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CuI-Mediated Sequential Iodination/Cycloetherification of *o*-Arylphenols: Synthesis of 2- or 4-Iododibenzofurans and Mechanistic Studies

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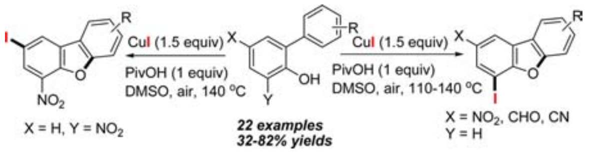
ABSTRACT



An efficient synthesis of 2- or 4-iododibenzofurans through CuI-mediated sequential iodination/cycloetherification of two aromatic C−H bonds in *o*-arylphenols has been developed. Both the preexisting electron-withdrawing groups (NO_2, CN, and CHO) and the newly introduced iodide are readily modified for a focused dibenzofuran library synthesis. Mechanistic studies and DFT calculations suggest that a Cu(III)-mediated rate-limiting C−H activation step is involved in cycloetherification.

The copper-catalyzed/mediated annulation reaction via C−H activation has been recognized as an atom-economic and cost-effective alternative to classical coupling methods using prefunctionalized substrates in the construction of heterocycles.[1] However, only one chemical bond, such as a C−C,[2] C−N,[3] or C−O[4] bond, is formed in most of these processes. In contrast, domino reactions are highly efficient in bond formation, in which multiple chemical bonds are usually formed in one pot.[5] Incorporation of transition-metal-catalyzed C−H functionalization into a domino reaction is arguably an ideal but challenging strategy. Compared with Pd-catalyzed domino reactions involving C−H activation,[6] similar approaches catalyzed

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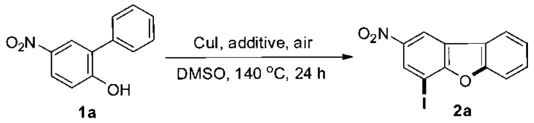
or mediated by Cu are underdeveloped.[7] In addition to atom economy and bond-forming efficiency, the feasibility of further modification on the heterocyclic scaffold thus formed is particularly important in medicinal chemistry. Considering the versatility of organic iodides in chemical transformations, a domino iodination/annulation reaction via C–H activation is of great interest.[8] Herein, we report a CuI-mediated sequential iodination/cycloetherification of *o*-arylphenols for the synthesis 2- or 4-iododibenzofurans, in which CuI acts as both an iodinating reagent under aerobic conditions and a promotor in C–H cycloetherification.

The dibenzofuran skeleton exists in a wide range of biologically active compounds.[9] Methods leading to the construction of this scaffold are mainly based on Pd- or Cu-catalyzed intramolecular O-arylation of 2-chlorobiphenyl-2′-ols,[10] Pd-catalyzed cyclization of 1-halo-2-phenoxybenzenes,[11] tandem decarboxylation/C–C coupling of 2-phenoxybenzoic acids,[12] and oxidative C–C cyclization of diphenylethers.[13] Independently, Liu and Yoshikai reported concise approaches to construct the dibenzofuran scaffold from 2-arylphenols through Pd-catalyzed intramolecular C–H activation C–O bond formation.[14] We also disclosed a similar strategy for the synthesis of electron-deficient dibenzofurans using inexpensive CuBr and $Cu(OAc)_2$ as catalysts.[4d,e]

During the course of catalyst optimization in C–H cycloetherification using 2-phenyl-4-nitrophenol **1a** as a substrate, an unexpected iodinated cyclization product, 4-iodo-2-nitrodibenzofuran **2a**, was produced in 55% yield when 1 equiv of CuI was employed (entry 1, Table 1). The yield of **2a** was maximized to 63% as the loading of CuI increased (entries 2–3). The reaction efficiency diminished slightly when the reaction was performed under a dioxygen atmosphere, while an inert argon atmosphere deteriorated the reaction dramatically, indicating a vital role played by O_2 (entries 4–5). Efforts toward using a catalytic amount of CuI along with a stoichiometric amount of other iodide sources were unsuccessful (see Supporting Information (SI)). Screening of additives revealed that the presence of PivOH (1 equiv) could enhance the yield of **2a** significantly to 82%.[15]

Table 1. Optimization of Reaction Conditions[a]



entry	CuI (equiv)	additive (equiv)	yield (%)[b] **2a**
1	1.0	–	55
2	1.5	–	63
3	2.0	–	63
4[c]	1.5	–	60
5[d]	1.5	–	9
6	1.5	AcOH (1.0)	79
7	**1.5**	**PivOH (1.0)**	**82**
8	1.5	PivOH (2.0)	82

[a] The reactions were carried out at 0.2 mmol scale in 1 mL of DMSO. [b] Isolated yield. [c] The reaction was performed under O_2 (1 atm). [d] The reaction was performed under Ar (1 atm).

To determine the sequence of C–I and C–O bond formation in **2a**, 2-nitrodibenzofuran **3**[4d] was subjected to the conditions described in entry 7, Table 1. Compound **3** was totally stable under the reaction conditions, which suggested that iodination took place prior to cycloetherification (eq 1, Scheme 1). The conclusion was further confirmed by the fact that when the reaction of **1a** was performed at 60 °C for 40 h, the reaction stopped at the stage of iodination (eq 2). The isolated uncyclized iodide **1b** could be further cyclized at a higher temperature (140 °C) with the aid of an excess amount of CuI, indicating that the active copper species cannot be regenerated (eq 3). It is notable that although there are many methods available for iodination of phenols,[16] to the best of our knowledge, this is the first example of using CuI as an iodinating reagent.

Having identified the optimized conditions, we next explored the substrate scope of this sequential iodination/C–H cycloetherification reaction. It was found that, in some cases, the desired iodinated dibenzofurans were contaminated with noniodinated cyclization products as a result of competitive cyclization of the starting phenols. To solve this problem, the reactions

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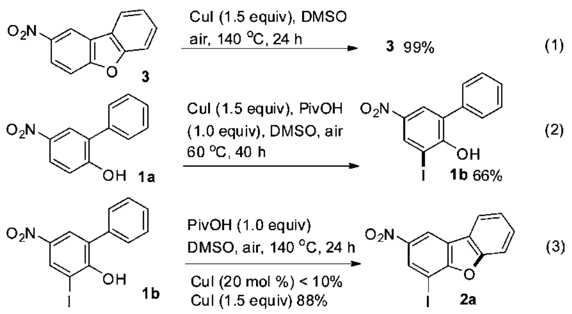
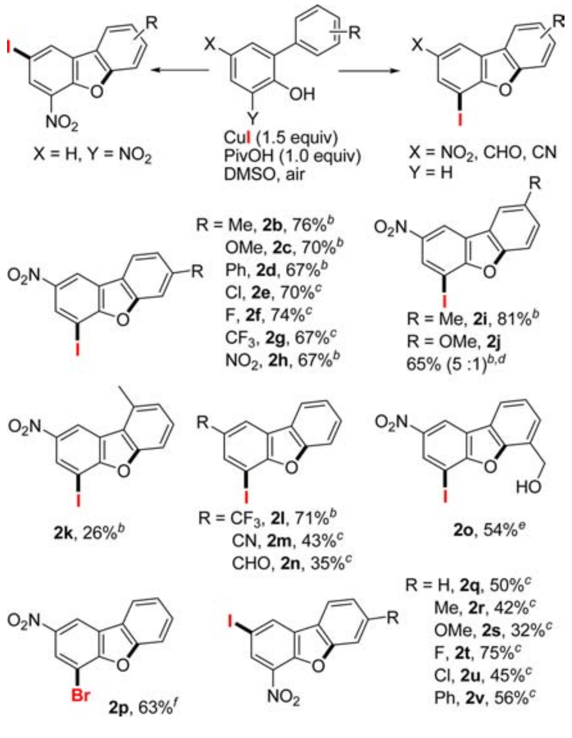
Scheme 1. Verification of the Reaction Sequence



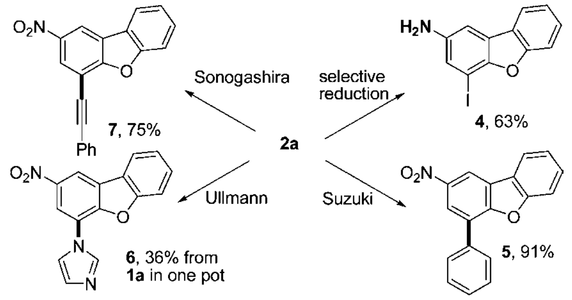
were performed first at lower temperature (110 °C) for complete iodination and then at elevated temperature (140 °C) to promote the cyclization. For other substrates, this kind of operation was not necessary probably because the iodination step was relatively fast. Investigation on the substitution effect on the nonphenolic ring disclosed that the reaction was not sensitive to the electronic properties of the substituents (Scheme 2). Substrates containing both electron-donating (Me, OMe) and -withdrawing (F, Cl, CF$_3$, NO$_2$) groups on the para position produced the corresponding 4-iodo-2-nitrodibenzofurans **2b**−**2h** in good yields. Regioselectivities were excellent to good for meta methyl and methoxy substituted phenols (**2i**−**2j**). The presence of a methyl group on the ortho position seriously retarded the cyclization due to steric effects (**2k**). The para nitro on the phenol ring could be replaced by other electron-withdrawing groups (EWG), such as CF$_3$, CN, and CHO, albeit in reduced yields (**2l**−**2n**). A dual chelation effect was observed in the preparation of **2o**, where the benzylic alcohol acted as an additional directing group besides the phenolic OH to activate the sterically more hindered C−H bond preferentially.[4e] In this case, the reaction temperature should be kept under 80 °C to avoid oxidation of the benzyl alcohol. For substrates bearing a nitro group on the ortho position, corresponding 2-iodo-4-nitrodibenzofuran derivatives were obtained in moderate to good yields (**2q**−**2v**). In addition, when CuBr was used in place of CuI, a sequential bromination/C−H cycloetherification reaction took place, leading to 4-bromo-2-nitrodibenzofuran **2p** in 63% yield. Unfortunately, substrates without an EWG group on the phenolic ring quickly decomposed under the reaction conditions.

Scheme 2. Substrate Scope[a]



[a] All reactions were carried out at 0.2 mmol scale, CuI (1.5 equiv), PivOH (1.0 equiv) in 1 mL of DMSO, under air, isolated yield. [b] 110 °C for 10 h and 140 °C for 10 h (for **2k**, 26 h). [c] 140 °C for 10 h (for **2q**−**2v**, 24 h). [d] The ratio of para/ortho in the parentheses was determined by ^{1}H NMR analysis. [e] 60 °C for 90 h and 80 °C for 40 h. [f] CuBr (1.5 equiv) was used instead of CuI, 100 °C for 24 h and 140 °C for 10 h.

Scheme 3. Diversification of **2a**



The feasibility of diversifying the dibenzofuran scaffold was demonstrated by using **2a** as an example (Scheme 3). The C-4 of **2a** can be modified smoothly with a phenyl ring, an imidazole heterocycle, and an acetylene by Suzuki, Ullmann, and Sonogashira couplings, respectively. In addition, the preexisting nitro group could be reduced selectively to NH$_2$ with the iodide intact.

Although Cu-catalyzed bromination and chlorination of electron-rich arenes and heterocycles have been reported in literature,[1a,17,18] CuI-mediated iodination of phenols has not been documented. In the current protocol, the phenol substrates were most likely iodinated by molecular I$_2$ which was formed by cooperative oxidation of O$_2$ and Cu. Actually, the nonpolar I$_2$ with its distinctive purple color was observed during column chromatography of the reaction mixture using only petroleum ether as an eluent.

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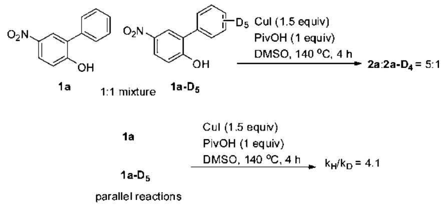
Scheme 4. Isotope Labeling Experiments



To gain insight into the mechanism of the C−H cycloetherification step, isotope labeling experiments were performed (Scheme 4). When a 1:1 mixture of **1a** and **1a-D$_5$** was subjected to the standard conditions for 3 h, a 5:1 mixture of **2a** and **2a-D$_4$** was isolated in 38% total yield. In parallel reactions using **1a** and **1a-D$_5$** as substrates respectively, a significant k_H/k_D (4.1) was also observed by comparing the rate of product formation (see SI).[19] No deuterium scrambling was observed in the recovered **1a-D$_5$**. These results confirmed that an irreversible rate-limiting C−H cleavage was involved in cyclization. Therefore, a mechanism of concerted metalation−deprotonation (CMD) rather than electrophilic aromatic substitution (S$_E$Ar) or single-electron transfer (SET) is more likely involved in the step of C−H activation.[20]

The oxidation state of Cu involved in the C−H activation step is still a question to be answered. Density functional theory (DFT) calculations were carried out for both Cu(III)- and Cu(II)-mediated CMD mechanisms. The overall free energy barrier for the Cu(III)-mediated CMD process is 21.9 kcal/mol as shown in Figure 1. In contrast, the CMD mechanism for Cu(II) species needs to overcome an energy barrier of 27.1 kcal/mol. Being consistent with the experimental results, data of DFT calculations suggest that mechanisms of both SET (37.8 kcal/mol) and S$_E$Ar (25.8 kcal/mol) are less favorable.[21]

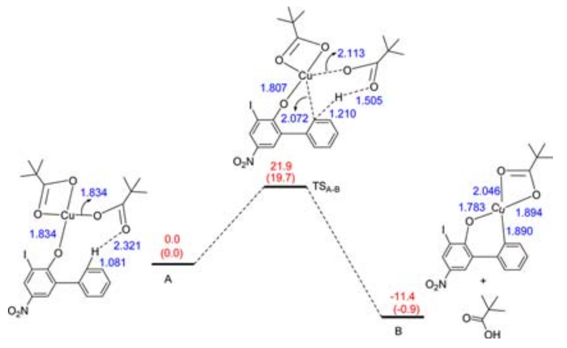
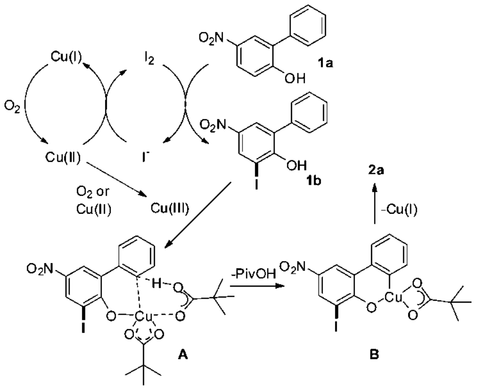


Figure 1. Energy profiles of the CMD mechanism for the C−H cycloetherification step with a Cu(III) catalyst. The calculated relative free energies and electronic energies (in parentheses) are given in kcal/mol. Selected bond distances (Å) calculated for species are shown in blue.

Scheme 5. Proposed Mechanism



Based on the investigations described above, we propose the reaction mechanism in Scheme 5. Initial oxidation of the iodide anion by a Cu(II) species forms I$_2$ which serves as an iodinating reagent to iodinate **1a** to **1b**. Coordination of **1b** with a pivalate coordinated Cu(III) species formed by either disproportionation or aerobic oxidation of Cu(II) and the following pivalate assisted CMD yield the intermediate **B** via **A**. Subsequent reductive elimination leads to the cyclized product and concurrent formation of a Cu(I) species. It is noteworthy that CMD is very rare for Cu-catalyzed C−H activation reactions.[4d]

In conclusion, we have developed a one-pot sequential iodination/C−H cycloetherification of electron-deficient 2-arylphenols for the synthesis of electron-withdrawing group substituted 2- or 4-iododibenzofurans. The reaction is mediated by 1.5 equiv of CuI which serves as an iodinating reagent first and then a promoter for C−H cycloetherification. Both the preexisting EWGs (NO$_2$, CN, and CHO) and the newly introduced iodide are readily transferred to diversify the dibenzofuran skeleton. Deuterium labeling experiments suggest that an irreversible rate-limiting C−H cleavage step is involved. Results of DFT calculations prefer Cu(III) rather than Cu(II) species in the pivalate-assisted CMD process.

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

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The authors declare no competing financial interest.