Copper Catalyzed Oxidative Arylation of Tertiary Carbon Centers

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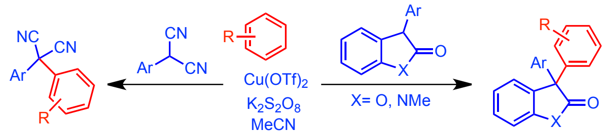
Supporting Information Placeholder



Arenes= Phenols, Anilines, Anisoles, and Heteroarenes

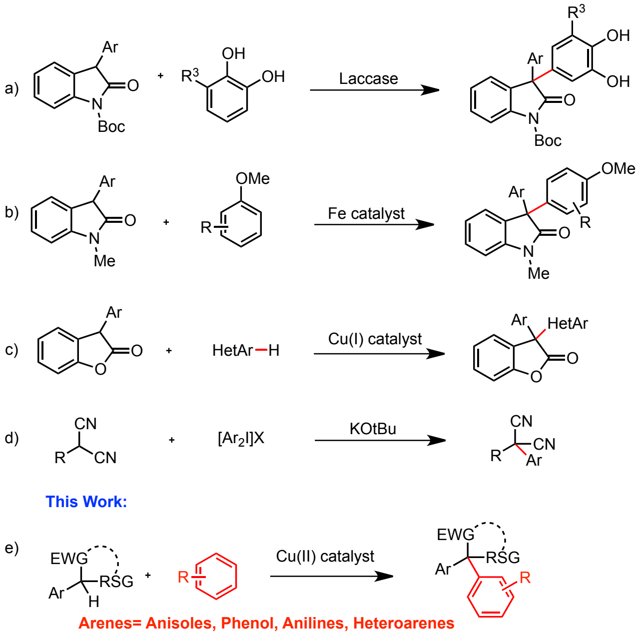
•41 examples with yield up to 98% •Mild condition •All carbon quaternary centers •Functional group tolerance

ABSTRACT: We describe herein a Cu(OTf)$_2$ catalyzed oxidative arylation of a tertiary carbon-containing substrates including aryl malononitriles, 3-aryl benzofuran-2-ones, and 3-aryl oxindoles. In some cases, the nitrile groups of the aryl malononitriles undergo further reactions leading to lactones or imines. These reaction conditions are applicable for a range of arenes, including phenols, anilines, anisoles and heteroarenes. Mechanistic studies support the formation of a cationic intermediate via a two-electron oxidation.

Quaternary carbon centers are frequently found in natural products and bioactive molecules, and their construction is still a challenging task.[1] In one approach, all-carbon quaternary centers are constructed by cross-coupling between a tertiary alkyl halide and an organometallic reagent in the presence of a transition metal catalyst.[2] Alternatively, these structures can be prepared by C-H activation reactions of one substrate and combining with either an organometallic reagent or an organic halide.[3] In recent years, oxidative coupling has drawn considerable attention due to its more step and atom economical approach.[4] This transformation avoids using pre-functionalized reagents such as organometallic reagents and organic halides and can undergo coupling with the selective cleavage of two C-H bonds. Although this transformation is highly attractive and efficient, challenges remain in the regioselective cleavage of specific C-H bonds.

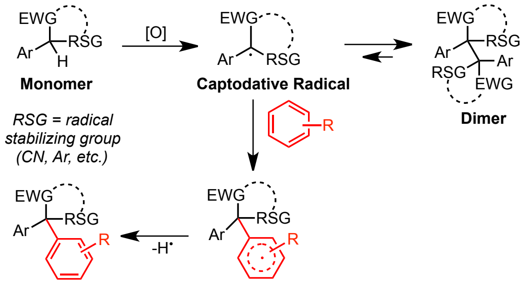
Despite recent advancements, there are limited examples of oxidative arylation on tertiary carbon centers. *ortho*-Quinones have been used as electrophiles in the arylation of tertiary aryl cyanoacetates and dicarbonyl compounds.[5,6] The Pietruszka group performed a similar arylation of 3-aryl oxindoles with Laccase as the catalyst (Scheme 1a).[7] Later, the Li group and the Loh group independently reported oxidative arylations of 3-aryl oxindoles with anisoles and heteroarenes, but no phenols, using an iron catalyst and stoichiometric graphene oxides, respectively (Scheme 1b).[8] More recently, the Kambe group reported a copper-catalyzed coupling between 3-aryl benzofuran-2-ones and heteroarenes[9] (Scheme 1c), and the Oshima group reported an iron-catalyzed coupling between azlactones and heteroarenes.[10] The nonoxidative arylation of aryl malononitriles has only been reported using diaryliodonium salts but was limited due to the nature of the iodonium species (Scheme 1d).[11] Overall, the oxidative coupling of these species with phenols and anilines has not been documented and is the focus of this report (Scheme 1e).

Scheme 1. Previous Reports and This Work



Our group previously reported the palladium-catalyzed oxidative coupling of azlactones with toluene analogs through benzylic C-H activation.[12] Recently, this reaction was also found to be effective for other hindered substrates like aryl malononitriles, aryl cyanoacetates, 3-aryl oxindoles, and 3-aryl benzofuranones.[13] The reaction forms all carbon quaternary centers and is believed to proceed via oxidation of tertiary carbon containing substrates to form dimers (Scheme 2). These dimers are in equilibrium with the monomer captodative radicals in solution at elevated temperature.[14] To take advantage of the unique ability of these substrates as radical precursors, we envisioned a novel oxidative coupling reaction of these substrates with arenes and heteroarenes (Scheme 2).

Scheme 2. Hypothesis



The resultant adducts give rise to the structural assemblies found in biologically active natural products (Figure 1)[15] In this work, we describe oxidative coupling of the tertiary carbon centers in aryl malononitriles, 3-arylbenzofuranones, and 3-aryl oxindoles with a range of arenes including phenols, anilines, and heteroarenes. Experimental and computational studies were also performed to investigate the reaction pathway.

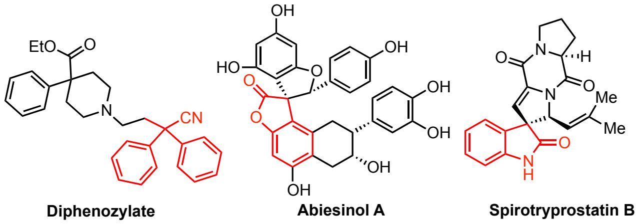
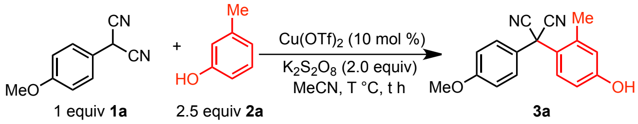


Figure 1. Selected bioactive compounds containing 3-aryl-substituted benzofuran-2-ones and oxindoles.

Our investigation commenced with 2-(4-methoxyphenyl) malononitrile **1a** and *m*-cresol **2a** as the coupling partners in the presence of 20 mol % CuCl$_2$ and $K_2S_2O_8$ in acetonitrile at 100 °C. After 24 h, the reaction furnished the oxidative coupling product in 65% (Table 1, entry 1). Use of 10 mol % Cu(OTf)$_2$ instead provided the product in 92% isolated yield at 60 °C after 15 h (entry 2). In the absence of copper salt, the reaction was slow and only afforded 19% yield after 24 h (entry 3). When *tert*-butyl hydroperoxide (TBHP) was used as an oxidant, the yield decreased significantly to 30% (entry 4). We also observed that the yield of coupled product was lower when $K_2S_2O_8$ or **2a** was reduced to 1 equivalent relative to the aryl malononitrile (entries 5 and 6).

Table 1. Development of Catalytic Arylation[a]



entry	change to conditions	T (°C)	t (h)	yield (%)[b]
1	CuCl$_2$ (20 mol %) instead of Cu(OTf)$_2$	100	24	65
2	none	60	15	96 (92)
3	no copper	60	14	19
4	*t*-BuOOH instead of $K_2S_2O_8$	60	15	30
5	1 equiv $K_2S_2O_8$	60	15	56
6	1 equiv **2a**	60	15	67

[a] Reaction condition: **1a** (0.1mmol), **2a** (0.25 mmol), Cu(OTf)$_2$ (0.01 mmol), $K_2S_2O_8$ (0.2 mmol), MeCN (0.75 mL), 60 °C for 15 h. [b] 1H NMR yields using CH$_2$Br$_2$ as an internal standard. The value in parentheses is an isolated yield.

With these optimized conditions, we examined the substrate scope of aryl malononitriles with various arenes (Scheme 3). In our initial examination, different mono-substituted and di-substituted phenols were tested with aryl malononitriles. Several phenols worked well with the yield of the coupled products up to 98% (**3a**, **3c-3l**). In addition, an anisole variant also coupled well (**3b**). Usually, the aryl malononitriles regioselectively coupled at the *para*-position of the phenols/anisole (**3a-3l**). When the *para*-position of the phenol was blocked, coupling occurred at the *ortho*-position and was accompanied by tandem coupling/cyclization to form benzofuran-2-one derivatives (**3m-3o**).[16] The proximity of phenolic and nitrile group allows the nucleophilic addition of the phenolic oxygen to the electrophilic nitrile group.

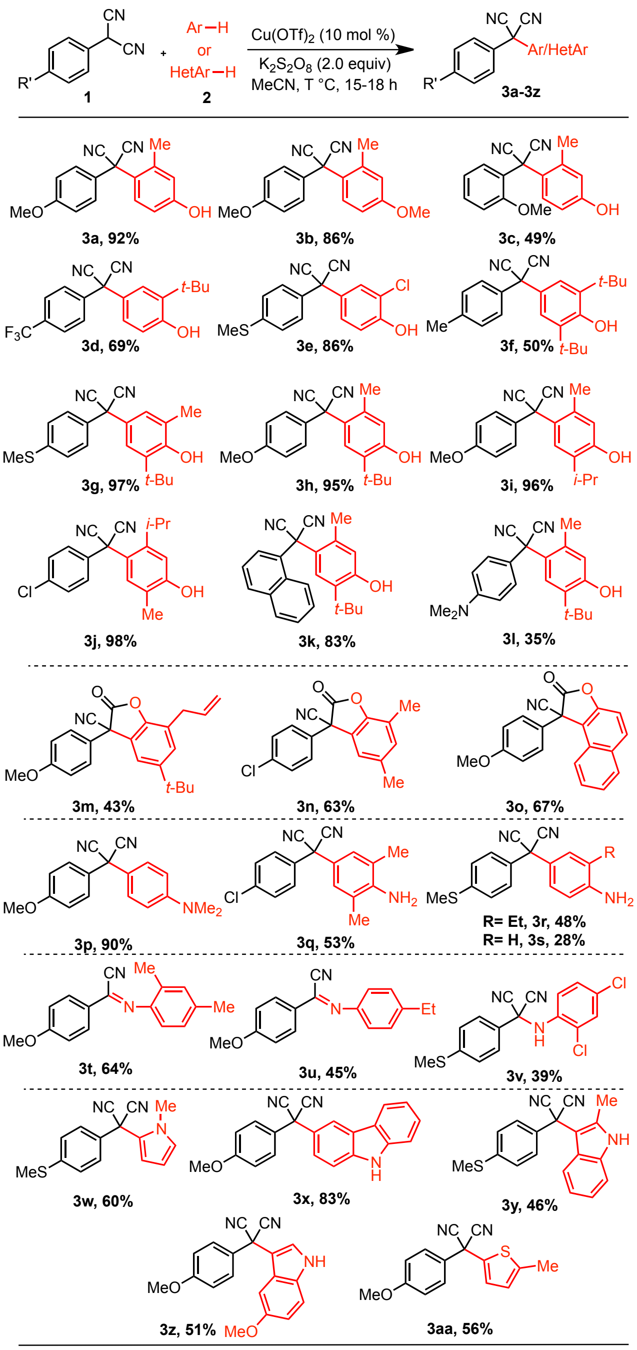
Subsequently, we investigated this reaction condition with several substituted and non-substituted anilines. *N*,*N*-Dimethylaniline generated the coupling product in excellent yield (**3p**). However, other anilines gave lower yields of the products (**3q-3s**). The lower yield may be due to the propensity of anilines to polymerize under oxidative conditions.[17] *para*-Coupling of anilines was also observed similar to that of phenols. The site selectivity correlates well to the relative nucleophilicity of the available sites both here and with phenols.[18]

Unlike the *para*-substituted phenols where cyclization was observed, *para*-substituted anilines coupled via the nitrogen centers (**3t-3v**). When electron rich anilines were employed, subsequent E1-like elimination of HCN afforded the α-imino nitriles (**3t-3u**), which are useful in the synthesis of α-amino nitriles and α-amino acids. These α-iminonitriles are usually synthesized using toxic trimethyl silane or hydrogen cyanides.[19] In accord with this hypothesis, electron-poor anilines, which would be less effective at stabilizing the cationic intermediate arising from cyanide loss in an E1-like mechanism, formed the α-aminonitrile instead (**3v**).[20]

Overall, a diverse range of outcomes were observed depending on the phenol or aniline used. *para*-Phenol coupling gave rise to a single C-C bond formation (**3a-3l**) while *ortho*-phenol coupling was accompanied by cyclization (**3m-3o**). Anilines are even more diverse with *para*-coupling (**3p-3s**), C-N coupling (**3v**), and C-N coupling accompanied by elimination(**3t-3u**).

Heteroarenes are common motifs in drug molecules and natural products. Owing to this central role, we aklso examined different heteroatom-containing arenes in these couplings. Nitrogen and sulfur derived heteroarenes were well tolerated with good to excellent yields (**3w-3aa**). On the other hand, the oxygen containing heteroarenes like furan were not effective in this reaction, which may arise from the sensitivity of furans to ring opening under oxidizing conditions.[21] Regarding the scope of aryl malononitriles, the reaction proceeded well for substrates with both electron-withdrawing and electron-donating groups. The parent 2-phenylmalononitrile afforded low yield likely due to polymerization at the *para*-position from the radical intermediate.[22] Even so, the reaction tolerates important functional groups like halides and alkenes (**3e, 3j, 3m, 3n, 3q**). The reaction performs well at larger scale (3.5 mmol) forming the product **3a** in 83% yield.

Scheme 3. Oxidative Coupling of Aryl Malononitriles With Phenols, Anilines, and Heteroarenes[a]

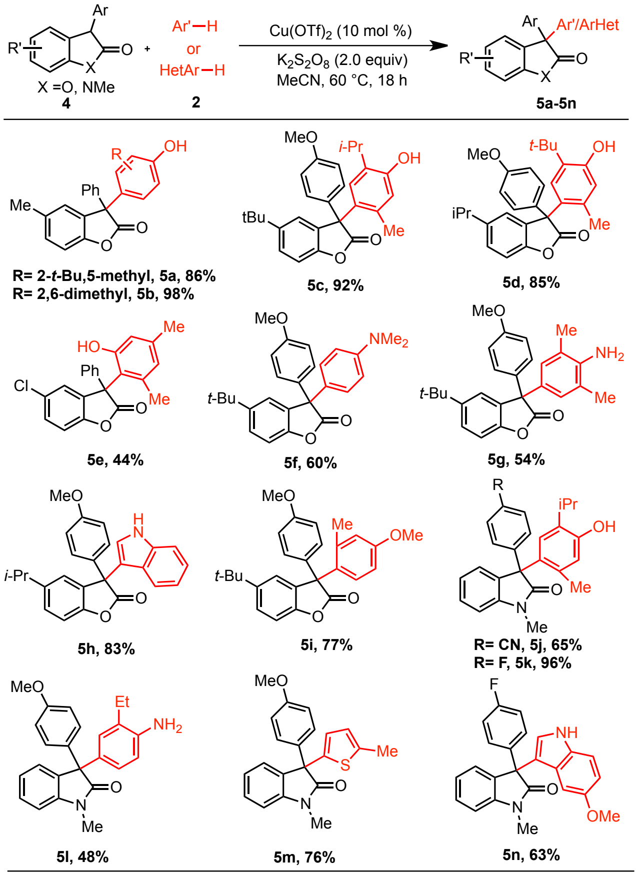


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.25 mmol), Cu(OTf)$_2$ (0.01 mmol), K$_2$S$_2$O$_8$ (0.2 mmol), acetonitrile (0.75 mL) at 60 °C or 100 °C.

Other tertiary carbon containing substrates including 3-aryl benzofuran-2-ones and 3-aryl oxindoles were investigated to establish scope of this process. These substrates are also known to undergo oxidative dimerization. As expected from this premise, these substrates were effective generating the corresponding products from phenols in moderate to excellent yields (Scheme 4, **5a-5e**, **5j-5k**), anilines (**5f-5g**, **5l**), an anisole (**5i**) and heteroarenes (**5h**, **5m-5n**). Several electron-donating and electron-withdrawing groups in these substrates as well were tolerated with a moderate to excellent yields.

Relative to other oxidative coupling methods, the scope of the current method is distinct. For example, the copper catalyzed protocols[9] and reactions of diaryliodonium salts[11] would not accommodate phenols or anilines without protection. On the other hand, the diaryliodonium salts are effective in installing a phenyl group while the current method is not (predominantly dimer is observed when benzene is employed with <5% arylation).

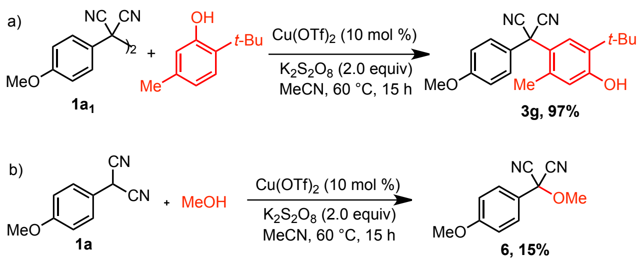
Scheme 4. Substrate Scope of 3-Arylbenzofuran-2-ones and 3-Aryloxindoles with Phenols, Anilines and Heteroarenes[a]



[a]Reaction conditions: **4** (0.1 mmol), **2** (0.25 mmol), $Cu(OTf)_2$ (0.01 mmol), $K_2S_2O_8$ (0.2 mmol), acetonitrile (0.75 mL) at 60 °C. [a]100 °C.

To learn more about whether the malononitrile, benzofuran, and oxindole dimers are involved in the reaction course, the dimer **1a**$_1$, which is known to form readily upon oxidation, was subjected with 2-*tert*-butyl *m*-cresol under the standard reaction condition. The reaction formed 97% yield of the desired product (Scheme 5a).

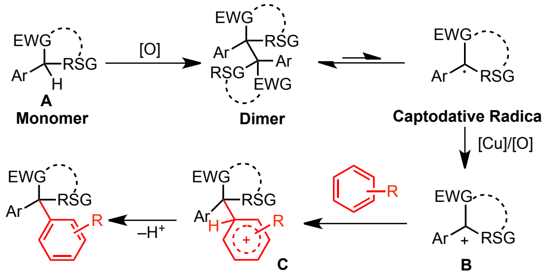
Scheme 5. Reactions with Dimer and Methanol



To assess the reactive species under oxidative conditions the oxidation potentials of 2-(4-methoxyphenyl) malononitrile and its dimer **1a**$_1$ were measured. Due to the insolubility of **1a**$_1$ in acetonitrile, the oxidation potentials were obtained in dichloromethane and were found to be 0.075 V and 0.105 V vs. SCE (see Supporting Information), respectively. Since we used $K_2S_2O_8$ (E_{ox}= 2.01 V) as an oxidant, these results suggest that the neutral substrate can undergo two successive oxidations to form a cationic species. In order to investigate the feasibility of such a cationic intermediate in the reaction, a reaction of **1a** with methanol in place of the arene partner was performed under standard conditions. The methoxy adduct **6** was isolated in 15% yield (Scheme 5b). Since alkanols are well known for trapping carbocation intermediates.[23,24]

Based on these results and the literature, a possible reaction pathway is outlined in Scheme 6. First the malononitrile (or benzofuran, oxindole) substrate oxidizes to form a dimer. This dimer remains in equilibrium with monomer radical in solution.[14] Further oxidation of this captodative radical provides cationic intermediate **B.** Nucleophilic arene addition to **B** forms arenium intermediate **C**, which upon deprotonation generates the product.

Scheme 6. Proposed Mechanism



Based on the qualitative relative rates (*para*-methoxyarylmalonontirle reacts faster than the *para*-CF_3 variant), it appears that the oxidation, not deprotonation, steps are rate limiting. Since oxidizability drives reactivity, shifting reactivity toward less substituted or more electron-poor systems will either require much stronger oxidants or a different mechanism. For example, alkyl malononitriles and oxindoles with hydrogen/alkyl in the place of the α-aryl subsitutent produced no product. Cyanoacetates also proceeded in low yield. These substrates are less capable of either stabilizing the captodative radical or carbocation intermediates in **B**.

In summary, we successfully developed simple and mild conditions to construct quaternary carbon centers via oxidative arylation catalyzed by $Cu(OTf)_2$. The reaction condition performs well with a range of substrates including aryl malononitriles, 3-arylbenzofuranones, and 3-aryloxindoles undergoing addition to several classes of arenes including phenols, anisole, anilines, and heteroarenes. Mechanistic experiments suggest the formation of tertiary carbocation intermediates which initiate S_EAr reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data (PDF)

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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