Copper-Mediated Decarboxylative C–H Arylation of Phenol Derivatives with *ortho*-Nitrobenzoic Acids Using Phenanthroline-Based Bidentate Auxiliary

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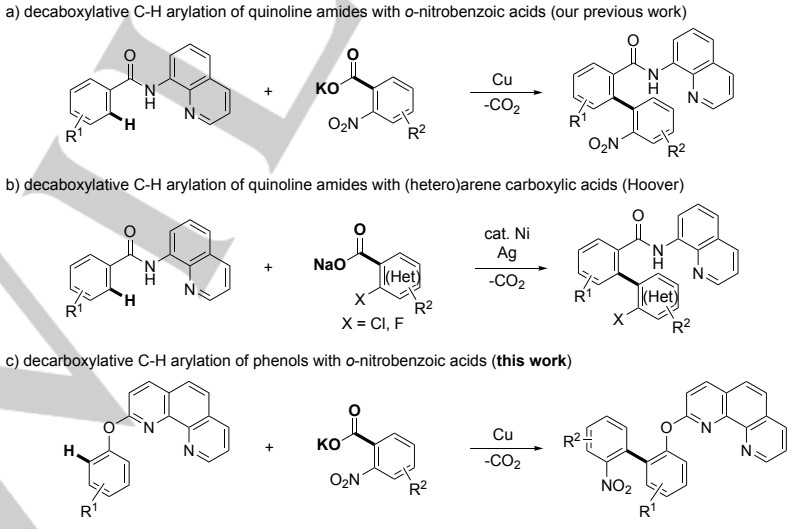
Abstract: A copper-mediated decarboxylative C–H arylation of phenol derivatives with *ortho*-nitrobenzoic acid salts via phenanthroline-directed C–H cleavage has been developed. The N,N-bidentate phenanthroline auxiliary uniquely promotes the reaction only in the presence of a copper salt to produce the corresponding biaryls in acceptable yields. Moreover, the directing group can be easily introduced and removed. Additionally, preliminary computational mechanistic studies with DFT have also been performed.

Introduction

Transition-metal-promoted decarboxylative coupling has attracted significant attention as a convenient method for the formation of C-C and C-heteroatom bonds due to the ready availability of inexpensive, stable, and abundant carboxylic acids as carbon nucleophiles.[1] Since the pioneering work by Nilsson[2] and Gooßen,[3] a variety of metal-catalyzed decarboxylative coupling reactions with various carbon electrophiles such as halides[4] and pseudohalides[5] have been reported. Recently, transition-metal-catalyzed decarboxylative C–H functionalization has also received great interest as the more atom- and step-economical methods than traditional synthetic methods with organic halides and organometallic reagents.[1,6-8] In particular, decarboxylative coupling reactions of benzoic acids with aromatic C–H bonds can be an efficient and powerful tool to construct biaryl skeletons.[7] However, few examples of decarboxylative arylation via directed C–H cleavage were reported[8] although there are many successful examples of directing-group-assisted regioselective C–H transformation.[9] Moreover, noble transition metals such as palladium are essential in most cases.



Scheme 1. Decarboxylative C–H arylation with benzoic acids via directed C–H cleavage.

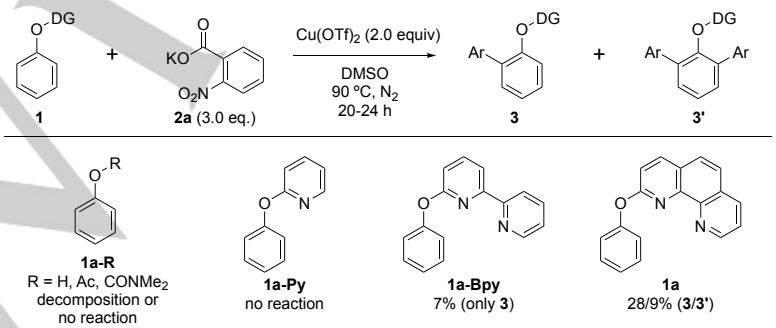
On the other hand, our group[10] and others[11] focused on copper salts as inexpensive, less toxic, and abundant alternatives to noble transition metals, and developed copper-mediated unique C–H functionalization reactions. As part of this research project, we previously reported the copper-mediated decarboxylative C–H arylation of benzamides with *ortho*-nitrobenzoic acids via 8-aminoquinoline-type bidentate-auxiliary-directed[12] C–H cleavage (Scheme 1a).[10e] This is one of limited successful examples of decarboxylative C–H arylations via directed C–H cleavage. Around the same time, Hoover also developed the nickel-catalyzed similar transformations with (hetero)arene carboxylic acids (Scheme 1b).[13] However, the scope of aromatic C–H substrates is still restricted: only 8-aminoquinoline-derived benzamides showed acceptable reactivity.

Meanwhile, we recently developed the phenanthroline-type N,N-bidentate directing group and successfully applied it to the regioselective C–H amination of phenols with diarylamines.[10f] We envisioned that the phenanthroline-based auxiliary could expand the scope of decarboxylative C–H arylation to phenols, which are important classes of compounds in the field of food, material, polymer, and pharmacy.[14] Herein, we report a copper-mediated decarboxylative arylation of phenol derivatives with potassium *ortho*-nitrobenzoates via phenanthroline-directed C–H cleavage (Scheme 1c). The reaction proceeds even in the presence of copper alone to form the corresponding biaryls in synthetically useful yields. This strategy can be a good earth abundant metal-mediated alternative to the reported *ortho*-selective C–H arylations of phenols under noble transition metal catalysis.[15]

Results and Discussion

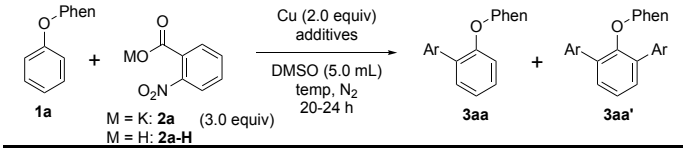
We initially checked the effect of directing groups on oxygen in the copper-mediated decarboxylative coupling of phenol derivatives **1** with potassium 2-nitrobenzoate (**2a**) (Scheme 2). With $Cu(OTf)_2$ (2.0 equiv) under N_2 in DMSO at 90 ºC, simple phenol (**1a-H**), phenyl acetate (**1a-Ac**), and phenyl dimethylcarbamate (**1a-CONMe$_2$**) as well as commonly used monodentate phenoxypyridine (**1a-Py**) did not react with **2a** at all. On the other hand, the reaction of a phenol derivative with the bidentately coordinating bipyridyl group (**1a-Bpy**) produced the mono-arylated product albeit in only 7% yield. Prompted by the preliminary but intriguing result, we next tested the more rigid phenanthroline-type bidentate directing group (**1a**), which is readily synthesized from the simple phenol (**1a-H**) and commercially available and easily prepared chlorophenanthroline (see the Supporting Information). Pleasingly, the reaction efficiency increased, and the mono- and di-arylated products (**3aa** and **3aa'**) were obtained in 28% and 7%, respectively. From the viewpoint of the availability and reactivity, we identified **1a** to be the promising substrate and carried out further optimization (Table 1). Neither increasing nor decreasing the reaction temperature improved the product yield (entries 2 and 3). On the basis of our previous success of copper-mediated decarboxylative C–H arylation of benzamide,[10e] we also tested the combination of $Cu(OAc)_2$ and free 2-nitrobenzoic acid (**2a-H**); the reaction proceeded, but the yield was not improved (entries 4 and 5). The effect of base (1.0 equiv) was then examined (entries 6-10), and the addition of alkali metal *tert*-butoxides, especially KO*t*Bu increased the yield (entry 8). Finally, we found that the C-H arylation occurred in the presence of 2.0 equiv of $Cu(OTf)_2$ and 40 mol% of KO*t*Bu in DMSO at 90 ºC for 22 h to produce **3aa** and **3aa'** in 45% combined yield (entry 11). Increasing and decreasing the amount of **2a** did not further improve the reaction efficiency (entries 12 and 13). The control experiment without $Cu(OTf)_2$ confirmed the necessity of the copper salt in this reaction (entry 14). Additional observations are to be noted: the reaction with the simple nitrobenzene instead of potassium 2-nitrobenzoate (**2a**) or 2-nitrobenzoic acid (**2a-H**) did not proceed at all; attempts to make the reaction catalytic in copper by using terminal oxidant such as O_2, $K_2S_2O_8$, and $(t\text{BuO})_2$ remained unsuccessful (data not shown).

While still preliminary, under conditions of entry 11 in Table 1, we examined the substrate scope (Scheme 3; 0.25 mmol scale). The reaction of phenol derivatives bearing both electron-donating and electron-withdrawing substituents at the *para*-position with potassium 2-nitrobenzoate proceeded to form a mixture of separable mono- and di-arylated products without notable electronic effects (**3ba**-**3ha**). It is noteworthy that the decarboxylative C–H arylation preferably occurred over the decarboxylative coupling with the aryl halide moiety to afford **3fa** with the Ar-Br bond left intact, which can be a good synthetic handle for further derivatizations. The *meta*-substituted substrates reacted at the less sterically hindered positions to produce the mono-arylated products selectively (**3ia** and **3ja**).



Scheme 2. Effects of directing group on nitrogen in copper-mediated decarboxylative C–H arylation of phenols **1** with potassium 2-nitrobenzoate (**2a**). Ar = 2-nitrophenyl.

Table 1. Optimization studies for copper-mediated decarboxylative C–H arylation of **1a**[a]



entry	Cu	**2** (eq.)	additives (eq.)	temp (˚C)	yield (%, **3aa**/**3aa'**)[b]
1	$Cu(OTf)_2$	**2a**, 3.0	none	90	28/9
2	$Cu(OTf)_2$	**2a**, 3.0	none	110	25/8
3	$Cu(OTf)_2$	**2a**, 3.0	none	70	8/trace
4	$Cu(OAc)_2$	**2a-H**, 3.0	none	90	22/5
5	$Cu(OAc)_2$	**2a-H**, 3.0	none	150	9/trace
6	$Cu(OTf)_2$	**2a**, 3.0	KOAc (1.0)	90	24/12
7	$Cu(OTf)_2$	**2a**, 3.0	K_2CO_3 (1.0)	90	16/5
8	$Cu(OTf)_2$	**2a**, 3.0	KO*t*Bu (1.0)	90	32/11
9	$Cu(OTf)_2$	**2a**, 3.0	LiO*t*Bu (1.0)	90	27/15
10	$Cu(OTf)_2$	**2a**, 3.0	NaO*t*Bu (1.0)	90	31/1
11	$Cu(OTf)_2$	**2a**, 3.0	KO*t*Bu (0.40)	90	(34/11)
12	$Cu(OTf)_2$	**2a**, 4.0	KO*t*Bu (0.40)	90	25/19
13	$Cu(OTf)_2$	**2a**, 2.0	KO*t*Bu (0.40)	90	15/3
14[c]	none	**2a**, 3.0	KO*t*Bu (0.40)	90	0/0

[a] Reaction conditions: **1a** (0.25 mmol), **2**, Cu (0.50 mmol), additives, DMSO (5.0 mL). [b] Determined by ^{1}H NMR with dibenzyl ether as internal standard. Isolated yield in parentheses. [c] Without $Cu(OTf)_2$. Phen = 2-(1,10-phenanthrolyl), Ar = 2-nitrophenyl.

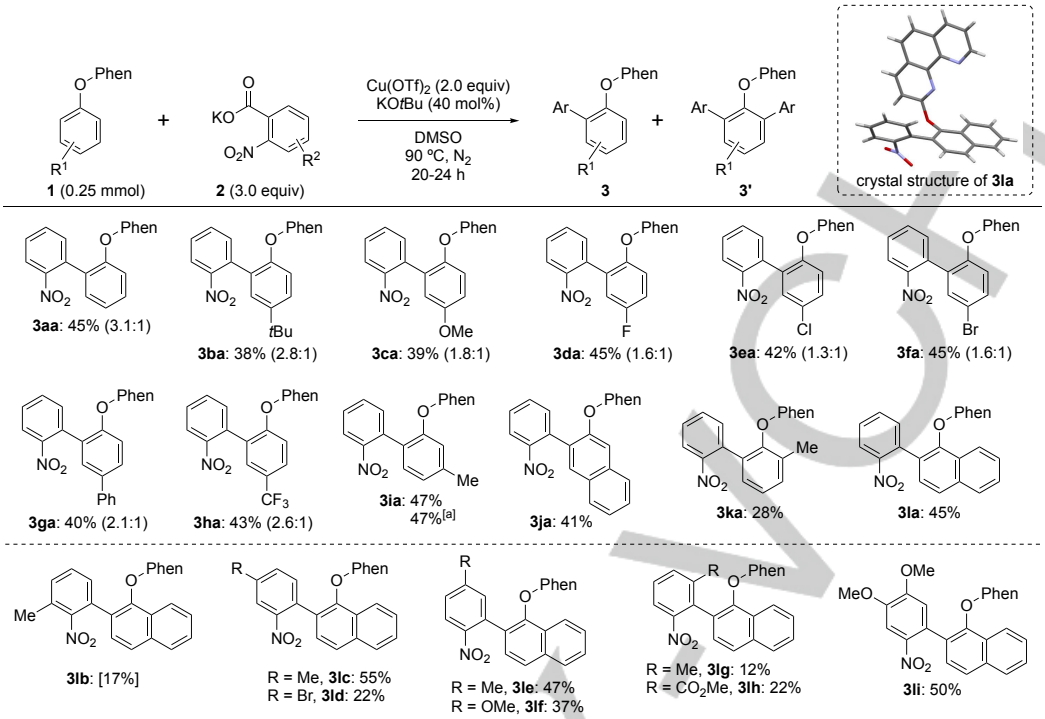
The reaction of phenol derivatives bearing substituents at the *ortho* position also proceeded to form the biaryl products **3ka** and **3la**, although the reaction efficiency with *ortho*-methyl-substituted **1k** was slightly decreased. In addition, the structure of **3la** was unambiguously confirmed by X-ray analysis.[16] We next performed the decarboxylative C–H arylation of **1l** with various potassium benzoates **2**. Although the lower yields were observed with the 2-nitrobenzoates bearing substituents at the 3-position (**3lb**) and 6-position (**3lg** and **3lh**) because of steric effects, methyl (**3lc** and **3le**), methoxy (**3lf** and **3li**), and even bromo groups (**3ld**) were compatible to produce the arylated products in moderate yields. Notably, the decarboxylative C–H arylation could be easily conducted on a four-fold larger scale, thus indicating the good reproducibility and practicality of this process (**3ia**).

To gain insight into the mechanism, we carried out deuterium-labeling experiments. Even at an early stage of reaction, the D/H exchange of [D_5]-**1a** was not observed (Scheme 4, eq 1). This result suggests that the C–H bond cleavage is irreversible. Additionally, KIE value of the parallel reactions with **1a** and [D_5]-**1a** was determined to be 1.05 (eq 2, see the Supporting Information for detailed kinetic profiles in the parallel reaction), thus indicating that the C–H cleavage step appears not to be involved in the rate-determining step. Moreover, the reaction of **2a** without **1a** produced nitrobenzene (**4a**) in only 8% even under otherwise identical reaction conditions (eq 3). This outcome supports that phenol substrate **1** is a ligand to copper and accelerates the decarboxylation process.

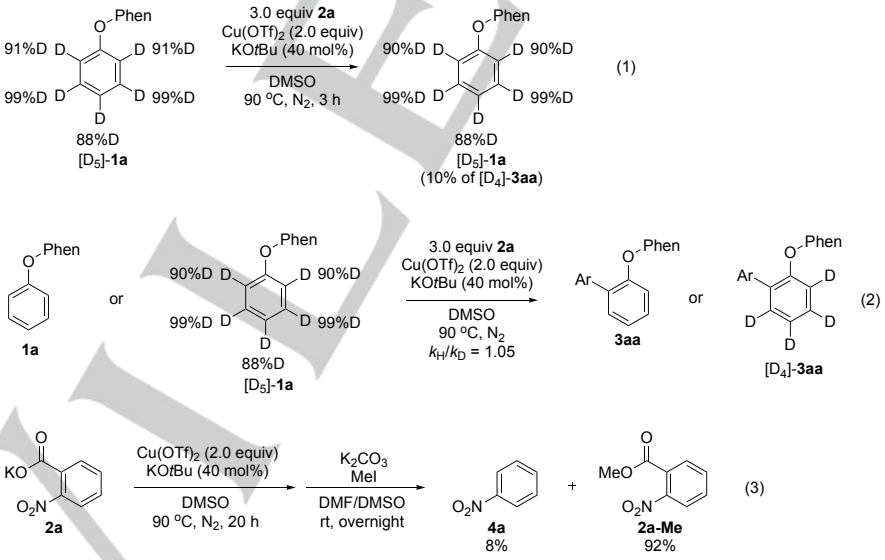
On the basis of literature information and our aforementioned findings, the plausible reaction course can include three important elementary steps: C–H activation, decarboxylation, and disproportionation-induced Cu(III) formation. However, the order still remained unclear only with experimental studies. To clarify the detailed reaction mechanism, we performed computational studies based on DFT. We proposed six scenarios and calculated their overall energy profiles (see the Supporting Information for details). As a result, we were pleased to find that the pathway with the order of decarboxylation, C–H activation, and disproportionation-induced Cu(III) formation is more likely.

The enthalpy profile of the most plausible mechanism is shown in Figure 1, where $Cu(OAc)_2$ and 2-nitrobenzoic acid are used as the mediator and aryl source, respectively, to decrease the cost of calculation. In the mechanism, a chelate complex **A** undergoes ligand exchange of an acetate with $ArCOO^-$ leading to **B**. Then, **B** is decarboxylated to **C** with 29.1 kcal mol^{-1} of activation enthalpy and 7.3 kcal mol^{-1} of reaction enthalpy. The C–H cleavage of *ortho*-position in the phenoxy moiety of **C** via the concerted metalation deprotonation mechanism[17] leads to the six-membered intermediate **D** with 24.4 kcal mol^{-1} of activation enthalpy and 17.9 kcal mol^{-1} of reaction enthalpy. After dissociation of acetic acid (**D** to **E**), **E** is oxidized with the additional $[Cu(OAc)_2]_2$ forming the copper(III) species **F**.[18] This step is 18.1 kcal mol^{-1} exothermic. The reductive elimination of **F** leading to the mono-coupled product **G** is nearly barrierless and 51.4 kcal mol^{-1} exothermic reaction. Therefore, the rate-determining step of this mechanism is the decarboxylation step, which is consistent with KIE observation in Scheme 4. As side reactions, it can be considered that **C** undergoes a protonation with acetic acid or 2-nitrobenzoate acid to form the simply decarboxylated byproduct, that is, nitrobenzene (**4a** in Scheme 4). Actually, some amounts of simple nitrobenzenes were detected as the side products in Scheme 3. The activation enthalpy and reaction enthalpy of the side reactions were 3.8 and –9.3 kcal mol^{-1}, respectively, for acetic acid and 1.6 and –18.9 kcal mol^{-1}, respectively, for 2-nitrobenzoate acid. The use of potassium salt **2a** instead of free acid **2a-H** as well as addition of basic KO*t*Bu can suppress the somewhat feasible but undesired protonation pathway to some extent to improve the yield of the targeted arylated product (Table 1).[19]

Finally, we attempted the removal of the directing group from **3ia** (Scheme 5). Upon treatment of **3ia** with a $Cu(OTf)_2$ catalyst and piperidine in THF under microwave irradiation (2 cycles), the phenanthroline moiety was readily removed to deliver the free phenol derivative **5ia** in 67% yield.[20] Although the directed and nondirected C–H arylation of phenol derivatives were already reported by several research groups, the compatibility with the nitro group still remained somewhat a challenge.[21] Thus, the synthetic advantage of present protocol is successful introduction of nitro group, which can be a good synthetic handle for further manipulations.



Scheme 3. Copper-mediated decarboxylative C–H arylation of various phenol derivatives **1** with potassium 2-nitrobenzoates **2.** Reaction conditions: **1** (0.25 mmol), **2** (0.75 mmol), $Cu(OTf)_2$ (0.50 mmol), KO*t*Bu (0.10 mmol), DMSO (5.0 mL), 90 ˚C, 20-24 h. The combined yield of monoarylated product **3** and diarylated product **3'** is shown. The ratio of **3**/**3'** is in parentheses. Value in brackets indicates NMR yield. [a] On a 1.0 mmol scale. Phen = 2-(1,10-phenanthrolyl), Ar = 2-nitrophenyl.



Scheme 4. Mechanistic studies. Phen = 2-(1,10-phenanthrolyl), Ar = 2-nitrophenyl.

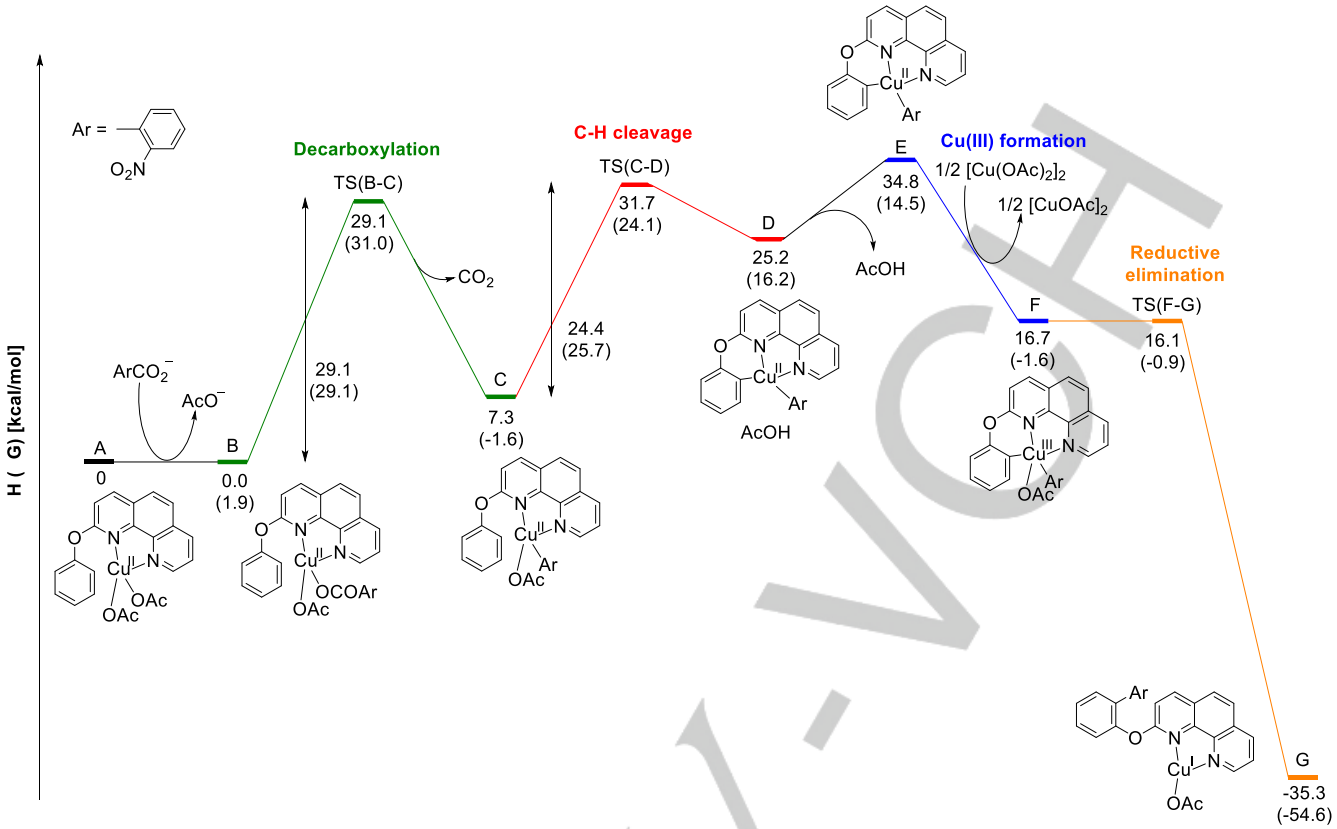
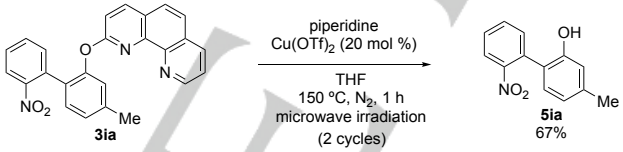


Figure 1. Enthalpy (Gibbs energy) profile of the plausible mechanism.



Scheme 5. Removal of the directing group.

Conclusions

In conclusion, we have developed a copper-mediated decarboxylative C–H arylation of phenol derivatives with potassium 2-nitrobenzoates. The phenanthroline-based N,N-bidentate auxiliary enables the otherwise challenging C–H cleavage of phenol derivatives under copper-mediated conditions to successfully expand the scope of decarboxylative C–H coupling strategy. Moreover, the directing group can be easily introduced and removed. Additionally, preliminary computational studies with DFT have also been performed to provide the plausible reaction mechanism. Further development of C–H activation reactions with copper catalysts and application of the phenanthroline-based bidentate auxiliary in more challenging C–H activation are ongoing in our laboratory.

Supporting Information Summary

Experimental section, Detailed kinetics, Characterization data, Detailed DFT studies

Acknowledgements

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Keywords: bidentate auxiliary • copper • C-H arylation • decarboxylation • phenols

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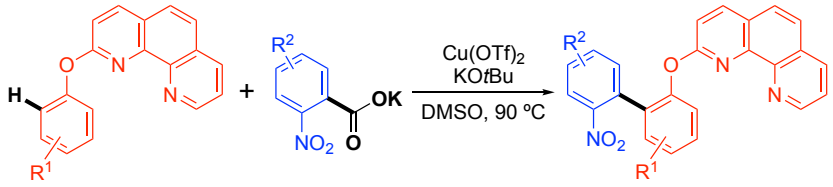

A copper-mediated decarboxylative arylation of phenol derivatives with potassium 2-nitrobenzoates via phenanthroline-directed C–H cleavage has been developed. The reaction proceeds even in the presence of copper alone to form the corresponding biaryls in synthetically useful yields. Moreover, the directing group can be easily introduced and removed. Preliminary computational mechanistic studies with DFT are also described.