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Cu-Catalyzed Oxidative C(sp^2)–H Cycloetherification of *o*-Arylphenols for the Preparation of Dibenzofurans

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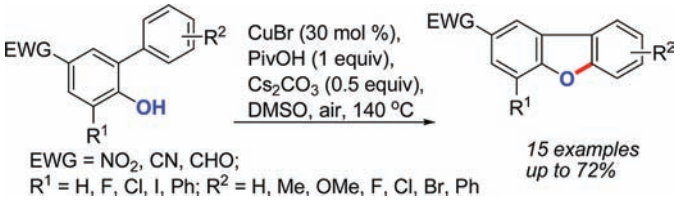
ABSTRACT



A new process involving copper-catalyzed aerobic C(sp^2)–H activation, followed by cycloetherification, has been developed. This reaction serves as a direct method for the preparation of multisubstituted dibenzofurans starting with *o*-arylphenols. The presence of a strong *para*-electron-withdrawing group (*e.g.*, NO_2) on the phenol is essential for the success of the reaction.

Transition-metal-catalyzed C–H functionalization serves as an atom-economical and environmentally benign alternative for C–C and C–heteroatom bond formation. Substantial advances have been made during the past decade in developing these processes.[1] In most cases, the requirement for a directing group in the substrate lessens the advantageous impact of C–H functionalization processes over other traditional methods that use prefunctionalized C–(pseudo)halogen bond-containing substrates. However, intramolecular C–H heterofunctionalization, in which heteroatoms act as directing groups as well as intramolecular nucleophiles, are ideal and atom-economical processes that can be used for the construction of heterocyclic architectures.[2] Following the pioneering efforts by Buchwald in 2005,[3a] this strategy has been applied to the preparation of a variety of N-heterocycles,[3] especially carbazoles.[3a–f]

In contrast, applications of a similar strategy to the preparation of oxygen-containing heterocycles have been less successful. In this regard, recent studies have revealed that hydroxyl groups in carboxylic acids can be used as nucleophiles in oxidative lactonization via Pt- or Pd-catalyzed C(sp^3)–H activation.[4] In 2008, Nagasawa et al. developed a novel method for the synthesis of benzoxazole derivatives based on intramolecular Cu-catalyzed C–O

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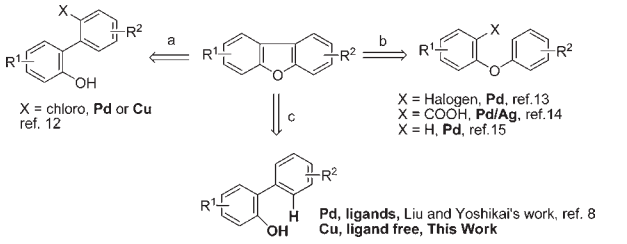
bond forming reactions between carbonyl oxygens of the anilide moiety and aromatic C−H bonds.[5] In 2010, Yu et al. described the first example of a dihydrobenzofuran synthesis that involves a tertiary aliphatic alcohol-directed cycloetherification process that is catalyzed by $Pd(OAc)_2$ and $PhI(OAc)_2$ as the oxidant.[6] Despite the success of these earlier studies and other oxidative C−O bond forming cyclization reactions,[7] C−H cycloetherification reactions that employ phenols as nucleophiles remain underdeveloped.[8] Reasons for this situation include the fact that (1) phenols are prone to oxidation in the presence of strong oxidants such as $PhI(OAc)_2$, (2) homocoupling of phenols occurs when transition metals such as Cu are present,[9] and (3) reductive elimination of C−O from the presumed Pd(II) intermediates is a sluggish process that requires the assistance of specially designed ligands to occur.[10]

Dibenzofuran is an important structural motif that exists in a wide variety of biologically active compounds.[11] Previously developed approaches for preparation of members of this family include Pd- or Cu-catalyzed intramolecular O-arylation of 2-chlorobiphenyl-2′-ols (path a, Scheme 1),[12] Pd-catalyzed cyclization of 1-halo-2-phenoxybenzenes,[13] tandem decarboxylation/C−C coupling of 2-phenoxybenzoic acids,[14] and oxidative C−C cyclization of diphenylethers[15] (path b, Scheme 1). Recently, Liu et al. described a novel and elegant approach to the synthesis of dibenzofurans that employs Pd-catalyzed C−H activation/C−O cyclization reactions of *o*-arylphenols.[8a] Very recently, Yoshikai et al. reported a similar Pd-catalyzed process involving 3-nitropyridine as a ligand and *tert*-butyl peroxybenzoate as an oxidant.[8b]

Scheme 1. Approaches toward Dibenzofurans



Inspired by the recent advantages of Cu-catalyzed C−H functionalization processes,[16] we hypothesized that inexpensive Cu catalysts should also be capable of promoting C−O cyclization reactions of 2-arylphenols. Below, we describe a new process for the preparation of multisubstituted dibenzofurans through aerobic $C(sp^2)$−H cycloetherification starting with *o*-arylphenols. The methodology relies on a simple reaction system and inexpensive Cu salts as catalysts.

Reactions using 2-phenylphenol as the substrate and various Cu salts as catalysts under an air atmosphere were not successful owing to the fact that the electron-rich substrate is labile under these conditions. To overcome this problem, reactions of 4-nitro-2-phenylphenol (**1a**), in which the potential for oxidation is reduced significantly, were explored (Table 1). No cyclization occurred even at 140 °C for 14 h when 20 mol % of $Cu(OAc)_2$ were used (1 equiv of PivOH, DMSO, 140 °C, under an air atmosphere). To our delight, addition of various carbonate salts to the reaction mixture leads to significantly improved cyclization efficiencies (entries 2−5). Among the bases screened, Cs_2CO_3 was observed to be the most effective, producing **2a** in 50% yield.[17] Surprisingly, the reaction did not take place when excess Cs_2CO_3 (2.0 equiv) was present and the use of 0.25 equiv of Cs_2CO_3 led to a 25% yield of **2a** (entries 6−7). Screening of other Cu sources resulted in the identification of CuBr as the optimal catalyst (entries 8−12). The yield of **2a** was further increased to 72% when 30 mol % of CuBr are used for the process. When CuBr was absent or the Cu catalyst was replaced by $Pd(OAc)_2$, no product **2a** was detected in both cases, indicating that the reaction was indeed catalyzed by Cu (entries 14−15). When the reaction was operated in argon, the cyclization was considerablly less efficient, suggesting that O_2 played a vital role in the catalytic cycle (entry 16).

The scope of substrates was probed under the optimized reaction conditions (Scheme 2). Substrates with either electron-donating or -withdrawing substituents in the *para*-position were found to be reactive under these conditions, giving the desired products **2b**−**2g** in 59−70%

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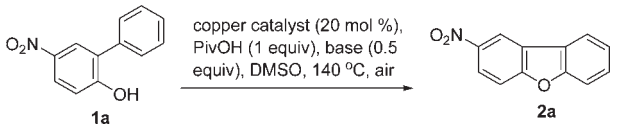
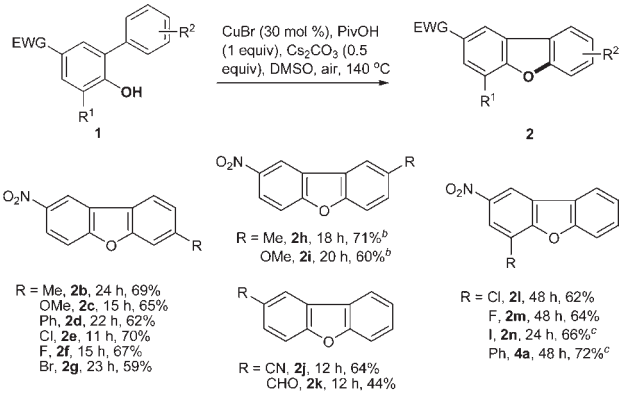
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (20 mol %)	base	time (h)	yield (%)[b]
1	$Cu(OAc)_2$	–	14	0
2	$Cu(OAc)_2$	Li_2CO_3	14	36
3	$Cu(OAc)_2$	Na_2CO_3	14	36
4	$Cu(OAc)_2$	K_2CO_3	14	41
5	$Cu(OAc)_2$	Cs_2CO_3	14	50
6	$Cu(OAc)_2$	Cs_2CO_3	14	0[c]
7	$Cu(OAc)_2$	Cs_2CO_3	14	25[d]
8	$Cu(TFA)_2$	Cs_2CO_3	24	50
9	$Cu(OTf)_2$	Cs_2CO_3	24	48
10	CuI	Cs_2CO_3	22	53
11	CuCl	Cs_2CO_3	15	55
12	CuBr	Cs_2CO_3	21	63
13	**CuBr**[e]	**Cs_2CO_3**	**14**	**72**
14	–	Cs_2CO_3	17	0
15	$Pd(OAc)_2$[f]	Cs_2CO_3	17	0
16	CuBr[g]	Cs_2CO_3	14	28

[a] All reactions were carried out at 0.2 mmol scale, with Cu catalyst (20 mol %), PivOH (1 equiv), base (0.5 equiv), in DMSO (1 mL), at 140 °C, in air. [b] Isolated yield. [c] 2 equiv of Cs_2CO_3 were used. [d] 0.25 equiv of Cs_2CO_3 was used. [e] 30 mol % CuBr was used. [f] 10 mol %. [g] In argon.

Scheme 2. Scope of the Catalytic C−H Cycloetherification[a]

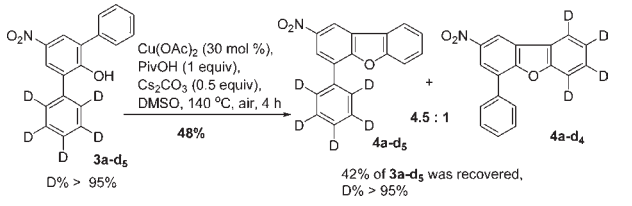


[a] All reactions were carried out at 0.2 mmol scale, with CuBr (30 mol %), PivOH (1 equiv), Cs_2CO_3 (0.5 equiv), in DMSO (1 mL), at 140 °C under air, isolated yield. [b] Regioisomers (*para*/*ortho* = 20:1, by ^1H NMR) were obtained. [c] 30 mol % of $Cu(OAc)_2$ were used instead of CuBr.

yields. It is notable that the bromine-containing substrate reacts to yield the corresponding cyclization product **2g**, which along with the corresponding methoxylated product **2c** can serve as a suitable intermediate for further modification of the dibenzofuran skeleton. The reactions of the *meta*-substitued reactants generate the sterically favored products **2h** and **2i** with a *ca.* 20:1 selectivity. However, the exsitence of a methyl group in the *ortho*-position completely hampers the cyclization (result not shown). Replacement of the *para*-NO_2 by cyano and formyl groups leads to substrates that undergo reaction to form the corresponding products in respective 64% and 44% yields. When other substituents are present adjacent to the phenolic hydroxyl group, cyclization reactions take place with comparable efficiencies (**2l**−**2m**). In addition, in the cases of **2n** and **4a** where bulky iodo and phenyl groups are present, a change in the catalyst from CuBr to $Cu(OAc)_2$ is necessary to avoid the formation of unidentified byproducts.

For the purpose of gaining insight into the mechanism of the C−H cycloetherification reaction, the diphenyl substrate **3a-d_5** bearing one fully deuterated phenyl ring was prepared and subjected to the reaction conditions described for **4a** in Scheme 2. ^1H NMR analysis of the isolated product mixture generated after 4 h demonstrated that the process displayed a large kinetic isotope effect (KIE) of 4.5.[18] In addition, this analysis showed that proton scrambling did not take place in the recovered starting material **3a-d_5**, indicating that the C−H activation process is irreversible (Scheme 3).

Scheme 3. Intramolecular Kinetic Isotope Effect Study



To obtain further information about the mechanism for C−H activation, intramolecular competition experiments were carried out using the unsymmetrical 2,6-diaryl-4-nitrophenols (**3b**−**e**), which possess one electron biased aryl ring (Table 2). To determine the ratio of the two regioisomers formed in each reaction, the possible regioisomeric products **4b**−**e** and **5b**−**e** were synthesized by using Suzuki coupling reactions of the iodinated dibenzofuran **2n** and corresponding arylboronic acids (see Supporting Information). As the results in Table 2 indicate, C−H bonds in electron-deficient aromatic rings are more easily cleaved (entries 3−4), although the reactivity trend for the electron-rich arene ring containing substrates **3b** and **3c** is not clear. This finding suggests that a concerted-metalation-deprotonation (CMD)[19] rather than electrophilic metalation process is likely occurring.[3g,5] Furthermore, the addition of TEMPO, a radical scavenger,

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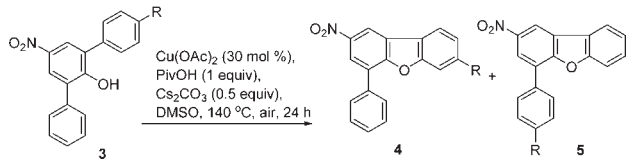
Table 2. Intramolecular Competition Study[a]



3 4 5

entry	substrate	ratio of **4**/**5**[b]	yield of **4**+**5** (%)[c]
1	**3b** R = Me	1:1	80
2	**3c** R = OMe	1:0.9	96
3	**3d** R = Cl	1:0.66	71
4	**3e** R = F	1:0.88	84

[a] All reactions were carried out in 0.2 mmol scale, $Cu(OAc)_2$ (30 mol %), PivOH (1 equiv), Cs_2CO_3 (0.5 equiv), in DMSO (1 mL), at 140 °C under air. [b] The ratios were determined by ^1H NMR analysis. [c] Isolated yield.

has no influence on the product formation, which rules out the possibility of a radical mechanism.

Based on the results of the mechanistic studies described above, two pathways for the cycloetherification reaction displayed in Scheme 4 are plausible. In path a, initial coordination of Cu(II) species with the phenolic hydroxyl group forms intermediate **A**, which undergoes rate-limiting, irreversible ligand assisted CMD through intermediate **B**. Subsequent reductive elimination gives the cyclized product with concurrent formation of Cu(0), which is then oxidized by O_2 in the presence of acid. Alternatively, activation of the aromatic ring by Cu(II) can take place via the η^2 π complex **D**.[3j] Nucleophilic attack of the phenolic OH on the activated arene results in production of the cyclized intermediate **E**, which then undergoes *cis* hydride elimination to generate the product and Cu(0). Considering the severe influence of the *ortho*-methyl group on product formation, path a involving a coplanar transition state is more likely followed in this process. However, a possible Cu(I) to Cu(III) cycle cannot be ruled out at the current time.[20]

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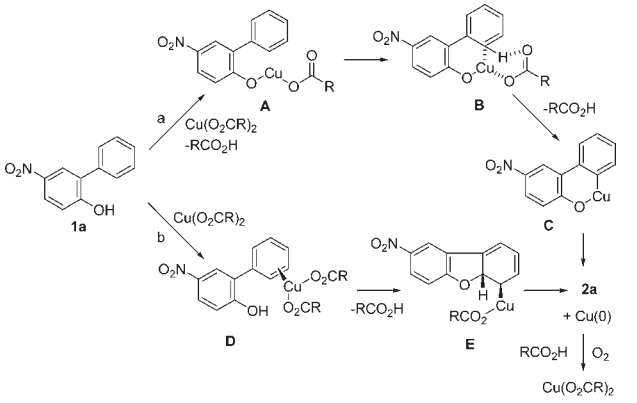
Scheme 4. Proposed Reaction Mechanism



In conclusion, a Cu-catalyzed process for the synthesis of a variety of dibenzofuran derivatives has been developed. A catalytic amount of Cu can promote the cycloetherification reaction when 0.5 equiv of Cs_2CO_3 and 1.0 equiv of PivOH are employed as additives under an air atmosphere. Although an electron-withdrawing group prelocated at the *para*-position relative to the phenolic OH is essential to prevent direct oxidation of the substrate, these electron-withdrawing groups (NO_2, CN, CHO) may serve as versatile functionalities for further transformations. The new methodology not only serves as an alternative approach for the synthesis of dibenzofurans but also broadens the application of Cu-catalyzed C−H activation reactions in the preparation of oxygen-containing heterocycles. The results of mechanistic studies suggest that an irreversible, rate-limiting CMD step is most likely involved in the mechanistic pathway for C−H activation. However, detailed studies are needed to gain deeper insight into the mechanism of the process, especially for elucidating the valence of Cu involved in the C−H activation step.

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Supporting Information Available. Experimental procedure, and characterization data for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.