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# A Catalyst-Controlled Aerobic Coupling of *ortho*-Quinones and Phenols Applied to the Synthesis of Aryl Ethers

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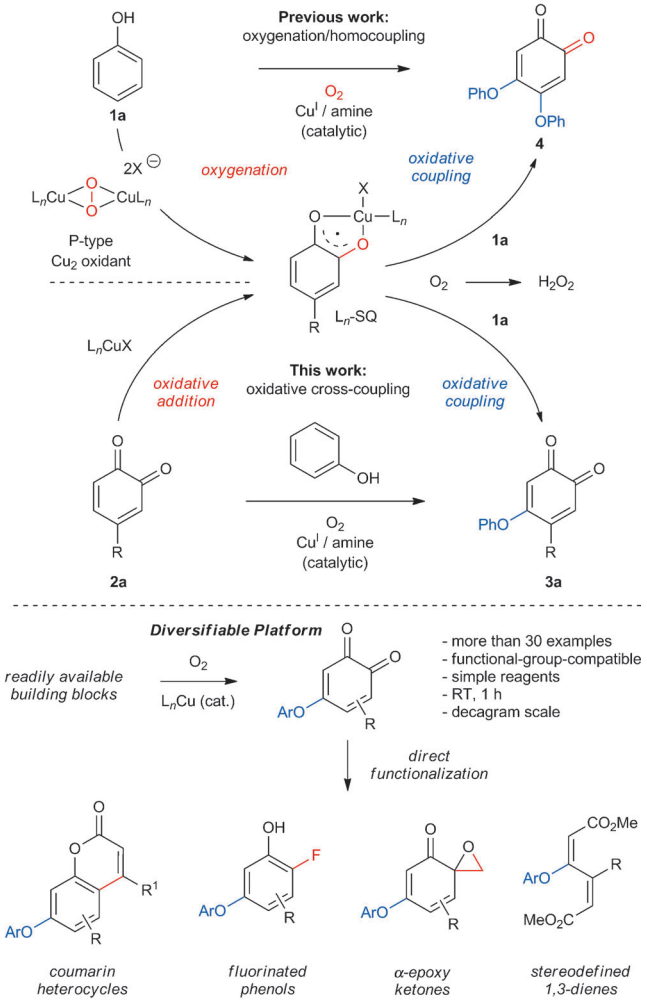
***Abstract:*** *ortho-Quinones are underutilized six-carbon-atom building blocks. We herein describe an approach for controlling their reactivity with copper that gives rise to a catalytic aerobic cross-coupling with phenols. The resulting aryl ethers are generated in high yield across a broad substrate scope under mild conditions. This method represents a unique example where the covalent modification of an ortho-quinone is catalyzed by a transition metal, creating new opportunities for their utilization in synthesis.*

In spite of their occurrence in nature,[1] materials science,[2] catalysis,[3] organometallic chemistry,[4] and synthesis,[5] *ortho*-benzoquinones have remained underexplored functional groups.[6,7] Their redox lability, complex coordination chemistry, and sensitivity towards nucleophiles are amongst the obstacles that complicate their utilization.[8] Methods that overcome these challenges benefit from downstream transformations that dramatically alter the topology and polarity of the *ortho*-quinone.[9] This can diversify chemical space around a key functional group, which we recently illustrated for oxindole heterocycles.[8] In this previous work, *ortho*-quinones were formed by *ortho*-oxygenation of a phenol with a P-type dinuclear Cu oxidant (Scheme 1).[10] This forms a $Cu^{II}$ semiquinone radical ($L_n$-SQ) following atom transfer, which undergoes coupling with the starting phenol prior to dissociation of $L_nCu^{I}$.[11] While the resulting *ortho*-quinones are versatile,[12] this method is currently limited to the homocoupling of phenols (**1a** to **4**, Scheme 1).[13]

$Cu^{II}$ semiquinones can also be formed by oxidation of $Cu^{I}$ with an *ortho*-quinone,[4b,10] which suggested to us that a cross-coupling between a phenol and an *ortho*-quinone might provide a more versatile fragment coupling. Existing addition reactions to *ortho*-quinones are either low-yielding or limited in scope, and have not been investigated as general synthetic methods.[14] Successful reaction development would require chemoselectivity for cross-C–O bond formation over oxidative homocoupling[15] or *ortho*-oxygenation of the phenol,[16] while avoiding decomposition of the *ortho*-quinone. Herein, we overcome these challenges and describe a catalytic aerobic synthesis of vinyl aryl ethers by an *ortho*-quinone/phenol cross-coupling. Ligand and counterion effects have a pronounced impact on rate and selectivity, and provide parameters for optimization that extend the method to a broad selection of coupling partners. Aryl ethers are omnipresent in natural products, pharmaceuticals, agrochemicals, and materials,[17] justifying continued efforts to improve the efficiency of their synthesis.[18] Our reactions employ commercially available components, occur at room temperature in 1 h, and provide access to a diverse array of aryl ethers by post-coupling diversification of the *ortho*-quinone (Scheme 1).




***Scheme 1.*** Synthesis and reactivity of *ortho*-quinones.

The challenges of utilizing *ortho*-quinones are highlighted by the reaction of phenol (**1a**) and 4-*tert*-butyl-*ortho*-quinone (**2a**; Table 1). As a homogenous solution in $CH_2Cl_2$, **1a** and **2a** undergo about 25% decomposition upon standing for 1 h (entry 1). Upon addition of catalytic amounts of either *N*,*N*′-di-*tert*-butyl-ethylenediamine (DBED) or 4-methoxypyridine (4-MeO-Py; see below for why these amines were chosen),

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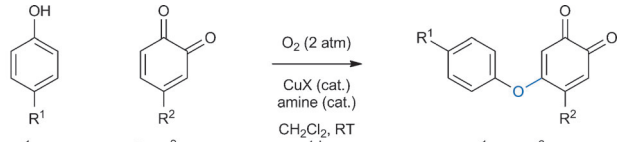
***Table 1:*** Optimization of the reaction conditions.[a]




**1a**: $R^1$ = H
**1b**: $R^1$ = OMe
**1c**: $R^1$ = CN

**2a**: $R^2$ = *t*Bu
**2b**: $R^2$ = Me

**3a**: $R^1$ = H / $R^2$ = *t*Bu
**3b**: $R^1$ = H / $R^2$ = Me
**3c**: $R^1$ = OMe / $R^2$ = Me
**3d**: $R^1$ = CN / $R^2$ = Me

| Entry | Phenol | Quinone | CuX (mol%) | Amine (mol%) | Conv. [%] **1**/**2** | **3a–3d**[b] (yield [%]) |
|---|---|---|---|---|---|---|
| 1[c] | **1a** | **2a** | – | – | 8/17 | – |
| 2[c] | **1a** | **2a** | – | DBED (5) | 33/81 | **3a** (20) |
| 3[c] | – | **2a** | – | DBED (20) | –/40 | – |
| 4[c,d] | – | **2b** | – | DBED or 4-MeO-Py (20) | –/100 | – |
| 5[e] | **1a** | **2a** | $CuPF_6$ (4) | DBED (5) | 58/48 | **3a** (40) |
| **6** | **1a** | **2a** | **CuBr (4)** | **DBED (5)** | **100/100** | **3a (97)** |
| **7**[f] | **1a** | **2a** | **CuBr (4)** | **4-MeO-Py (10)** | **97/100** | **3a (97)** |
| **8**[f,g] | **1a** | **2b** | **CuCl (10)** | **4-MeO-Py (20)** | **81/100** | **3b (73)** |
| 9[f,g] | **1b** | **2b** | CuCl (10) | 4-MeO-Py (20) | >95/>95 | **3c** (74) |
| 10[g] | **1b** | **2b** | CuCl (10) | DBED (10) | >95/>95 | **3c** (<5) |
| 11[g] | **1c** | **2b** | CuCl (10) | DBED (10) | 86/>95 | **3d** (79) |
| 12[f,g] | **1c** | **2b** | CuCl (10) | 4-MeO-Py (20) | 22/>95 | **3d** (<10) |

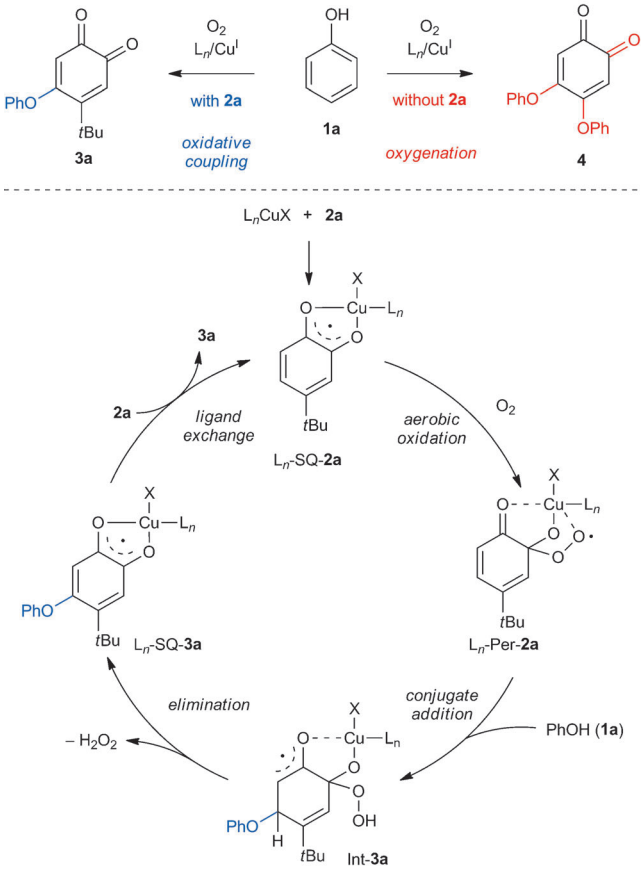
[a] The reactions were performed with 0.5 mmol of **1** and 0.5 mmol of **2**. [b] Yield determined by $^1$H NMR spectroscopy using hexamethylbenzene as an internal standard. [c] Reactions performed under $N_2$. [d] Reaction time: 5 min. [e] Reaction time: 4 h. [f] With 4 Å M.S. (100 mg). [g] 0.75 mmol of **2** were slowly added over 10 min.

a complex mixture quickly evolves, from which **3a** is isolated in low yield (entry 2). Factors leading to decomposition include the sensitivity of **2a** towards the amine (entry 3), and redox exchange between **3a** and quinone **2a**.[19] These problems are amplified for 4-methyl-*ortho*-quinone (**2b**), which undergoes complete decomposition within 5 min under similar conditions (entry 4).

The addition of $Cu^I$ salts and molecular oxygen ($O_2$) has a dramatic impact on the selectivity and rate of the reaction. In the presence of $[Cu(CH_3CN)_4](PF_6)$ (abbreviated as $CuPF_6$), DBED, and 2 atm of $O_2$, the addition becomes selective for **3a** at about 50% conversion after 4 h (entry 5). By simply changing to a halide counterion, the reaction is complete after only 1 h, and the yield of **3a** is >95% (entry 6). An equally pronounced effect is observed for the ligand. After an extensive survey (>20 amines; see the Supporting Information, Table S2), only 4-MeO-Py emerged as an equally efficient ligand for the coupling of **1a** and **2a** in the presence of 4 Å molecular sieves (M.S.; entry 7).

DBED and 4-MeO-Py display a surprising, yet highly desirable, complementarity that enables couplings of either electron-rich or electron-poor phenols. This is illustrated with quinone **2b**, whose overall sensitivity requires slow addition to the reaction mixture over 10 min (entry 8). **2b** undergoes a relatively clean coupling with electron-rich phenol **1b** in the presence of 4-MeO-Py (entry 9), whereas the use of DBED leads to complete decomposition (entry 10). In contrast, DBED promotes the coupling of **2b** with electron-poor phenol **1c** (entry 11), whereas 4-MeO-Py does not (entry 12). Fine-tuning reaction conditions by ligand design is a hallmark of traditional metal-catalyzed cross-coupling reactions.[20] Our results suggest that a similar opportunity may extend to metal semiquinones.

A working mechanistic hypothesis that considers the ligand and counterion effects, the requirement for $O_2$, and the complete absence of **4** is presented in Scheme 2. The catalytic cycle begins with oxidation of $L_nCuX$ with **2a** to provide $L_n$-SQ-**2a**. Stack, Pierpont, and our group have previously shown that amines influence the geometry, nuclearity, and electronic structure of Cu semiquinones,[4b,21] which helps explaining the pronounced ligand and counterion effects on rate and selectivity.[22] The requirement of $O_2$ for selective C–O coupling leads us to propose an aerobic oxidation of $L_n$-SQ-**2a** prior to C–O bond formation, which should be accelerated by more-coordinating counterions, such as Cl or Br, relative to $PF_6$. The resulting peroxide ($L_n$-Per-**2a**)

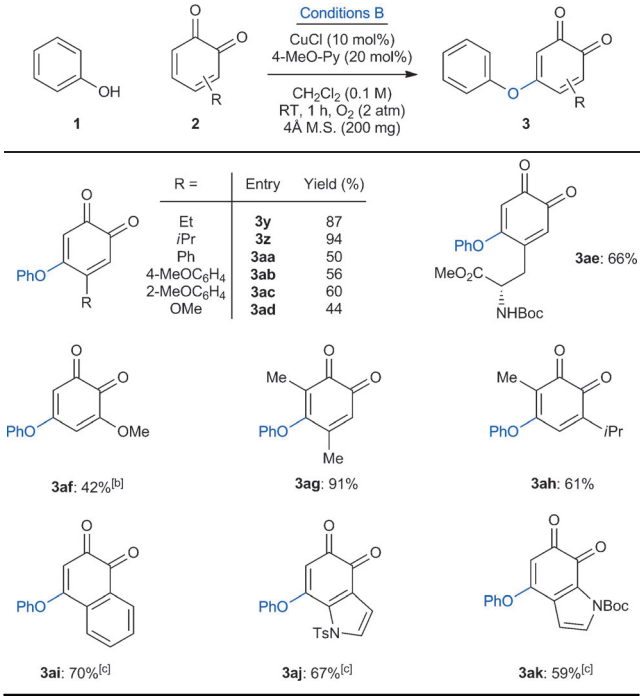



***Scheme 2.*** Mechanistic proposal for the catalytic aerobic coupling of **1a** and **2a** to **3a**.

resembles complexes of Fe,[23] Cu,[24] Co,[25] Rh,[26] and Ir,[27] involved in both the enzymatic and non-enzymatic cleavage of semiquinones to muconic esters.[24a,28] Oxidative cleavage is avoided under our conditions by trapping of $L_n$-Per-**2a** with **1a**, in what we tentatively describe as a radical addition.[29] Elimination of $H_2O_2$ would then provide $L_n$-SQ-**3a**,[26–27] and would form the key C–O bond of the product while avoiding redox exchange.[8] Ligand exchange with **2a** would then release **3a** and close the catalytic cycle. The chemoselectivity for **3a** over **4** (Scheme 2) results from the sequestration of $Cu^{I}$ as a $Cu^{II}$ semiquinone, preventing $O_2$ activation as a P-type oxidant, and thus *ortho*-oxygenation of **1a** (Scheme 1).[11] This is a rare example of chemoselective oxidation over oxygenation,[16] which finds parallels in the work of Kozlowski and Stahl.[30]

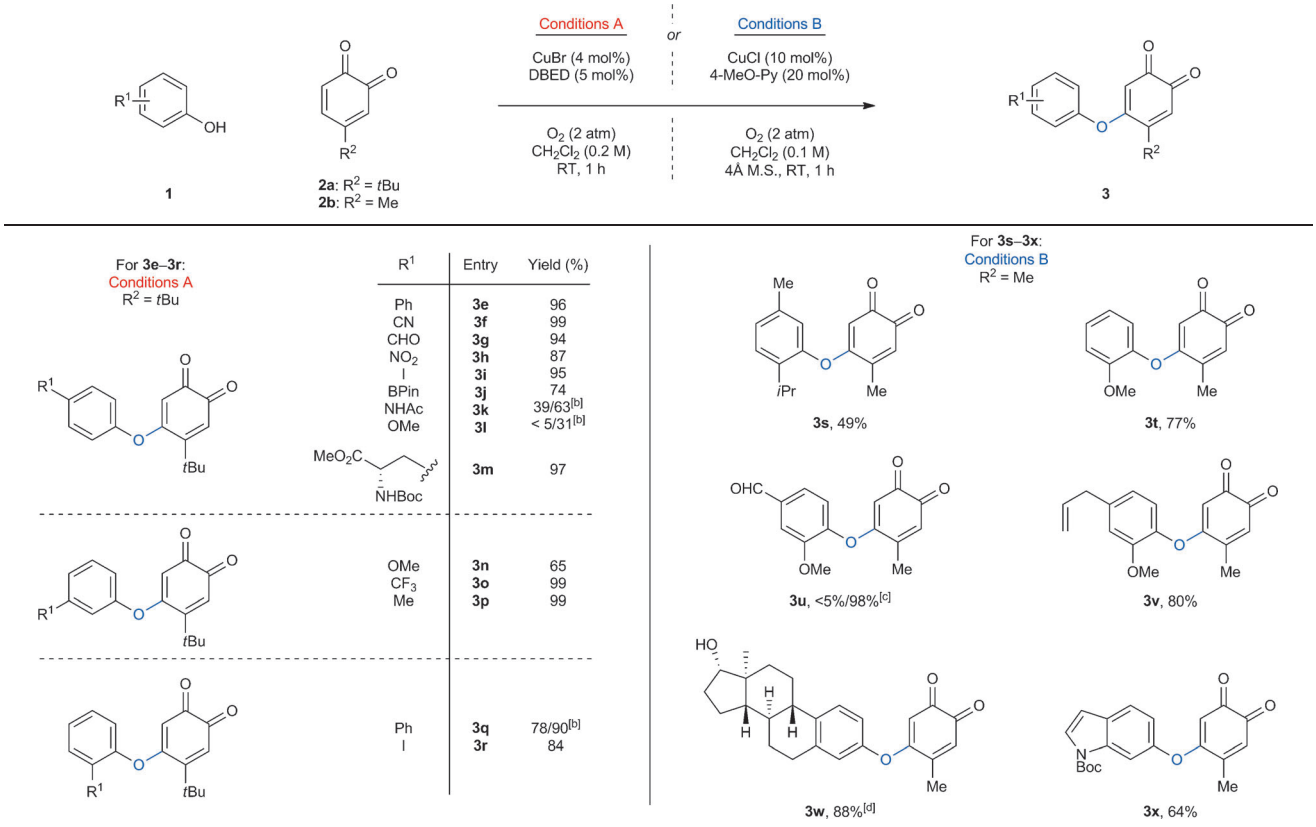
Coupling remains efficient across a broad range of phenols (Table 2) and can include substituents that are used in more traditional cross-coupling reactions (**3i**, **3j**, and **3r**) or groups that are sensitive to aerobic oxidation (**3g**, **3j**, **3m**, **3p**, and **3u**–**3w**). The scope of the *ortho*-quinone is equally broad (Table 3), and includes alkyl, aryl, and heteroatom substitution (**3y**, **3z**, **3ae**, and **3ag**), demonstrating regioselectivity for either the less sterically encumbered (**3ah**) or more electrophilic position of the quinone (**3af**). Fused quinones, including *ortho*-naphthoquinone and the 4,5- and 6,7-quinones of

***Table 3:*** Quinone scope.[a]

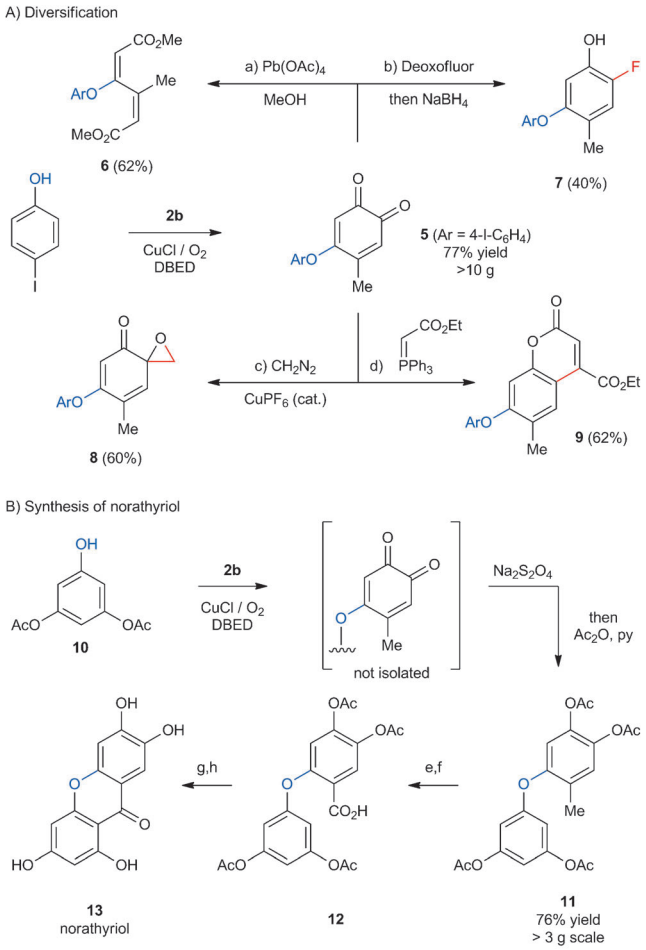



[a] The reactions were performed with 1 mmol of **1** and 1.5 mmol of **2**. **2** was added to the reaction mixture over 10 min. [b] CuCl (20 mol%) and 4-methoxypyridine (40 mol%) were used. [c] 1 mmol of **2** was used; reaction time: 4 h.

***Table 2:*** Phenol scope.[a]




[a] The reactions were performed with 1.0 mmol of **1** and 1.0–1.5 mmol of **2**. [b] 4-Methoxypyridine (10 mol%) with 200 mg of 4 Å M.S. [c] DBED (10 mol%) without 4 Å M.S. [d] Reaction performed on 0.1 mmol scale, with a catalyst loading of 15 mol%.




***Scheme 3.*** Diversification of *ortho*-quinone **5** and synthesis of norathyriol (**13**). Conditions: a) $Pb(OAc)_2$ (2.2 equiv), MeOH/PhMe, RT, 18 h, 62%; b) Deoxofluor, $CHCl_3$, 0 °C→RT, 1 h, then $NaBH_4$, DBU, MeOH, 50 °C, 30 min, 40%; c) $[Cu(MeCN)_4](PF_6)$ (4 mol%), $CH_2N_2$, THF, −78 °C→RT, 30 min, 60%; d) $Ph_3P{=}CHCO_2Et$ (2 equiv), $CH_2Cl_2$, 40→100 °C, 4 h, 62%; e) benzoyl peroxide (10 mol%), *N*-bromosuccinimide (1.2 equiv), $CCl_4$, 80 °C, 4 h, then *N*-methylmorpholine *N*-oxide (3 equiv), MeCN, RT, 12 h, 73% yield; f) $NaClO_2$ (3 equiv), $NaH_2PO_4$, $DMSO/H_2O$, RT, 2 h, 71% yield; g) $(CF_3CO)_2O$ (2 equiv), $CH_2Cl_2$, RT, 30 min, then $BF_3{\cdot}Et_2O$ (5 equiv), RT, 2 h, 87%; h) $K_2CO_3$ (5 equiv), RT, 12 h, 87% yield over two steps.

indole (**3aj** and **3ak**), are also tolerated, whereas *para*-quinones are not.

The decagram synthesis and diversification of **5** highlights the versatility of *ortho*-quinones (Scheme 3A). As the two carbonyl groups in **5** are electronically differentiated, deoxyfluorination,[31] Wittig olefination,[32] and nucleophilic addition[33] occur selectively at the more electrophilic carbon atom, directly elaborating **5** into *ortho*-fluorophenol **7**, coumarin **9**, or α-epoxy ketone **8**. Alternatively, cleavage of the diketone with lead tetraacetate in methanol[34] provides muconic ester **6** as a single geometric isomer, which underscores the diversity of aryl ethers that can be accessed from a single *ortho*-quinone precursor.

Our method also provides a unique and convergent synthesis of the xanthone norathyriol (**13**; Scheme 3B).[35] Norathyriol and its C-glycosylated analogue mangiferin[36] are xanthone natural products isolated from the skin of mangoes that exhibit a broad range of biological activities.[37] The synthesis of **13** is accomplished by cross-coupling of phloroglucinol **10** with **2a** on multigram scale (Scheme 3B). Oxidation of the C5 methyl group to the carboxylic acid provides **12**, which is subsequently converted into **13** by a Friedel–Crafts acylation.

In summary, we have developed a mild and diversifiable synthesis of aryl ethers that highlights the synthetic value of *ortho*-quinones. An important future direction will explore the reactivity of metal–quinone complexes more generally, as they provide a unique mechanism for controlling covalent modification. Metal semiquinones have been studied as non-innocent ligands with unique electronic properties, but mainly for applications in materials science. Our work makes an important departure from this precedent, and demonstrates that these non-innocent ligands can also be viewed as redox-active substrates that are suitable for dehydrogenative coupling.[38] This highlights the increasingly popular trend of controlling organic radical chemistry with organometallic complexes as the reactivity of these species can be carefully tuned by ligand design.[39]

## Acknowledgements

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**Keywords:** aerobic oxidation · aryl ethers · copper catalysis · *ortho*-quinones · phenols

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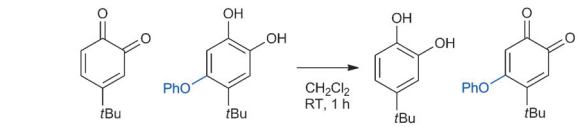


**2a** cat-**3a** cat-**2a** **3a**

Conversion: 75% 100% Yield: 64% 50%

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# Communications

## Copper Catalysis

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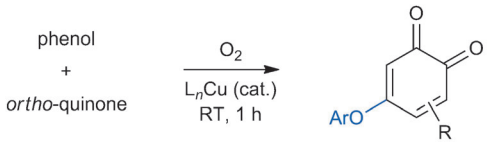
A Catalyst-Controlled Aerobic Coupling of *ortho*-Quinones and Phenols Applied to the Synthesis of Aryl Ethers




**The reactivity** of *ortho*-quinones can be controlled with copper, and a catalytic aerobic cross-coupling with phenols was developed that provides access to a broad range of aryl ethers under mild conditions. This reaction is a unique example of covalently modifying an *ortho*-quinone in the presence of a transition-metal catalyst, creating new opportunities for their utilization in synthesis.