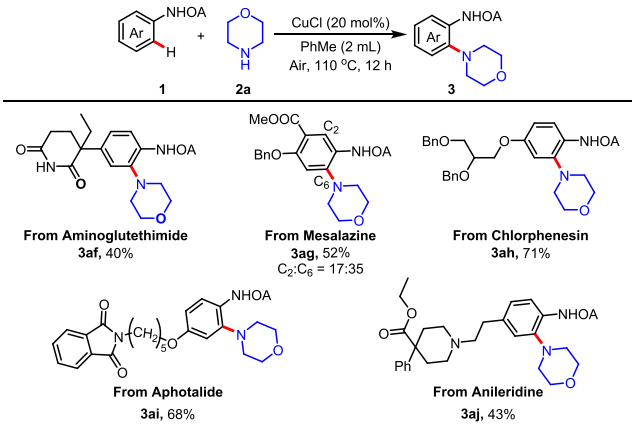
Scheme 3. Substrate Scope of Alkylamines[a,b]



[a]Reaction conditions: **1i** (0.1 mmol), **2** (0.2 mmol), CuCl (20 mol %). PhMe (2 mL), air, 110 °C, 12 h. [b]Isolated yield. [c]CuCl (0.1 mmol).

medicinal drugs Aminoglutethimide (**1af**), Mesalazine (**1ag**), Chlorphenesin (**1ah**), Aphotalide (**1ai**), and Anileridine (**1aj**), which furnished the amination products in moderate to good yields (Scheme 4).

Scheme 4. Late-Stage Diversification of Medicinal Drugs[a,b]



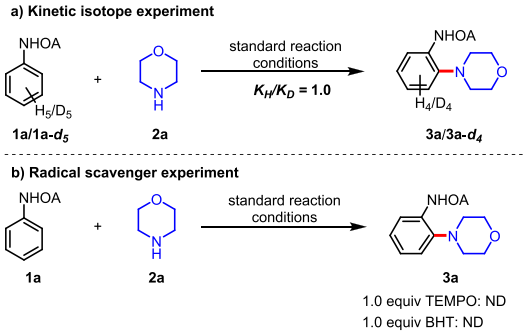
[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), CuCl (20 mol %). PhMe (2 mL), air, 110 °C, 12 h. [b]Isolated yield.

For a better understanding of the mechanism of copper-catalyzed C–H amination, control experiments were carried out, as shown in Scheme 5. Intermolecular kinetic isotope competition experiments between **1a** and **1a-d_5** produced a kinetic isotope effect (KIE) value of 1.0, indicating that C–H cleavage was not the rate-limiting step. The addition of radical scavenger TEMPO or BHT completely inhibited the reaction under the standard conditions, which indicated that a SET) pathway might be involved in the reaction.

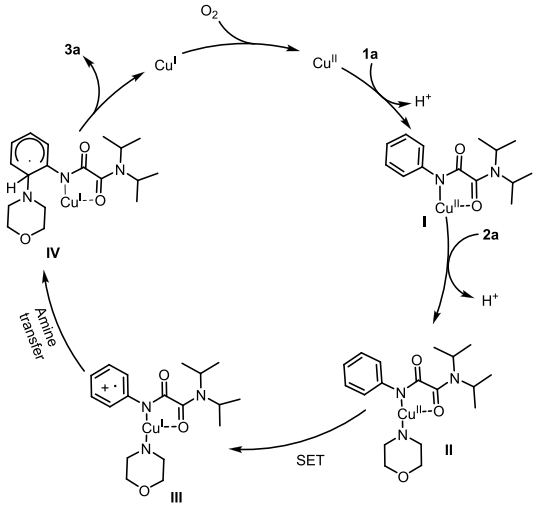
On the basis of the previously described control experiments and previous reports, a possible mechanism is proposed, as shown in Scheme 6. Initially, Cu(I) is oxidized in situ under air to form the Cu(II) species.[11d] Because of the two isopropyl

https://dx.doi.org/10.1021/acs.orglett.0c01632
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Mechanistic Experiments



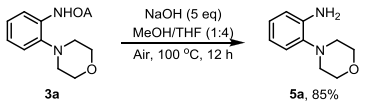
Scheme 6. Proposed Mechanism of Copper-Catalyzed C−H Amination of Anilines



substituents on the amide nitrogen, we proposed that Cu(II) species coordinate with N and O of substrate **1a** to form the five-membered ring metal species **I**. The coordination mode of OA has been demonstrated to be palladium-catalyzed intramolecular amination by Zhao.[15] Then, ligand exchange with alkylamine **2a** forms intermediate **II**. Subsequently, intermediate **III** is formed via the SET process from the aryl ring to the coordinated Cu(II). Finally, amine transfers to the arene, followed by deprotonation to provide **3a** with the regeneration of Cu(I) species for the next catalytic cycle.[3,10d]

The directing group OA in the amination product could be easily removed. For example, treatment of **3a** with NaOH in MeOH−THF at 100 °C gave the aniline derivative **5a** in 85% yield (Scheme 7).

Scheme 7. Removal of the Directing Group



In summary, we have developed a copper-catalyzed *ortho*-C−H amination by using oxalamide as a weakly coordinating directing group. By using 1 atm of air as the sole oxidant, the reaction could smoothly proceed with good functional group tolerance. Notably, a variety of heterocyclic amines such as indole, benzothiophene, benzothiazole, quinoline, isoquinoline, and quinoxaline could be well compatible in the reaction, giving the corresponding products in good to excellent yields. We further demonstrate the synthetic utility of this protocol in the late-stage diversification of medicinal drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01632.

Experimental procedures, characterizations of new compounds, and NMR spectra data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hui-Xiong Dai − *Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai 201203, China; State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0002-2937-6146; Email: hxdai@simm.ac.cn

Authors

Peng Wu − *Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China*

Wei Huang − *School of Pharmacy, Nanchang University, Nanchang 330006, China*

Tai-Jin Cheng − *Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai 201203, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Hai-Xia Lin − *Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China*

Hui Xu − *Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai 201203, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01632

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Shanghai Institute of Materia Medica, Chinese Academy of Sciences, National Natural Science Foundation of China (no. 21772211), Youth Innovation Promotion Association CAS (nos. 2014229 and 2018293), Institutes for Drug Discovery and Development, Chinese Academy of Sciences (no. CASIMM0120163006), Science and Technology Commission of Shanghai Municipality (no. 17JC1405000), Program of Shanghai Academic Research Leader (no. 19XD1424600), National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (no. 2018ZX09711002-006), and the State Key Laboratory of Natural and Biomimetic Drugs for financial support.

■ REFERENCES

(1) (a) Timsina, Y. N.; Gupton, B. F.; Ellis, K. C. Palladium-Catalyzed C−H Amination of $C(sp^2)$ and $C(sp^3)$−H Bonds: Mechanism and Scope for N-Based Molecule Synthesis. *ACS Catal.* **2018**, *8*, 5732−5776. (b) Kim, H.; Chang, S. The Use of Ammonia as

https://dx.doi.org/10.1021/acs.orglett.0c01632
Org. Lett. XXXX, XXX, XXX−XXX

an Ultimate Amino Source in the Transition Metal-Catalyzed C−H Amination. *Acc. Chem. Res.* **2017**, *50*, 482−486. (c) Kim, H.; Chang, S. Transition-Metal-Mediated Direct C−H Amination of Hydrocarbons with Amine Reactants: The Most Desirable but Challenging C−N Bond-Formation Approach. *ACS Catal.* **2016**, *6*, 2341−2351. (d) Shin, K.; Kim, H.; Chang, S. Transition-Metal-Catalyzed C−N Bond Forming Reactions Using Organic Azides as the Nitrogen Source: A Journey for the Mild and Versatile C−H Amination. *Acc. Chem. Res.* **2015**, *48*, 1040−1052. (e) De Sarkar, S.; Liu, W.-P.; Kozhushkov, S. I.; Ackermann, L. Weakly Coordinating Directing Groups for Ruthenium(II)-Catalyzed C−H Activation. *Adv. Synth. Catal.* **2014**, *356*, 1461−1479. (f) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp^2)− or C(sp^3)−H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304−8329. (g) Kuai, C.; Wang, L.; Cui, H.; Shen, J.; Feng, Y.; Cui, X. Efficient and Selective Synthesis of (E)-Enamides via Ru (II)-Catalyzed Hydroamidation of Internal Alkynes. *ACS Catal.* **2016**, *6*, 186−190. (h) Bu, Q.; Rogge, T.; Kotek, V.; Ackermann, L. Distal Weak Coordination of Acetamides in Ruthenium(II)-Catalyzed C−H Activation Processes. *Angew. Chem., Int. Ed.* **2018**, *57*, 765−768. (i) Zhang, S.-K.; Samanta, R. C.; Sauermann, N.; Ackermann, L. Nickel-Catalyzed Electrooxidative C−H Amination: Support for Nickel(IV). *Chem. - Eur. J.* **2018**, *24*, 19166−19170. (j) Gao, X.; Wang, P.; Zeng, L.; Tang, S.; Lei, A. Cobalt(II)-Catalyzed Electrooxidative C−H Amination of Arenes with Alkylamines. *J. Am. Chem. Soc.* **2018**, *140* (12), 4195−4199.

(2) For selected reviews, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative C−H Functionalizations: Trends and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (b) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Wang, M.-M.; Dai, H.-X. Recent Progress on Copper-Mediated Directing-Group-Assisted C(sp^2)−H Activation. *Synthesis* **2016**, *48*, 4381−4399. (c) Rao, W.-H.; Shi, B.-F. Recent advances in copper-mediated chelationassisted functionalization of unactivated C−H bonds. *Org. Chem. Front.* **2016**, *3*, 1028−1047.

(3) (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. Cu(II)-Catalyzed Functionalizations of Aryl C−H Bonds Using O_2 as an Oxidant. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791. (b) Smrcina, M.; Lorenc, M.; Hanus, V.; Sedmera, P.; Kocovsky, P. Synthesis of enantiomerically pure 2,2'-dihydroxy-1,1'-binaphthyl, 2,2'-diamino-1,1'-binaphthyl, and 2-amino-2'-hydroxy-1,1'-binaphthyl. Comparison of processes operating as diastereoselective crystallization and as second order asymmetric transformation. *J. Org. Chem.* **1992**, *57* (6), 1917−1920. (c) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. Synthesis of enantiomerically pure binaphthyl derivatives. Mechanism of the enantioselective, oxidative coupling of naphthols and designing a catalytic cycle. *J. Org. Chem.* **1993**, *58* (17), 4534−4538. (d) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S.-I. Catalytic asymmetric synthesis of binaphthol derivatives by aerobic oxidative coupling of 3-hydroxy-2-naphthoates with chiral diamine-copper complex. *Tetrahedron Lett.* **1995**, *36*, 9519−9520. (e) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I.; Noji, M.; Koga, K. Enantioselective Synthesis of Binaphthol Derivatives by Oxidative Coupling of Naphthol Derivatives Catalyzed by Chiral Diamine·Copper Complexes. *J. Org. Chem.* **1999**, *64*, 2264−2271. (f) Gao, J.; Reibenspies, J. H.; Martell, A. E. Structurally Defined Catalysts for Enantioselective Oxidative Coupling Reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 6008−6012. (g) Kim, K. H.; Lee, D.-W.; Lee, Y.-S.; Ko, D.-H.; Ha, D.-C. Enantioselective oxidative coupling of methyl 3-hydroxy-2-naphthoate using mono-N-alkylated octahydrobinaphthyl-2, 2'-diamine ligand. *Tetrahedron* **2004**, *60*, 9037−9042.

(4) Tran, L. D.; Popov, I.; Daugulis, O. Copper-Promoted Sulfenylation of sp^2 C−H Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 18237−18240.

(5) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. Copper-Mediated C−H/C−H Biaryl Coupling of Benzoic Acid Derivatives and 1,3-Azoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457−4461.

(6) (a) Tran, L. D.; Roane, J.; Daugulis, O. Directed. Amination of Non-Acidic Arene C−H Bonds by a Copper-Silver Catalytic System. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043−6046. (b) Roane, J.; Daugulis, O. A General Method for Aminoquinoline-Directed, Copper-Catalyzed sp^2 C−H Bond Amination. *J. Am. Chem. Soc.* **2016**, *138*, 4601−4607.

(7) Truong, T.; Klimovica, K.; Daugulis, O. Copper-Catalyzed, Directing Group-Assisted Fluorination of Arene and Heteroarene C−H Bonds. *J. Am. Chem. Soc.* **2013**, *135*, 9342−9345.

(8) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. Divergence between Organometallic and Single-Electron-Transfer Mechanisms in Copper(II)-Mediated Aerobic C−H Oxidation. *J. Am. Chem. Soc.* **2013**, *135*, 9797−9804.

(9) (a) Shang, M.; Sun, S.-M.; Dai, H.-X.; Yu, J.-Q. Cu (II)-Mediated C−H Amidation and Amination of Arenes: Exceptional Compatibility with Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 3354−3357. (b) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. Cu(II)-Mediated *Ortho* C−H Alkynylation of (Hetero)Arenes with Terminal Alkynes. *J. Am. Chem. Soc.* **2014**, *136*, 11590−11593. (c) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. Exceedingly Fast Copper(II)-Promoted *ortho* C−H Trifluoromethylation of Arenes using $TMSCF_3$. *Angew. Chem., Int. Ed.* **2014**, *53*, 10439−10442. (d) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. $Cu(OAc)_2$-Catalyzed Coupling of Aromatic C−H Bonds with Arylboron Reagents. *Org. Lett.* **2014**, *16*, 5666−5669. (e) Wang, H.-L.; Shang, M.; Sun, S.-Z.; Zhou, Z.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. Cu(II)-Catalyzed Coupling of Aromatic C−H Bonds with Malonates. *Org. Lett.* **2015**, *17*, 1228−1231. (f) Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. Cu(II)-Mediated C(sp^2)−H Hydroxylation. *J. Org. Chem.* **2015**, *80*, 8843−8848. (g) Shang, M.; Wang, M.-M.; Saint-Denis, T. G.; Li, M.-H.; Dai, H.-X.; Yu, J.-Q. Copper-Mediated Late-Stage Functionalization of Heterocycle Containing Molecules. *Angew. Chem., Int. Ed.* **2017**, *56*, 5317−5321. (h) Xu, L.-L.; Wang, X.; Ma, B.; Yin, M.-X.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. Copper mediated C−H amination with oximes: en route to primary anilines. *Chem. Sci.* **2018**, *9*, 5160−5164. (i) Wang, X.; Yi, X.; Xu, H.; Dai, H.-X. Cu-Mediated C−H Thioetherification of Arenes at Room Temperature. *Org. Lett.* **2019**, *21*, 5981−5985.

(10) (a) Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. Copper-catalyzed *ortho*-C−H amination of protected anilines with secondary amines. *Chem. Commun.* **2014**, *50*, 2801−2803. (b) Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. Copper-Catalyzed Carboxamide-Directed *Ortho* Amination of Anilines with Alkylamines at Room Temperature. *Org. Lett.* **2014**, *16*, 1764−1767. (c) Yang, Q.-L.; Wang, X.-Y.; Lu, J.-Y.; Zhang, L.-P.; Fang, P.; Mei, T.-S. Copper-Catalyzed Electrochemical C−H Amination of Arenes with Secondary Amines. *J. Am. Chem. Soc.* **2018**, *140*, 11487−11494. (d) Begam, H. M.; Choudhury, R.; Behera, A.; Jana, R. Copper-Catalyzed Electrophilic *Ortho* C(sp^2)-H Amination of Aryl Amines: Dramatic Reactivity of Bicyclic System. *Org. Lett.* **2019**, *21*, 4651−4656.

(11) (a) Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-J.; Shi, B.-F. Copper-Mediated Hydroxylation of Arenes and Heteroarenes Directed by a Removable Bidentate Auxiliary. *Org. Lett.* **2014**, *16*, 3904−3907. (b) Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. Cu(II)-Mediated C−S/N−S Bond Formation via C−H Activation: Access to Benzoisothiazolones Using Elemental Sulfur. *Org. Lett.* **2014**, *16*, 5644−5647. (c) Hao, X.-Q.; Chen, L.-J.; Ren, B.-Z.; Li, L.-Y.; Yang, X.-Y.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. Copper-Mediated Direct Aryloxylation of Benzamides Assisted by an N, O-Bidentate Directing Group. *Org. Lett.* **2014**, *16*, 1104−1107. (d) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, K.; Ren, B.-Z.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. Copper-Mediated Direct Alkoxylation of Arenes Using an N, O-Bidentate Directing System. *J. Org. Chem.* **2014**, *79*, 10399−10409. (e) Lee, W.-C. C.; Shen, Y.; Gutierrez, D. A.; Li, J. J. 2-Aminophenyl-1*H*-pyrazole as a Removable Directing Group for Copper-Mediated C−H Amidation and Sulfonamidation. *Org. Lett.* **2016**, *18*, 2660−2663.

(12) (a) Kang, Y.-S.; Zhang, P.; Li, M.-Y.; Chen, Y.-K.; Xu, H.-J.; Zhao, J.; Sun, W.-Y.; Yu, J.-Q.; Lu, Y. Ligand-Promoted Rh^{III}-Catalyzed Thiolation of Benzamides with a Broad Disulfide Scope.

https://dx.doi.org/10.1021/acs.orglett.0c01632
Org. Lett. XXXX, XXX, XXX−XXX

Angew. Chem., Int. Ed. **2019**, *58*, 9099−9103. (b) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C−H Bonds. *Chem. Rev.* **2017**, *117*, 8754−8786. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C−H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802. (d) Qiu, Y.; Struwe, J.; Ackermann, L. Metallaelectro-Catalyzed C−H Activation by Weak Coordination. *Synlett* **2019**, *30*, 1164−1173. (e) Cera, G.; Ackermann, L. Weak O-Assistance Outcompeting Strong N, N-Bidentate Directing Groups in Copper-Catalyzed C−H Chalcogenation. *Chem. - Eur. J.* **2016**, *22*, 8475−8478.

(13) Shang, M.; Shao, Q.; Sun, S.-Z.; Chen, Y.-Q.; Xu, H.; Dai, H.-X.; Yu, J.-Q. Identification of monodentate oxazoline as a ligand for copper-promoted *ortho* C−H hydroxylation and amination. *Chem. Sci.* **2017**, *8*, 1469−1473.

(14) (a) Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. CuI/Oxalic Diamide Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amines. *J. Am. Chem. Soc.* **2015**, *137*, 11942−11945. (b) Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. CuI/Oxalamide Catalyzed Couplings of (Hetero)aryl Chlorides and Phenols for Diaryl Ether Formation. *Angew. Chem., Int. Ed.* **2016**, *55*, 6211−6215. (c) Xia, S.; Gan, L.; Wang, K.; Li, Z.; Ma, D. Copper-Catalyzed Hydroxylation of (Hetero)aryl Halides under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138*, 13493−13496. (d) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. Discovery of N-(Naphthalen-1-yl)-N'-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers. *Org. Lett.* **2017**, *19*, 2809−2812. (e) Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D. Oxalic Diamides and *tert*-Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 3541−3549.

(15) (g) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. Easily Accessible Auxiliary for Palladium-Catalyzed Intramolecular Amination of C(sp^2)−H and C(sp^3)−H Bonds at *δ*- and *ε*-Positions. *Angew. Chem., Int. Ed.* **2014**, *53*, 9884−9888.

https://dx.doi.org/10.1021/acs.orglett.0c01632
Org. Lett. XXXX, XXX, XXX−XXX