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Synthesis of Dibenzofurans via Palladium-Catalyzed Phenol-Directed C−H Activation/C−O Cyclization

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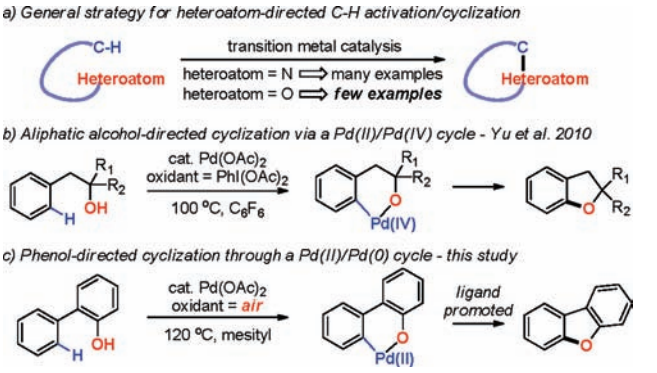
Supporting Information

ABSTRACT: A practical, Pd(0)/Pd(II)-catalyzed reaction was developed for phenol-directed C−H activation/C−O cyclization using air as an oxidant. The turnover-limiting step of the process was found to be C−O reductive elimination instead of C−H activation. This reaction can tolerate a variety of functional groups and is complementary to the previous methods for the synthesis of substituted dibenzofurans.

The ubiquity of heterocycles continues to make the development of new methods for their preparation an important objective in chemical synthesis.[1] Among the many ring-forming reactions in heterocycle preparation, the directed cyclization of tethered heteroatoms onto adjacent C−H bonds emerged recently as an attractive and efficient method (Scheme 1a).[2] For azaheterocycles, the intramolecular C−H activation/C−N cyclization strategy has been successfully applied to the synthesis of a variety of structures including oxathiazinane,[3] oxazolidinone,[4] carbazoles,[5] indoles,[6] indazoles,[7] and benzimidazoles[8] through Rh, Ru, Pt, Pd, or Cu-catalyzed transformations. By comparison, much less success has been achieved for the preparation of oxaheterocycles via C−H activation/C−O cyclization. In 2001, Sames et al. reported a very rare instance of Pt-catalyzed chelate-directed C−H functionalization of amino acids to produce lactones.[9] In 2008, Nagasawa et al. described Cu-catalyzed oxidative C−O coupling of benzanilides to prepare 2-aryl-benzoxazoles.[10] More recently, Yu et al. showed the first example for Pd-catalyzed aliphatic alcohol-directed C−H activation/C−O cyclization for the synthesis of dihydrobenzofuran (Scheme 1b).[11] These studies highlight that the intramolecular C−H activation/C−O coupling still offers a distinct challenge.

Here we report a practical phenol-directed C−H activation/C−O cyclization reaction as an efficient route to dibenzofurans (Scheme 1c). The significance of the present finding is twofold: (1) Although there are some intermolecular examples for Pd-catalyzed phenol directed C−H functionalization,[12] all of these examples result in C−C bond formation rather than intramolecular C−O bond formation. The main reason that intramolecular coupling of phenol hydroxyls with C−H bonds has not been reported to date is that C−O reductive elimination from putative Pd(II) intermediates is difficult to induce.[13] By using strong oxidants such as $PhI(OAc)_2$, Yu et al. achieved C−O reductive elimination in aliphatic alcohol-directed C−H activation/C−O cyclization from Pd(IV).[11] However, the same method *is not applicable here* because phenols are not stable to strong oxidants (Note: in our experiment, treatment of phenol with $PhI(OAc)_2$ causes complete decomposition of phenol). (2) Dibenzofuran is an important structural motif in many optoelectronically and biologically active compounds,[14] but the synthesis of substituted dibenzofurans can remain difficult. Earlier methods (e.g., radical phenolic homocoupling[15]) involve tedious steps, so that new approaches evolve rapidly (e.g., C−O cyclization of 2-halobiphenyl-ols,[16] C−C cyclization of diphenyl ethers[17] and 1-halo-2-phenoxybenzenes,[18] and decarboxylative C−H coupling of 2-phenoxybenzoic acids[19]). Nonetheless, all the existing methods have limitations as to the functional group tolerance and substrate availability. The present method uses readily accessible 2-arylphenols as substrates and offers a new complementary route to substituted dibenzofurans.

Scheme 1. Heteroatom-Directed C−H Activation/Cyclization



We commenced our study by examining the C−H activation/C−O cyclization of 2-phenylphenol (**1a**) to dibenzofuran (**2a**) in the presence of the $Pd(OAc)_2$ catalyst and IPr ligand (Table 1). Different weak oxidants were tested first (entries 1−3) because a strong oxidant (e.g., $PhI(OAc)_2$) was found to destroy phenol. Unfortunately, none of these oxidants induce the desired reaction until we accidentally discovered that **2a** was produced in 23% when the reaction proceeded without inert gas protection (entry 4). This observation indicated that air constitutes an effective oxidant in the transformation. Next, we found that the addition of sodium pivalate (PivONa) significantly improved the reaction (entry 6). We also successfully obtained a colorless

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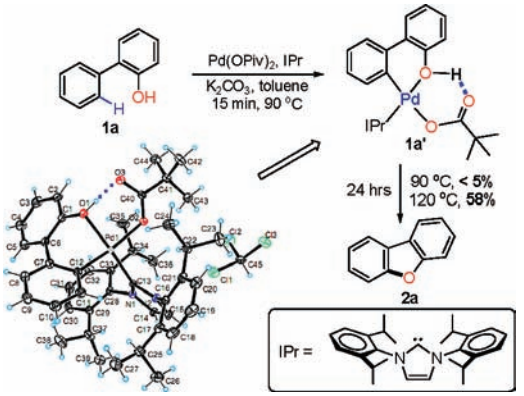
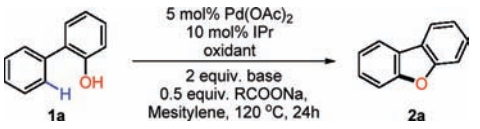
Scheme 2. Stoichiometric Reaction between 1a and $Pd(OPiv)_2$[a]



[a] Note that we tested the stoichiometric conversion from **1a** to **2a** in both air and Ar atmospheres. The two experiments showed identical results.

Table 1. Optimization of the Reaction Conditions[a]

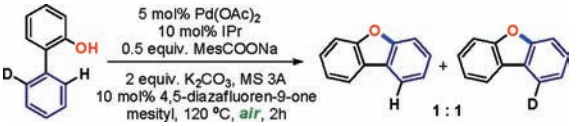


Entry	Base	Oxidant	RCOONa additive	Yield %[b]
1	K_2CO_3	$Cu(OAc)_2$	–	0
2	K_2CO_3	AgOAc	–	0
3	K_2CO_3	benzoquinone	–	0
4	K_2CO_3	air	–	23
5	K_2CO_3	air	AcONa	15
6	K_2CO_3	air	PivONa	47
7	K_2CO_3	air	1-AdCOONa	27
9	K_2CO_3	air	MesCOONa	59
10	K_2CO_3	air	2,4,6-$OMeC_6H_2COONa$	24
11	K_2CO_3	air	2,4,6-^{i}PrC_6H_2COONa	11
12	–	air	MesCOONa	0
13	CsOPiv	air	MesCOONa	0
14	Na_2CO_3	air	MesCOONa	0
15	Cs_2CO_3	air	MesCOONa	trace
16	KO^{t}Bu	air	MesCOONa	0
17[c]	K_2CO_3	air	MesCOONa	67
18[c,d]	**K_2CO_3**	**air**	**MesCOONa**	**90 (85[e])**
19[c,d]	K_2CO_3	O_2	MesCOONa	81
20[c,d,f]	K_2CO_3	air	MesCOONa	0

[a] All the reactions were carried out in 0.2 mmol scale in 1 mL mesitylene. [b] GC yields with *n*-decane as an internal standard. [c] MS 3A (200 mg) was added. [d] 10 mol % 4,5-diazafluoren-9-one was added. [e] Isolated yield. [f] IPr was NOT used.

crystal (**1a′**) by treating **1a** with a stoichiometric amount of $Pd(OPiv)_2$ in toluene at 90 °C for 15 min (Scheme 2). X-ray diffraction analysis revealed that **1a′** was a four-coordinate Pd(II) complex carrying an anionic pivalate ligand. This observation is consistent with the previous conclusion[20] that an anionic ligand can promote C−H activation by acting as a proton shuttle. Additionally, it was previously discussed that the alcohol directing group coordinated as a neutral or as an anionic ligand during

Scheme 3. Isotope Labeling Experiment



the C−H activation.[11,21] In the present study we obtained clear evidence that the phenol group coordinated with Pd(II) as a neutral σ donor.

Heating of **1a′** at 90 °C for 24 h generated a trace amount of **2a**, and an increase of the reaction temperature to 120 °C could raise the yield to 58% (Scheme 2). These observations indicated that C−O reductive elimination from the Pd(II) intermediate was *the most difficult step* in the designed C−H activation/C−O cyclization reaction. A similar conclusion was made previously in the studies on Pd-catalyzed diaryl ether synthesis,[13] where bulky ligands were shown to promote such C−O reductive elimination. Accordingly, we tested more bulky RCOONa additives (Table 1, entries 7−11) and found that sodium 2,4,6-trimethylbenzoate (MesCOONa) exhibited a better performance. Further optimization was conducted on the base (entries 12−16) revealing that K_2CO_3 provided the best performance. Note that Cs_2CO_3 was not favored in the reaction possibly because Cs_2CO_3 was too hygroscopic under the air oxidation conditions. Also, addition of molecular sieves[22] was found to improve the reaction (entry 17). A final breakthrough was made by using the recently developed 4,5-diazafluoren-9-one ligand that may help the aerobic oxidation of Pd(0) to regenerate Pd(II) (entry 18).[23] A good isolated yield (85%) of **2a** was obtained. Note that O_2 could also be used as the oxidant in the reaction (entry 19). On the other hand, in the absence of the IPr ligand the reaction did not proceed even with the addition of 4,5-diazafluoren-9-one (entry 20). Finally, the isotope labeling experiment showed that the extents of C−H and C−D activation were the same (Scheme 3). This experiment confirmed that C−O reductive elimination was the turnover-limiting step of the catalytic cycle.

With an optimized set of reaction conditions, we examined the scope of the phenol-directed C−H activation/C−O cyclization process (Table 2). It is found that a variety of 2-aryl phenols can be converted to the desired product in modest to good yields (up to 91%). The upper aromatic ring was found to be tolerant of substituents at R_2 that were electron-donating groups such as ketal (**2b**), silyl (**2c**), ether (**2h**, **2n**), and amine (**2k**), and electron-withdrawing groups such as cyano (**2d**), ketone (**2e**, **2r**), nitro (**2f**), amide (**2i**), ester (**2j**), and sulfonamide (**2q**) are tolerated. Fluoride (**2g**, **2l**), chloride (**2m**), and an unsaturated C=C double bond (**2p**) are also compatible with the process. Interestingly, the regioselectivity favored the formation of the less sterically hindered products (e.g., **2d**−**f**, **2o**, **2x**), whereas the other regioisomer was not observed from the reaction. This feature is of synthetic importance because the previous methods usually produced a mixture of regioisomers.[14d,17b,18a,18d,19] Moreover, the successful formation of **2n** indicates that the present method is complementary to the previous method for C−C cyclization of diphenyl ethers.[17] Finally, for the lower aromatic ring, both electron-donating (e.g., OMe) and electron-withdrawing (e.g., CF_3) groups are tolerated for the R_1 substituents in the reaction. Note that many functional groups in Table 2 allow for further synthetic functionalizations. Therefore, the present reaction provides a versatile method for the synthesis of substituted

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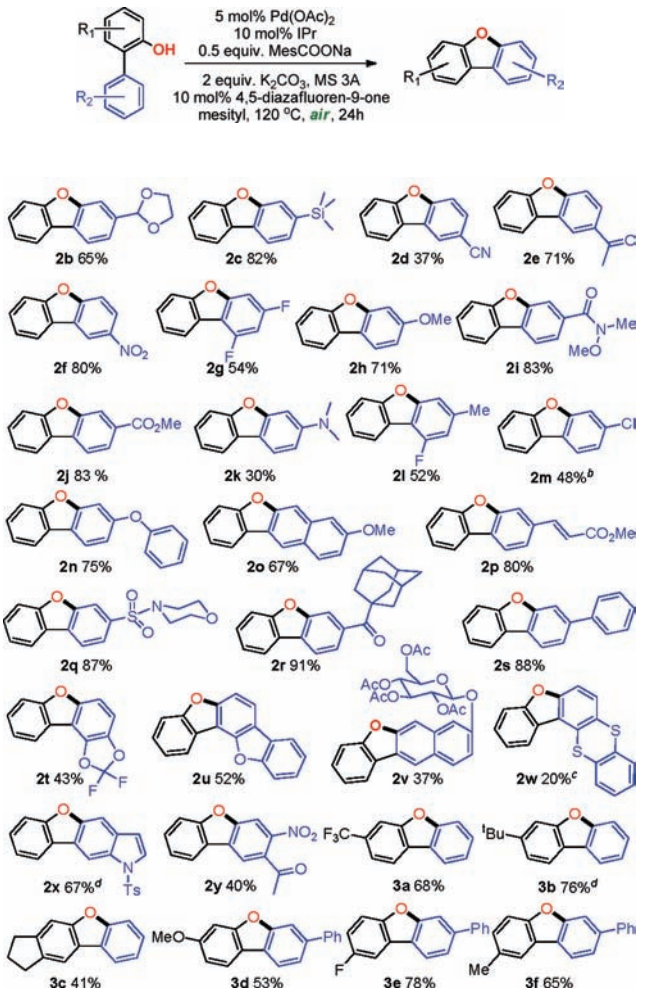
Table 2. Scope of Phenol-Directed C−H Activation/C−O Cyclization[a]



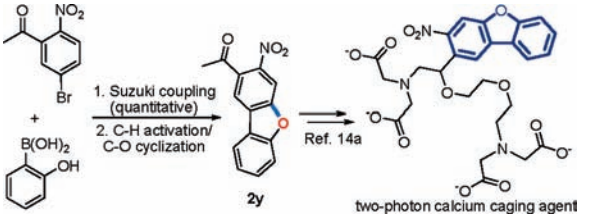
[a] Isolated yield. See Supporting Information for details. [b] Nitrobenzene was used as solvent. [c] With 57% starting material recovered. [d] The catalyst loading was doubled.

dibenzofurans. A particularly interesting substituted dibenzofuran is compound **2y**, which can be used to introduce the recently developed two-photon responsive 3-nitro-2-ethyldibenzofuran caging group into bioactive molecules (Scheme 4).[14a] In comparison to the previous preparation of **2y**, the present synthesis is less lengthy from commercially available reagents.

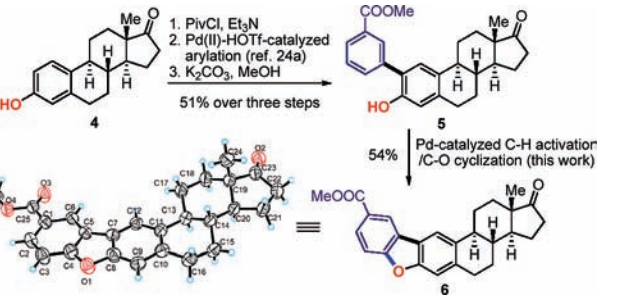
In a previous study we described Pd-catalyzed C−H activation/arylation of phenol esters at the *ortho* positions.[24] This method allows for a facile synthesis of 2-aryl phenols. Combining this method and the reaction developed in the present study, we can accomplish the synthesis of dibenzofuran directly from phenol. As shown in Scheme 5, estrone (**4**) can be selectively arylated at the less sterically hindered C−H bond in 51% yield by using the ester-directed approach. Subsequent C−H activation/C−O cyclization generates a highly functionalized dibenzofuran (**6**) in 54% yield.

Finally, to test the compatibility of the new method with the previous C−N cyclization, we prepared compound **7** that possesses both phenol and benzoylamino groups (Scheme 6). Under the reaction conditions described in the present study, **7** can be selectively converted to dibenzofuran **8** in 65% yield. Next, by

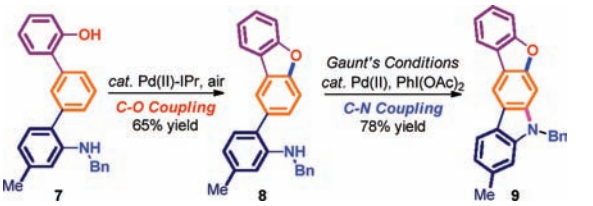
Scheme 4. Synthesis of a Two-Photon Caging Group



Scheme 5. Synthesis of Dibenzofuran Directly from Phenol



Scheme 6. C−O Cyclization versus C−N Cyclization



using the reaction described by Gaunt et al.,[5b] we can convert **8** to carbazole **9** in 78% yield. Thus, our new method favors C−O cyclization over C−N cyclization.

In summary, we have developed a practical phenol-directed C−H activation/C−O cyclization reaction that proceeds through a Pd(0)/Pd(II) catalytic cycle using air as an oxidant. The turnover-limiting step was found to be C−O reductive elimination instead of C−H activation. The new reaction can tolerate a variety of functional groups and is complementary to the previous methods for the synthesis of substituted dibenzofurans.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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