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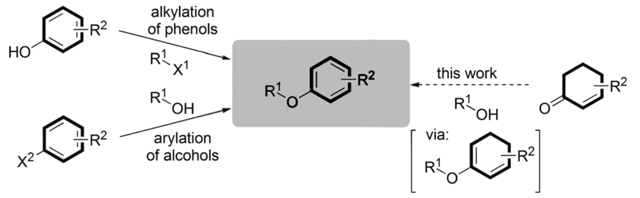
Aryl Ether Formation

Catalytic Aerobic Synthesis of Aromatic Ethers from Non-Aromatic Precursors**

Marc-Olivier Simon, Simon A. Girard, and Chao-Jun Li*

Aryl ethers are ubiquitous compounds and intermediates widely used in the synthesis of dyes, cosmetics, materials, fragrances, plant protection agents, stabilizers for plastics, natural products, and pharmaceuticals.[1] Within these molecules, the ether functionality confers particular properties to the aromatic ring. The ability to synthesize aryl ethers with a wide range of aliphatic and aromatic moieties represents a challenge and has thus attracted constant interest throughout the history of organic chemistry. Nevertheless, all existing methods for the preparation of aromatic ethers are based on the same reaction schemes, starting from aromatic precursors, either with a pre-existing oxygen atom (phenols) or with a pre-installed reactive functionality (Scheme 1, left). For example, aryl alkyl ethers can be prepared by nucleophilic substitution reactions of either a phenol with an aliphatic substrate (Williamson reaction),[2,3] or of an alcohol with an aromatic precursor.[4] In the same manner, other approaches have been developed more recently, such as transition-metal-catalyzed allylic O alkylation reactions of phenols, electrophilic addition reactions of phenols to alkenes,[5] coupling reactions between alcohols and aryl halides through palladium (Buchwald–Hartwig reaction)[6] or copper (Ullmann ether synthesis)[7,8] catalysis, and copper-catalyzed coupling reactions of alcohols with arylboron (Chan-Lam type coupling)[9] or arylbismuth[10] compounds, but all these approaches still require aromatic substrates. In addition, stoichiometric amounts of unwanted by-products are generated in most of these syntheses, which goes against the trend of developing more environmentally friendly processes.[11]



Scheme 1. General approaches for the preparation of aryl ethers

The development of new synthetic approaches toward known molecules is highly desirable, as it goes hand in hand with a re-evaluation of known procedures and generally allows access to a wider variety of related structures. We herein report a novel methodology for the synthesis of aromatic ethers through oxidative condensation of alcohols and 2-cyclohexenones (Scheme 1, right).

We reasoned that a straightforward and convenient approach toward aryl ethers could involve the in situ generation of the aromatic moiety through condensation of an alcohol and a 2-cyclohexenone, followed by an oxidative aromatization (Scheme 1, right). This pathway is very attractive, as it formally consists of the elimination of water and two hydrogen atoms from the starting materials. However, such a reaction is very challenging, because it requires the right catalyst that will efficiently mediate the formation of the adduct and its selective oxidation in the presence of the alcohol[12] and the 2-cyclohexenone,[13] both of which can potentially be oxidized. A few examples of such a reactivity have been reported earlier, but they suffer from the use of several equivalents of relatively expensive metal oxidants and the use of an alcohol as solvent.[14] It occurred to us that the use of copper catalysts might address this issue, because of their dual properties of Lewis acidity and oxidizing ability.[15–17]

To begin our study, we investigated the reaction of 3-phenyl-1-propanol (**1a**) with 2-cyclohexenone (**2a**; Table 1). We found that use of $CuCl_2$ in toluene under an O_2 atmosphere at 100 °C led to aryl alkyl ether **3aa** with a yield of 96 % (Table 1, entry 1). Interestingly, running the reaction under O_2 allowed the use of only one equivalent of the copper source instead of the two equivalents theoretically required, which was confirmed by the lower yield obtained under an inert atmosphere (Table 1, entry 2). Other copper sources were also screened (Table 1, entries 3–12). $CuBr_2$ was less effective with a yield of 44 % (Table 1, entry 3), and copper(I) halide complexes did not seem to catalyze the reaction (entries 4–6). Copper(I) and copper(II) trifluoromethanesulfonate showed moderate activities and gave the ether in 24 % and 21 %, respectively (Table 1, entries 7–8). Other precursors, such as CuO, $CuSO_4$, and $Cu(CN)_2$, did not afford any product (Table 1, entries 9–11). Finally, hydrated $CuCl_2$ turned out to be as efficient as anhydrous $CuCl_2$ and led to **3aa** with a yield of 97 % (Table 1, entry 12).

The optimized conditions were then applied to a wide range of substrates (Scheme 2). Phenyl alkyl ethers were obtained very efficiently from the reaction of 2-cyclohexenone and various primary and secondary alcohols.

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[*] Dr. M.-O. Simon, S. A. Girard, Prof. Dr. C.-J. Li
Department of Chemistry and FQRNT Center for
Green Chemistry and Catalysis, McGill University
Montreal, QC, H3A 2K6 (Canada)
E-mail: cj.li@mcgill.ca
Homepage: http://cjli.mcgill.ca/cj page.htm

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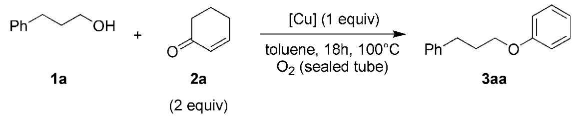
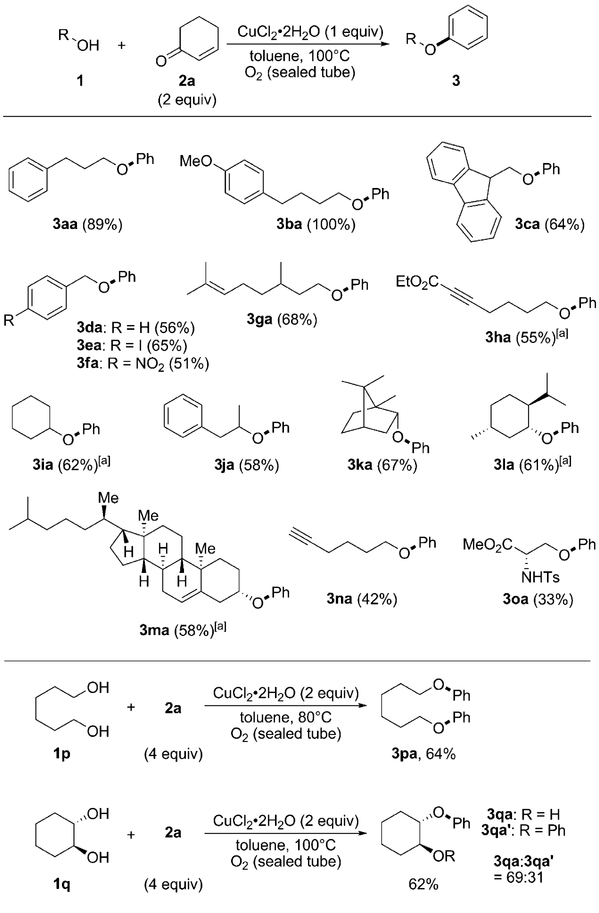
In particular, several functional groups, such as methoxy (**3ba**), nitro (**3fa**), ester, and internal alkynes (**3ha**), were well tolerated in this reaction. In addition, the reaction proceeded readily in the presence of an iodo-substituted aromatic derivative (**3ea**), which allows further functionalizations through classical coupling reactions.[18] Natural functionalized alcohols, such as β-citronellol (**3ga**), (−)-borneol (**3ka**), (−)-menthol (**3la**), and cholesterol (**3ma**), were also successfully converted into the corresponding phenyl ethers with good yields. Interestingly, 5-hexyn-1-ol, which bears a terminal alkyne functionality, can also be functionalized under these conditions (**3na**). Protected serine could also be used in this reaction, though it afforded the ether **3oa** in a moderate yield. 1,6-Diphenoxyhexane **3pa** was also prepared from 1,6-hexanediol (**1p**) and afforded the diether as the sole product. However, in the case of a secondary diol, such as *trans*-1,2-cyclohexanediol (**1q**), a mixture of mono- and diether (**3qa** and **3qa′**, respectively) was obtained with a good overall yield. The corresponding aryl ether was not observed when a tertiary alcohol (likely because of a steric effect) or phenol was used under the present conditions.

Table 1: Optimization of the copper catalyst for the oxidative condensation of **1a** with **2a**.



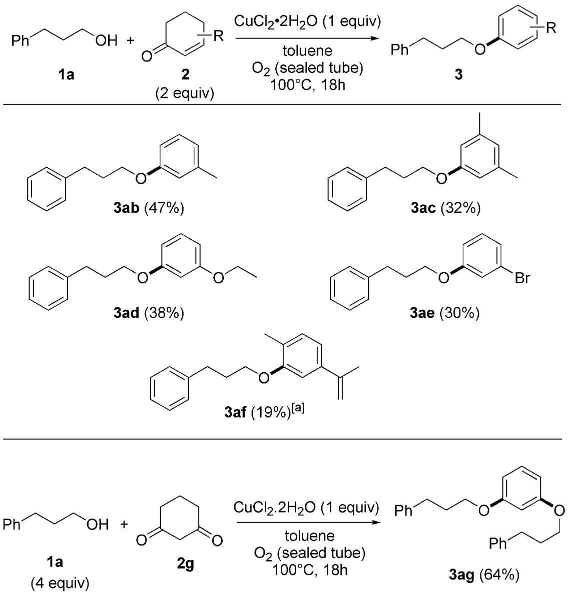
Entry	[Cu]	Yield [%][a]
1	$CuCl_2$	96
2	$CuCl_2$	38[b]
3	$CuBr_2$	44
4	CuCl	0
5	CuBr	9
6	CuI	0
7	$Cu(OTf)_2$	21
8	$[Cu(OTf)]_2$·toluene	24
9	CuO	0
10	$CuSO_4$	0
11	$Cu(CN)_2$	0
12	$CuCl_2·2\,H_2O$	97

[a] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] Reaction performed under inert argon atmosphere at 130 °C. OTf = trifluoromethanesulfonate.



Scheme 2. Oxidative condensation of alcohols and diols with 2-cyclohexenone. Reaction conditions: alcohol, **2a** (2 equiv), $CuCl_2·2\,H_2O$ (1 equiv), toluene, O_2, 100 °C, 18 h. Yields of isolated products are given. [a] Reaction conducted at 80 °C.

We also studied various 2-cyclohexenone derivatives to afford functionalized aryl ethers (Scheme 3). The reaction of 3-methyl-, 3,5-dimethyl-, 3-ethoxy-, and 3-bromo-substituted 2-cyclohexenone with **1a** proceeded smoothly under the optimized conditions, leading to the corresponding ethers in 30–47 % yield (**3ab**–**3ae**). Interestingly, even (*R*)-carvone could be used as a substrate, though at a higher temperature, and afforded **3af** with a low yield of 19 %. Finally, we also considered the reaction of **1a** with 1,3-cyclohexanedione **2g** (Scheme 3, bottom) and obtained diether **3ag** in 64 % yield.

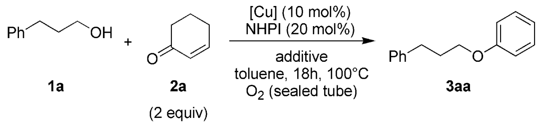


Scheme 3. Copper-catalyzed reaction of substituted 2-cyclohexenones and cyclohexane-1,3-dione (**2g**) with 3-phenyl-1-propanol (**1a**). Reaction conditions: alcohol, **2a** (2 equiv), $CuCl_2·2\,H_2O$ (1 equiv), toluene, O_2, 100 °C, 18 h. Yields of isolated products are given. [a] Reaction conducted at 130 °C.

In our continued efforts to develop more sustainable chemical reactions,[19] we next attempted to further improve this reaction by reducing the amount of copper catalyst required and using O_2 as the sole terminal oxidant. Toward this goal, we investigated the oxidative condensation of 3-

phenylpropan-1-ol (**1a**) with 2-cyclohexenone (**2a**) in the presence of 10 mol% of copper complexes and 20 mol% of *N*-hydroxyphthalimide (NHPI; Table 2). NHPI is a cheap and nontoxic precursor of the phthalimido-*N*-oxyl (PINO) radical, which is the actual reactive species that can abstract hydrogen atoms from organic molecules.[20] However, under these conditions, the use of $CuCl_2$ only gave the expected product in 6% yield (Table 2, entry 1). A screening of copper sources showed that $Cu(OTf)_2$ was the most active copper complex and allowed the formation of **3aa** in 47% yield (Table 2, entry 2; for additional screening results, see the Supporting Information, Table S1, entries 1–15). Subsequently, we studied the effect of various additives (Table S1, entries 16–41), and the addition of potassium iodide stabilized the catalytic species by preventing the formation of a dark precipitate, thus significantly improving the reaction and leading to **3aa** in 68% yield (Table 2, entry 3). NHPI turned out to be crucial, because only 13% of product was generated in its absence (Table 2, entry 4). Addition of one equivalent of water also proved to be beneficial, allowing the formation of the product in 86% yield (Table 2, entry 5). Finally, conducting the reaction under 1 bar of O_2 further increased the yield to 92% (Table 2, entry 6), which is comparable to the result obtained under the previous conditions (Scheme 2).

Table 2: Optimization of the reaction conditions for the oxidative condensation of **1a** with **2a** using catalytic amounts of copper.



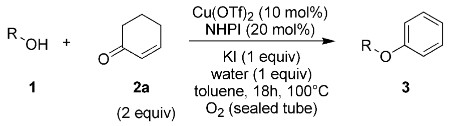
Entry	[Cu]	Additive (equiv)	Yield [%][a]
1	$CuCl_2$	–	6
2	$Cu(OTf)_2$	–	47
3	$Cu(OTf)_2$	KI (1)	68
4[b]	$Cu(OTf)_2$	KI (1)	13
5	$Cu(OTf)_2$	KI (1), water (1)	86
6[c]	$Cu(OTf)_2$	KI (1), water (1)	92 (83)[d]

[a] Yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] Reaction run without NHPI. [c] Reaction run under 1 bar of O_2. [d] Yield of isolated product.

We next investigated the scope of the reaction under these conditions (Table 3) and found that aryl ethers could be isolated with similar yields as under the initial conditions. In some cases, however, a higher temperature was found to be helpful to achieve higher conversions (Table 3, entries 4–6, 8, and 10), particularly in the case of benzylic alcohols.

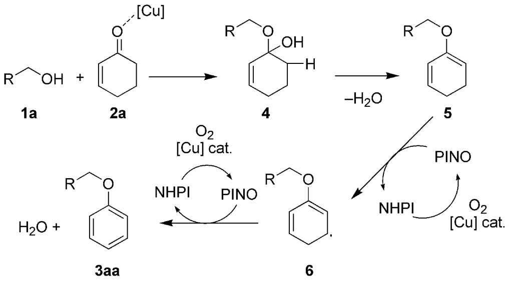
To gain insights into this reaction, several control experiments were carried out to elucidate the mechanism. When cyclohexenone **2a** was reacted under both optimized conditions in [D$_8$]toluene, no phenol was detected, whereas **3aa** was quantitatively formed in the presence of **1a**. When cyclohexanone was used, no reaction was observed. The use of phenol instead of **2a** under both reaction conditions did not afford any product. However, when the commercially available 1-methoxy-1,3-cyclohexadiene was submitted to the optimized conditions in [D$_8$]toluene, anisole was formed as the sole product. The following mechanism can thus be proposed (Scheme 4). The hemiacetal **4** may be formed through electrophilic activation of the ketone by the copper complex, and elimination of water could lead to the alkoxydiene **5** (or an isomer). The abstraction of a hydrogen atom by the in situ formed *N*-oxyl radical would lead to **6**, which undergoes another abstraction of a hydrogen atom to afford **3aa**.[20]

Table 3: Scope of the copper-catalyzed oxidative condensation.



Entry	Product	Yield[a]	Entry	Product	Yield[a]
1	**3aa**	83	8[b]	**3ha**	49
2	**3ba**	58	9	**3ia**	71
3	**3ca**	73	10[b]	**3ja**	64
4[b]	**3da**	38	11	**3ka**	40
5[b]	**3ea**	59	12	**3la**	81
6[b]	**3fa**	60	13	**3ma**	39
7	**3ga**	74			

[a] Yields of isolated products. [b] Reaction conducted at 120°C for 24 h.



Scheme 4. Proposed mechanism for the formation of aryl alkyl ether **3aa** from **1a** and **2a**.

In summary, we have developed an original approach for the synthesis of aryl ethers. The method advantageously enriches and complements the existing toolbox used by synthetic chemists, and allows a straightforward access to a wide range of functionalized products. In addition, the catalytic reaction with O_2 as the terminal oxidant generates water as the only by-product and provides a “greener” approach to aryl ethers. Considering the wide utility of ethers, these results will certainly pave the way for important applications and developments in both the academic and industrial fields through the shortening and simplification of synthetic sequences.

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