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Oxidative Cyclization of 2-Arylphenols to Dibenzofurans under Pd(II)/Peroxybenzoate Catalysis

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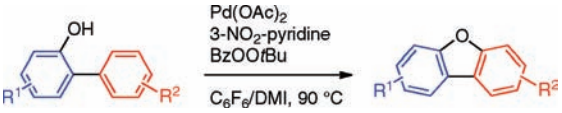
ABSTRACT



2-Arylphenols undergo intramolecular C−H bond activation/C−O bond formation to afford dibenzofuran derivatives under palladium catalysis in the presence of *tert*-butyl peroxybenzoate as an oxidant. Kinetic isotope effect experiments indicated that C−H bond cleavage is the rate-limiting step of the reaction.

Intramolecular carbon−heteroatom bond formation via transition-metal-catalyzed oxidative coupling of a C−H bond and a heteroatom functionality has recently attracted considerable interest from synthetic chemists, because it offers a straightforward route to heterocyclic compounds.[1] A series of this type of C−N bond-forming reaction has been developed, allowing access to various azaheterocycles such as carbazoles,[2,3] indazoles,[4] lactams,[5] indolines,[6] indoles,[7] and benzimidazoles,[8] where palladium catalysis particularly plays a significant role. On the other hand, a rather limited number of examples are known for intramolecular C−O bond formation via oxidative catalytic C−H functionalization, which leads to lactones,[9] benzoxazoles,[10] and dihydrobenzofurans.[11,12] While this manuscript was in preparation, Liu and co-workers reported palladium-catalyzed cyclization of 2-arylphenols to dibenzofuran derivatives using air as an oxidant (Scheme 1a).[13] While the use of air is attractive from economical and environmental points of view, the method requires a rather intricate combination of ligands (IPr and 4,5-diazafluoren-9-one) and additives ($MesCO_2Na$, K_2CO_3, and molecular sieves). We report here that the same transformation can be achieved by a simple alternative catalytic system consisting of $Pd(OAc)_2$, 3-nitropyridine as a ligand, and *tert*-butyl peroxybenzoate (BzOO*t*Bu) as an inexpensive oxidant (Scheme 1b). The method allows facile synthesis of dibenzofuran derivatives from a variety of 2-arylphenols and may complement existing C−H activation/C−C bond formation approaches to dibenzofurans.[14] Kinetic isotope effect (KIE) experiments indicated that our catalytic

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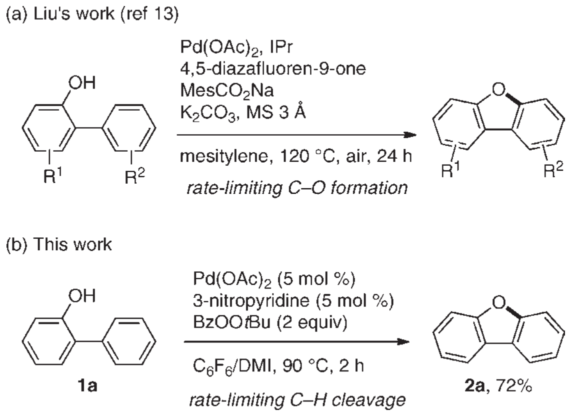
10.1021/ol202229w

system involves C−H bond cleavage as the rate-limiting step and is mechanistically distinct from Liu's system, where C−O bond formation is rate-limiting.

Scheme 1



After considerable experimentation on the reaction of 2-phenylphenol **1a**, we found that it underwent complete conversion in the presence of $Pd(OAc)_2$ (5 mol %), 3-nitropyridine (5 mol %), and BzOO*t*Bu (2 equiv) at 90 °C in C_6F_6/DMI (*N*,*N*′-dimethylimidazolidinone) within 2 h to afford dibenzofuran **2a** in 72% yield (Scheme 1b). The rest of the starting material decomposed into unidentified compounds, and efforts to further improve the product yield have not yet met with success.

Table 1 summarizes the key results obtained during the optimization process. The choice of the oxidant was the most critical. Common oxidants in palladium catalysis other than BzOO*t*Bu, such as *t*BuOO*t*Bu, *t*BuOOH, $Cu(OAc)_2$, $PhI(OAc)_2$, and air, did not promote the reaction at all, but 2-phenylphenol was either partially (entries 2−4 and 6) or totally (entry 5) decomposed . The reaction took place in the absence of ligand but afforded **2a** in a lower yield (entry 7). Among the various ligands examined, 3-nitropyridine performed the best,[15] while most of them (e.g., pyridine, 2,2′-bipyridine, and PPh_3) showed detrimental effects (entries 8−10). The addition of bases such as alkali metal carbonates (M_2CO_3; M = Li, Na, K) provided **2a** in poor yields (data not shown). While aromatic solvents such as C_6F_6, PhCl, toluene, and Lewis basic solvents such as DMI and NMP by themselves gave modest yields of 40−50% (entries 11−15), a mixture of aromatic and Lewis basic solvents improved the reaction (entries 1 and 16). Note that, in the absence of $Pd(OAc)_2$, **1a** decomposed and did not give any **2a**.

Table 1. Screening Conditions for Pd-Catalyzed Cyclization of 2-Phenylphenol to Dibenzofuran[a]

entry	oxidant	ligand	solvent[b]	yield (%)[c]
1	BzOO*t*Bu	3-nitropyridine	C_6F_6/DMI	72
2	*t*BuOO*t*Bu	3-nitropyridine	C_6F_6/DMI	0
3	*t*BuOOH	3-nitropyridine	C_6F_6/DMI	0
4	$Cu(OAc)_2$	3-nitropyridine	C_6F_6/DMI	0
5	$PhI(OAc)_2$	3-nitropyridine	C_6F_6/DMI	0
6	Air	3-nitropyridine	C_6F_6/DMI	0
7	BzOO*t*Bu	none	C_6F_6/DMI	49
8	BzOO*t*Bu	pyridine	C_6F_6/DMI	30
9[d]	BzOO*t*Bu	2,2′-bipyridine	C_6F_6/DMI	11
10	BzOO*t*Bu	PPh_3	C_6F_6/DMI	31
11	BzOO*t*Bu	3-nitropyridine	C_6F_6	43
12	BzOO*t*Bu	3-nitropyridine	PhCl	39
13	BzOO*t*Bu	3-nitropyridine	toluene	38
14	BzOO*t*Bu	3-nitropyridine	DMI	50
15	BzOO*t*Bu	3-nitropyridine	NMP	47
16	BzOO*t*Bu	3-nitropyridine	C_6F_6/NMP	57

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (5 mol %), oxidant (2 equiv), solvent (0.5 mL), 90 °C, 2 h. [b] The ratio of the mixed solvents was 3:2. [c] Isolated yields. [d] 2.5 mol % of 2, 2′-bipyridine was used.

With the optimized catalytic system in hand, we explored the scope of 2-arylphenol derivatives for dibenzofuran synthesis (Scheme 2). 2-Arylphenols bearing electron-neutral or -donating substituents (i.e., Ph, Me, OMe, $SiMe_3$) on the 3′- or 4′-position of the aryl ring afforded the corresponding dibenzofurans (**2b**−**2d**, **2f**, **2g**, and **2i**) in 49−76% yield. For 3′-substituted substrates, C−O bond formation took place exclusively at the less hindered position. A substituent on the 2′-position slowed down the reaction, presumably because of steric hindrance (**2e** and **2h**). A styryl group tolerated the oxidative conditions (**2j**). Aromatic carbon−halogen (Br, Cl, F) bonds remained intact, while the yields of the desired dibenzofurans **2k**−**2m** were modest. Other tolerable functional groups include ketone (**2n**), ester (**2o**), and acetal (**2p**). A brief examination of the variation of the phenol moiety successfully afforded dibenzofurans **2q** and **2r** in moderate yields, while naphthalene-2-ol turned out to be an inferior substrate for the present cyclization reaction (**2s**). Note that, even when the product yield was low (e.g., **2e**, **2m**, and **2s**), we did not recover the starting material but observed its decomposition to intractable products due to the background reaction with peroxybenzoate (vide infra).

To gain insight into the reaction mechanism, we performed a series of KIE experiments. First, cyclization of the monodeuterated substrate **1a**-*d* under the standard conditions for 5 min afforded a mixture of **2a**-*d* and **2a** in a ratio of 3.8 (eq 1), the magnitude of which is in line with H/D KIEs typically observed for the concerted metalation−deprotonation mechanism of aromatic C−H bond activation.[16,17] This is in stark contrast to the result of a similar experiment performed with Liu's catalytic system (Scheme 1a), where no isotope effect was observed.[13,18] Next, an intermolecular competition reaction using an equimolar mixture of **1a** and **1a**-d_5 afforded a mixture of **2a** and **2a**-d_4 in a ratio of

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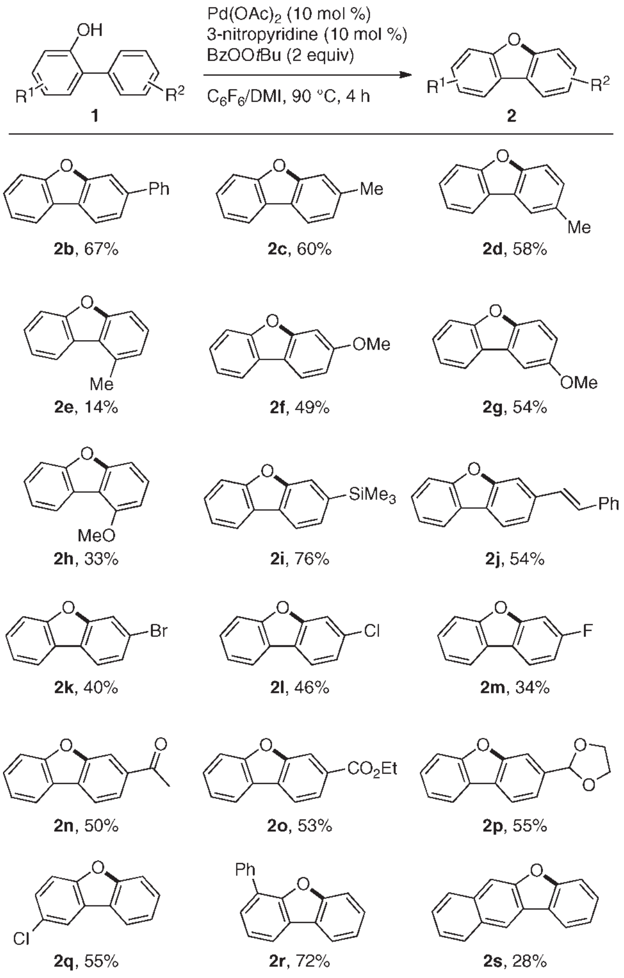
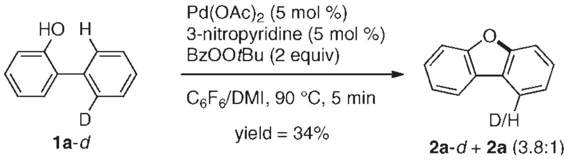
Scheme 2. Scope of Dibenzofuran Synthesis from 2-Arylphenol Derivatives[a]

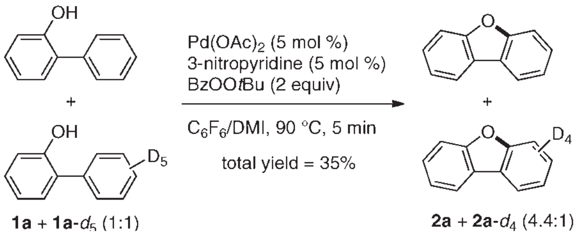


[a] Reaction was performed on a 0.2 mmol scale. Yields refer to isolated yields.

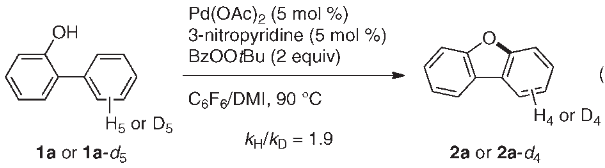
4.4 (eq 2), which is of similar magnitude to the product ratio of the intramolecular competition (eq 1). These two experiments strongly suggest that C−H bond cleavage is the first irreversible step of the reaction.[19] Finally, we compared individual reactions of **1a** and **1a**-d_5 and determined the KIE to be ca. 2 (eq 3), which indicates that C−H bond cleavage is also the rate-limiting step of the reaction.



(1)



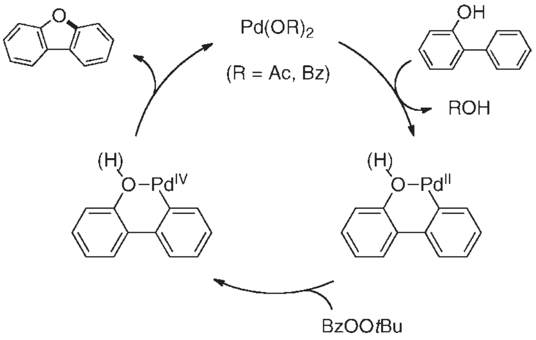
(2)



(3)

The above KIE experiments clearly demonstrated that the present catalytic system is mechanistically distinct from Liu's system, in which a Pd(II)/Pd(0) catalytic cycle involving rate-limiting C−O reductive elimination was proposed.[13] In addition, a stoichiometric reaction of **1a** with Pd(OAc)$_2$ in the absence of BzOO*t*Bu did not afford **2a** at all, indicating that the Pd(II)/Pd(0) mechanism is unlikely in the present case.[20] Given this and the stronger oxidizing power of BzOO*t*Bu compared with molecular oxygen, we suggest a catalytic cycle involving a high-oxidation-state palladium species,[21,22] as proposed by Yu et al. for Pd-catalyzed C−H activation/C−O cyclization directed by an aliphatic alcohol (Scheme 3).[11] Thus, the reaction is initiated by phenol-directed, rate-limiting C−H bond cleavage with a Pd(II) species.[23] The resulting pallada(II)cycle intermediate is oxidized to a higher oxidation state (e.g., Pd(IV)), from which C−O bond-forming reductive elimination takes place to afford the dibenzofuran product.

Scheme 3. Possible Catalytic Cycle



In summary, we have developed a Pd(II)-catalyzed oxidative cyclization reaction of a 2-arylphenol to a

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(18) The absence of intramolecular KIEs in Liu's system may reflect an electrophilic palladation process: (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

(19) Note that KIEs determined for competition reactions reflect the catalytic step in which the substrate is irreversibly consumed, but not necessarily the rate-limiting step: (a) Vo, L. K.; Singleton, D. A. *Org. Lett.* **2004**, *6*, 2469. (b) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 15258.

(20) For a Pd(II)/Pd(0) catalytic cycle involving BzOO*t*Bu as an oxidant, see: Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

(21) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

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dibenzofuran derivative. The catalytic system features a simple combination of a palladium(II) salt and a pyridine ligand and the use of peroxybenzoate as an inexpensive and convenient oxidant. Mechanistic experiments suggest that the reaction involves Pd(II)-mediated C–H bond cleavage as the rate-limiting step, which is followed by oxidation to a high-oxidation-state palladium species and subsequent C–O bond-forming reductive elimination.

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Supporting Information Available. Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.