Pd(II)-Catalyzed Hydroxyl-Directed C−H Activation/C−O Cyclization: Expedient Construction of Dihydrobenzofurans

Xisheng Wang, Yi Lu, Hui-Xiong Dai, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received June 18, 2010; E-mail: yu200@scripps.edu

Abstract: A Pd(II)-catalyzed C−H activation/C−O cyclization reaction directed by a proximate hydroxyl group has been developed. This reaction provides a new method for constructing dihydrobenzofurans, including spirocyclic analogues, a process that is potentially applicable to natural product synthesis.

Among the myriad ring-forming reactions in organic synthesis, the direct cyclization of tethered carbon atoms or heteroatoms onto proximate C−H bonds is uniquely straightforward and potentially one of the most versatile and practical methods (eq 1).[1] In this context, a number of Pd-catalyzed C−N bond-forming reactions based on amine-directed C−H activation have been developed for the synthesis of azaheterocycles.[2] In contrast, intramolecular reactions of hydroxyl groups with C−H bonds to form furan or pyran derivatives have not been reported to date.[3]

$$ H-\underset{X}{\frown} \xrightarrow{\text{C–H Activation}} \underset{X}{\frown} \qquad X = N, O \qquad (1) $$
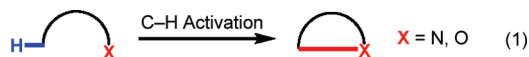
Dihydrobenzofuran rings are common structural motifs in many natural products[4] and pharmaceuticals, including those used to treat traumatic central nervous system (CNS) injury, arteriosclerosis, and hepatopathy (Scheme 1).[5] Hence, effective methods for the construction of dihydrobenzofurans have been actively pursued during the past several decades.[3,6] Notably, C−O coupling reactions catalyzed by Pd(0)[7] and Cu(I)[8] have become indispensible in the preparation of such motifs. Herein we report a new dihydrobenzofuran ring-forming process via hydroxyl-directed C−H activation/C−O bond formation. This reaction provides a potentially powerful disconnection for complex dihydrobenzofuran-containing natural products and drug molecules, particularly since the alcohol precursors can readily be prepared from ketones or esters and Grignard reagents.

Scheme 1. Natural Products and Pharmaceuticals That Contain Dihydrobenzofuran Rings

Stachybotrylactam

Methyl rocaglate: R = CO₂Me.
Rocaglamide: R = CONH₂.

Oxycontin
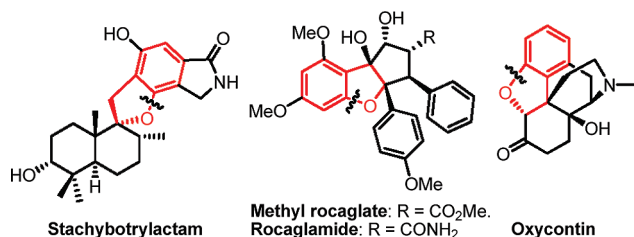
In comparison with amine-directed C−H activation/C−N bond-forming reactions, dihydrobenzofuran formation via C−H activation offers a distinct challenge. Hydroxyl-directed C−H activation is far from being well-established. Nevertheless, our recent report of the first example of hydroxyl-directed C−H

activation promoted by Li₂CO₃ provided us with a stepping stone to explore this idea.[9,10] Focusing on the combination of Pd(II) and Li₂CO₃, we surveyed a wide range of one- and two-electron oxidants in an effort to induce C−O reductive elimination from putative Pd(II), Pd(III),[11] or Pd(IV)[12] intermediates. For instance, we previously used Ag(I)/Cu(II) to promote C−N reductive elimination in a lactam-forming reaction.[2e] However, these oxidants were ineffective in this case (Table 1, entries 1−3). We further tested a one-electron oxidant, Ce(SO₄)₂, which gave complete recovery of starting material (entry 4).[2g] Since a wide range of peroxides have been reported to oxidize Pd(II) to Pd(IV) in a number of C−H oxygenation reactions,[12] we next screened these established peroxide oxidants but again failed to observe the desired product (entries 5−8). Although a few well-established oxidants for halogenation[12] could not induce this cyclization reaction (entries 9−12), we found that a strongly oxidizing fluorinating reagent, NFSI, gave the desired dihydrobenzofuran product in 23% yield, which improved to 73% when 10 mol % Pd(OAc)₂ was used (entry 13). Apparently, intramolecular C−O reductive elimination from the Pd(IV) species is favored over C−F reductive elimination. Encouraged by this result, we further tested PhI(OAc)₂, a generally effective oxidant,[13] and the yield increased to 88% (entry 14). Other high-valent iodonium salts, such as PhI(TFA)₂ and PhI(OPiv)₂, gave lower yields (entries 15 and 16). We extensively screened bases [see the Supporting Information (SI)] and found that Li₂CO₃ and Na₂HPO₄ were the most effective. In the absence of base, the reaction also proceeded to give the desired product in 45% yield, accompanied by substantial starting material decomposition (see the SI).
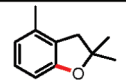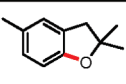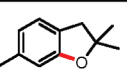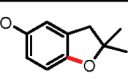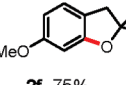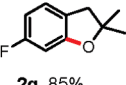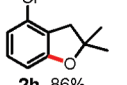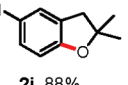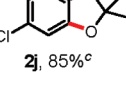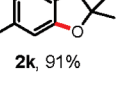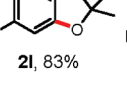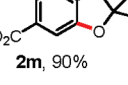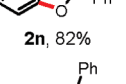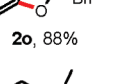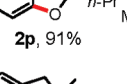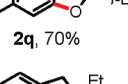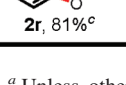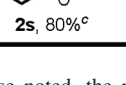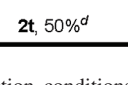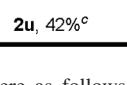
Table 1. Pd(II)-Catalyzed C−H Activation/C−O Cyclization: Survey of Oxidants[a,b,c]

entry	oxidant (equiv)	yield (%)	entry	oxidant (equiv)	yield (%)
1	AgOAc (3.0)	0	9	IOAc (3.0)	0
2	Cu(OAc)₂ (1.5)	0	10	NCS (1.5)	0
3	AgOAc/CuCl₂ (1.5/1.5)	0	11	NIS (1.5)	0
4	Ce(SO₄)₂ (2.0)	0	12	FTMPT (1.5)	0
5	MeCO₃t-Bu (1.5)	0	13	NFSI (1.5)	23 (73[d])
6	K₂S₂O₈ (5.0)	0	14	PhI(OAc)₂ (1.5)	88
7	oxone (5.0)	0	15	PhI(TFA)₂ (1.5)	13
8	(t-BuO)₂ (1.5)	0	16	PhI(OPiv)₂ (1.5)	50

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), Pd(OAc)₂ (0.01 mmol, 5 mol %), oxidant (0.3 mmol, 1.5 equiv), Li₂CO₃ (0.3 mmol, 1.5 equiv), C₆F₆ (2 mL), 100 °C, 36 h. [b] ¹H NMR yields using CH₂Br₂ as the internal standard are reported. [c] NCS = N-chlorosuccinimide, NIS = N-iodosuccinimide, NFSI = N-fluorobenzenesulfonimide, FTMPT = 1-fluoro-2,4,6-trimethylpyridinium triflate. [d] Using 10 mol % Pd(OAc)₂ at 70 °C.

Next, a variety of tertiary alcohols were cyclized to give the corresponding dihydrobenzofurans in good to excellent yields (Table 2). Both electron-donating groups, such as OMe and Me (**2b−f**), and electron-withdrawing groups, such as CF_3, F, Cl, Br, and COOMe (**2g−m**), were tolerated on the aryl ring. The presence of Cl and Br in the products is very useful for further synthetic elaborations. Alkyl and aryl substituents at the α- and β-positions of the alcohols did not adversely affect the reaction (**2n−s**), while the presence of an α-ester group decreased the yield to 50% (**2t**). Unsurprisingly, cyclization of secondary alcohol **1u** gave the desired product in substantially lower yield (**2u**), presumably because of competitive oxidation of the alcohol to the ketone, which was observed.

Table 2. Pd(II)-Catalyzed C−H Activation/C−O Cyclization[a,b]

2b, 88%   2c, 83%   2d, 85%   2e, 76%[c]
2f, 75%   2g, 85%   2h, 86%   2i, 88%
2j, 85%[c]   2k, 91%   2l, 83%   2m, 90%
2n, 82%   2o, 88%   2p, 91%   2q, 70%
2r, 81%[c]   2s, 80%[c]   2t, 50%[d]   2u, 42%[c]

[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), Pd(OAc)$_2$ (0.01 mmol, 5 mol %), PhI(OAc)$_2$ (0.3 mmol, 1.5 equiv), Li$_2$CO$_3$ (0.3 mmol, 1.5 equiv), C$_6$F$_6$ (2 mL), 100 °C, 36 h. [b] Isolated yields are reported. [c] Na$_2$HPO$_4$ was used instead of Li$_2$CO$_3$. [d] Using 10 mol % Pd(OAc)$_2$.

Since ortho-brominated substrates are known to undergo C−O cyclization through Pd(0) and Cu(I) catalysis,[7,8] substrate **1v** was subjected to this newly developed protocol, and the dihydrobenzofuran product **2v** was obtained in 88% yield. This result demonstrates the complementary reactivity of this new transformation (Scheme 2), and the remaining bromide is a very useful handle for subsequent transformations.

Scheme 2. Pd(0)- and Pd(II)-Catalyzed C−O Cyclization
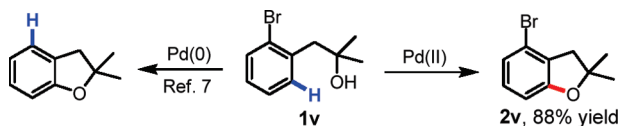
To test whether this transformation could be applied in the synthesis of natural products and drug molecules containing spirocyclic dihydrobenzofurans, we prepared tertiary alcohols **1w** and **1x** by reacting cyclohexanone and 1-decalone, respectively, with Grignard reagents. Gratifyingly, both alcohols smoothly cyclized to give the corresponding spirocyclic products in good yields (Scheme 3).

A plausible mechanism appears to involve Pd(II)-catalyzed C−H cleavage followed by oxidation of Pd(II) to a higher oxidation

Scheme 3. Construction of Spirocyclic Core Skeletons via Pd(II)-Catalyzed C−O Cyclization

1w, cyclohexanol
1x, decahydronaphthalenol

2w, 85% yield
2x, 83% yield

state,[11,12] from which C−O reductive elimination takes place (Scheme 4). Notably, the reaction was found to proceed to some extent in the absence of the base. Since the formation of the [Pd(II)−OR] species as the C−H activation precursor is unfavorable under neutral conditions, we propose that the hydroxyl moiety coordinates with Pd(II) as a neutral σ donor.

Scheme 4. Plausible Mechanism
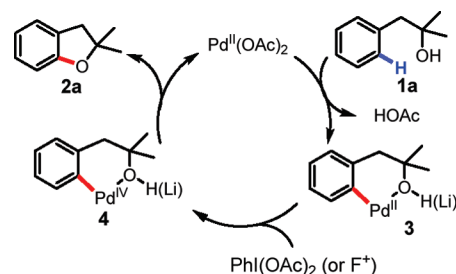
In summary, we have developed a Pd(II)-catalyzed hydroxyl-directed C−H activation/C−O cyclization reaction. This reaction provides a new method for constructing dihydrobenzofurans, including spirocyclic compounds that are potentially relevant to natural product synthesis.

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

References

(1) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.
(2) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (c) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (d) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (e) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (f) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (g) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (h) Neumann, J. J.; Rakshit, S.; Droege, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.
(3) For related dihydrobenzofuran syntheses via C−H activation/C−C bond formation, see: (a) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.
(4) (a) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 4. (b) Apers, S.; Vlietinck, A.; Pieters, L. *Phytochem. Rev.* **2003**, *2*, 201.
(5) (a) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559. (b) Aono, T.; Ohkawa, S.; Doi, T. EP Patent 483772, 1992.
(6) (a) Kuethe, J. T.; Wong, A.; Journet, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 3727, and references cited therein. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.
(7) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am.*

Chem. Soc. **2000**, *122*, 10718. (c) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202. (d) For a new strategy, see: Maimone, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 9990.

(8) (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (b) Wolter, M.; Nordmann, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (c) Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243. (d) Niu, J.; Guo, P.; Kang, J.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2009**, *74*, 5075.

(9) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916.

(10) For phenol-directed intramolecular C−H arylation via Pd(0) catalysis, see: (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

(b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740.

(11) (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

(12) For a recent review of Pd(IV) chemistry, see: Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412.

(13) (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

JA105366U