ORGANIC
LETTERS

2012
Vol. 14, No. 4
1098–1101

A Novel Entry to Functionalized Benzofurans and Indoles *via* Palladium(0)-Catalyzed Arylative Dearomatization of Furans

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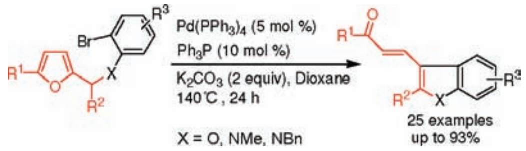
Received January 3, 2012

ABSTRACT



A novel entry to functionalized benzofurans and indoles from furans in moderate to good yields has been developed. This protocol involves palladium(0)-catalyzed dearomatizing intramolecular arylation of the furan ring, formation of a π-allylic palladium complex, furan ring opening, and a β-hydride elimination sequence.

Dearomatization of aromatic compounds has attracted considerable attention because it provides a simple method to achieve functionalized alicyclic synthetic building blocks which can be utilized as intermediates for the preparation of natural products and bioactive compounds.[1,2] Of particular interest is the dearomatization of furans due to their low Dewar resonance energy of 4.3 kcal mol and because furan rings contain masked functionalities of olefin, diene, enol ether, and 1,4-dicarbony. Accordingly, their partial dearomatization allows the reactivity of the remaining unsaturation to be intensively exploited. To date, there are a number of different methods that, with unequal scope, allow the dearomatization of the furan ring and which have been used extensively in the synthesis of numerous bioactive molecules.[3] Among these methods, there are only a few examples of transition-metal-catalyzed dearomatizing processes being used for organic synthesis. These examples are limited to the highly toxic metals omsium[4] and chromium[5] or noble metals such as gold.[6] Over the past decades,

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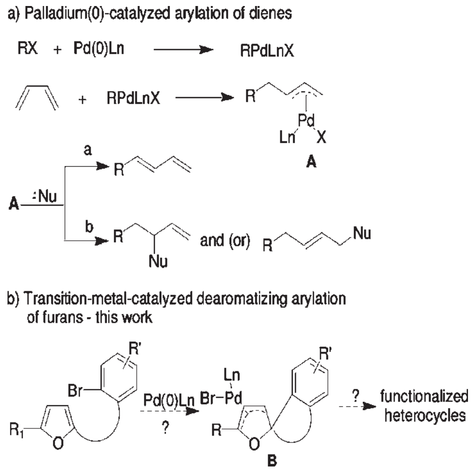
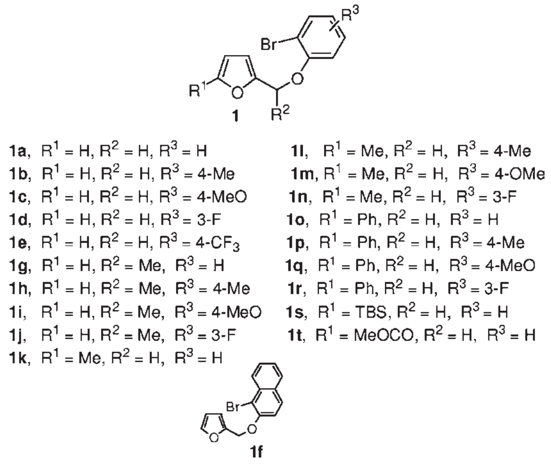
10.1021/ol300008d

palladium(0) catalysis of organic halides and reactions that occur *via* π-allyl palladium complexes have received tremendous interest as a consequence of the resulting C−C and C−heteroatom bonds.[7] However, palladium (0)-catalyzed dearomatization of a furan ring involving these two species to provide access to novel heterocyclic compounds has seldom been reported.

Scheme 1. Palladium-Catalyzed Arylation of Conjugated Dienes



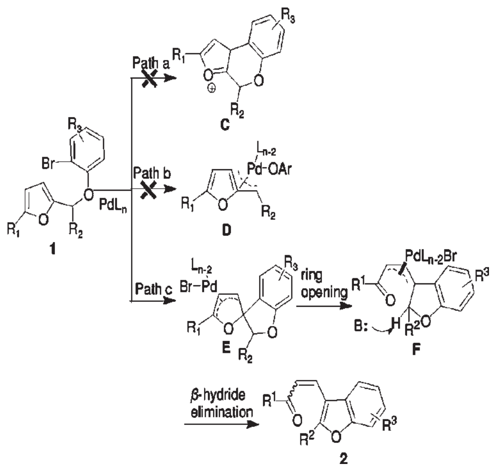
Palladium(0)-catalyzed reactions of aryl halides or vinylic halides with dienes produce a π-allylic palladium complex **A** which then undergoes a hydride elimination to form a substituted diene or reacts with mild nucleophiles such as amines and stabilized carbanions to form allylated products (Scheme 1a).[8] Furan rings have usually been characterized as a special class of dienes in organic synthesis. For example, furan rings undergo a Diels−Alder reaction with dienophiles during the construction of different bicyclic or tricyclic skeletons.[9] Acid-catalyzed dearomatizing nucleophilic substitutions of 2-furylcarbinol using a diverse range of nucleophiles gave rise to several conjugated enol ethers.[10] With this outcome considered, it was envisioned that the intramolecular palladium(0)-catalyzed α-arylation of a furan ring could also be used to form a π-allylic palladium complex **B** under suitable conditions (Scheme 1b). The exploration and further transformations of complex **B** would be particularly useful for the construction of functionalized heterocyclic compounds. For example, if methyloxy or methylamine were tethered between the furan and phenyl ring, after an elimination step, fuctionalized benzofurans and indoles could be obtained. Herein are presented the detailed results of this investigation into the novel use of palladium(0)-catalyzed arylative dearomatization of furan rings, which has resulted in fuctionalized benzofurans and indoles, two important classes of heterocycles presented in many pharmaceuticals and natural products.[11,12]



1a, $R^1 = H, R^2 = H, R^3 = H$
1b, $R^1 = H, R^2 = H, R^3 = 4\text{-Me}$
1c, $R^1 = H, R^2 = H, R^3 = 4\text{-MeO}$
1d, $R^1 = H, R^2 = H, R^3 = 3\text{-F}$
1e, $R^1 = H, R^2 = H, R^3 = 4\text{-CF}_3$
1g, $R^1 = H, R^2 = Me, R^3 = H$
1h, $R^1 = H, R^2 = Me, R^3 = 4\text{-Me}$
1i, $R^1 = H, R^2 = Me, R^3 = 4\text{-MeO}$
1j, $R^1 = H, R^2 = Me, R^3 = 3\text{-F}$
1k, $R^1 = Me, R^2 = H, R^3 = H$
1l, $R^1 = Me, R^2 = H, R^3 = 4\text{-Me}$
1m, $R^1 = Me, R^2 = H, R^3 = 4\text{-OMe}$
1n, $R^1 = Me, R^2 = H, R^3 = 3\text{-F}$
1o, $R^1 = Ph, R^2 = H, R^3 = H$
1p, $R^1 = Ph, R^2 = H, R^3 = 4\text{-Me}$
1q, $R^1 = Ph, R^2 = H, R^3 = 4\text{-MeO}$
1r, $R^1 = Ph, R^2 = H, R^3 = 3\text{-F}$
1s, $R^1 = TBS, R^2 = H, R^3 = H$
1t, $R^1 = MeOCO, R^2 = H, R^3 = H$

Figure 1. 2-(2-Bromo-phenoxy-methyl)-furans **1** used in this study.

Scheme 2. Strategy for Pd(0)-Catalyzed Dearomatization of Furan and Potential Challenges



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(7) For some recent books on palladium catalysis in organic synthesis, see: (a) Tsuji, J. *Palladium Reagents and Catalysts—Innovation in Organic Synthesis*; John Wiley & Sons: New York, 1995. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vols. 1 and 2. (c) Tsuji, J. *Palladium Reagents and Catalysts—New Perspectives for the 21st Century*; John Wiley & Sons: New York, 2004.

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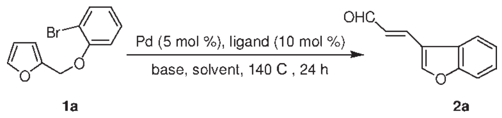
Initially the transformation of 2-(2-bromo-phenoxymethyl)-furans (**1**) (Figure 1), which were prepared *via* the Mitsunobu reaction of 2-furylcarbinols with phenols, into benzofurans was studied. The success of this dearomatization strategy (Scheme 2, Path c) relies on the careful selection of the substrate **1** and choosing suitable reaction conditions to suppress the C3 arylation of the furan ring[13] (Path a) and the C–O bond cleavage to form the π-allylic palladium complex **D** (Path b). With these considerations, the reaction conditions were optimized using furan **1a** as a model. With $Pd(PPh_3)_4$ (5 mol %), PPh_3 (10 mol %), and Cs_2CO_3 (1.5 equiv) in dioxane at 140 °C for 24 h, furan **1a** was transformed into (*E*)-3-benzofuran-3-yl-propenal **2a** in 17% yield (Table 1, entry 1). An evaluation of the effect of the base revealed a significant increase in yield to 34% when Cs_2CO_3 (1.5 equiv) was substituted for K_2CO_3 (entry 4). Increasing the amount of K_2CO_3 to 2 equiv further increased the yield to 61% (entry 7). However an excess of K_2CO_3 (3 equiv) gave a slightly lower yield (entry 8). By screening the solvent used, it was determined that dioxane was optimal (entries 9–11). Finally, it was noted that no yield improvement occurred when switching to $Pd_2(dba)_3$ as a palladium source or diphosphines as ligands (entries 12–13). It was therefore concluded that the optimal combination for this reaction was to use dioxane as the solvent, $Pd(PPh_3)$ (5% mol) as the catalyst, PPh_3 as the ligand (10%), and K_2CO_3 (2 equiv) as the base.

Table 1. Optimization of the Reaction Conditions[a,b]



entry	[Pd]	base (equiv)	solvent	yield (%)[c]
1	$Pd(PPh_3)_4$	Cs_2CO_3 (1.5)	dioxane	17
2	$Pd(PPh_3)_4$	K_3PO_4 (1.5)	dioxane	trace
3	$Pd(PPh_3)_4$	KO*t*-Bu (1.5)	dioxane	trace
4	$Pd(PPh_3)_4$	K_2CO_3 (1.5)	dioxane	34
5	$Pd(PPh_3)_4$	DBU (1.5)	dioxane	trace
6	$Pd(PPh_3)_4$	TEA (1.5)	dioxane	ND[d]
7	$Pd(PPh_3)_4$	K_2CO_3 (2)	dioxane	61
8	$Pd(PPh_3)_4$	K_2CO_3 (3)	dioxane	51
9	$Pd(PPh_3)_4$	K_2CO_3 (2)	CH_3CN	46
10	$Pd(PPh_3)_4$	K_2CO_3 (2)	DMF	23
11	$Pd(PPh_3)_4$	K_2CO_3 (2)	DMSO	31
12	$Pd_2(dba)_3$	K_2CO_3 (1.5)	dioxane	39[e]
13	$Pd_2(dba)_3$	K_2CO_3 (1.5)	dioxane	25[f]

[a] Reaction conditions: [Pd] (5 mol %), ligand (10 mol %), base (1 mmol), and furan **1a** (0.5 mmol) in solvent (5 mL) at 140 °C for 24 h. [b] Unless otherwise noted, the ligand was PPh_3. [c] The yield was determined by NMR methods using 1,3,5-trimethylbenzene as an internal standard. [d] ND: not detected. [e] With dppp (1,3-bis(diphenylphosphino)-propane) as the ligand. [f] With dppf (1,1′-bis(diphenylphosphino) ferrocene) as the ligand.

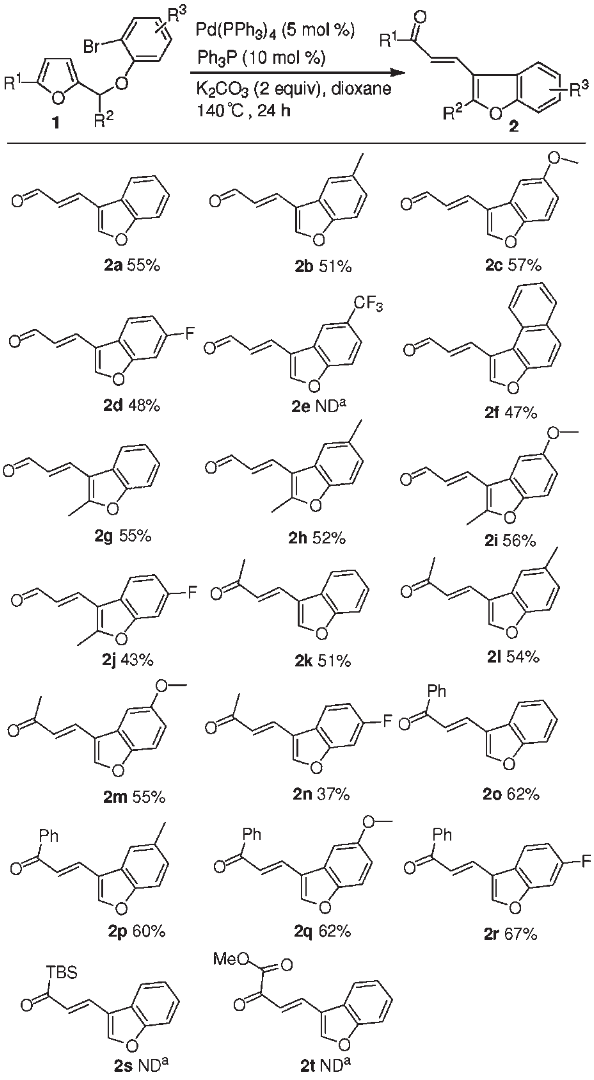


Figure 2. Scope of the Pd-catalyzed dearomatization of furans under the following reaction conditions: $Pd(PPh_3)_4$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (1 mmol), and **1** (0.5 mmol) in 1,4-dioxane (5 mL) at 140 °C for 24 h. The percentages correspond to the isolated yields. [a]ND: not detected.

To investigate the scope of the reaction, a series of furan **1** with variable R^1, R^2, and R^3 groups were used to produce a range of benzofurans **2** under the optimized reaction conditions. The resulting compounds illustrated in Figure 2 indicate that contribution of the electrons from the substituent groups (R^3) on the phenyl rings have a significant influence on the reaction. Electron-donating R^3 groups generally promoted higher yields. However **1e** which had a 4-CF_3 group on its phenyl ring did not provide the desired product **2e**; instead it produced a complicated reaction system. A possible explanation for this failure might lie in

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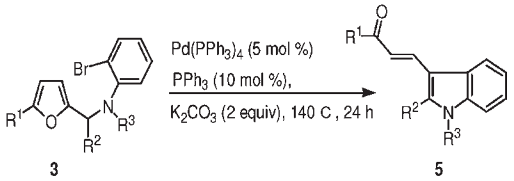
(12) For a review on the synthesis of indoles, see: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 215.

(13) For a review on C3 direct arylation of heteroaromatic compounds with aryl halides by C–H bond activation, see: Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

Scheme 3. Synthesis of Indoles



3a, R^1 = H, R^2 = H, R^3 = Me	**5a** (83%)
3b, R^1 = Me, R^2 = H, R^3 = Me	**5b** (87%)
3c, R^1 = Ph, R^2 = H, R^3 = Me	**5c** (93%)
3d, R^1 = H, R^2 = Me, R^3 = Me	**5d** (90%)
3e, R^1 = H, R^2 = H, R^3 = Bn	**5e** (88%)

the better leaving ability of the 4-CF$_3$-phenoxyl group resulting in the cleavage of the C–O bond in the presence of the Pd(0) catalyst. With respect to the substitution on the furan ring, some electron-neutral groups (R^1 = H, Me, Ph) were well tolerated. When R^1 was TBS, or methoxycarbonyl groups, the reactions were proven to be unsuccessful (**2s**, **2t**). It should also be noted that the yields of enals (R^1 = H) were generally lower than those of the corresponding enones (R^1 = Me or Ph) possibly as a result of the partial decomposition of the enals under basic reaction conditions.

The focus of the study then switched to the possibility of synthesizing functionalized indoles using the same reaction conditions as in the case of benzofurans (Scheme 3).[14] It was found that treatment of 2-furanmethanamines (**3a**–**3e**) under the same reaction condition as those used for furan **1** produced very high yields of five functionalized indoles (**5a**–**5e**).

In summary, a novel entry to functionalized benzofurans and indoles starting from furans has been developed. The protocol involves palladium(0)-catalyzed dearomatizing C2 arylation of the furan ring, the formation of a π-allylic palladium complex, furan ring opening, and a β-hydride elimination. This research demonstrates the possibility of carbopalladation of the double bond of the furan ring, in the same way as a common double bond, and expands the synthetic application of five-membered aromatic rings as building blocks. Further studies on the reaction scope and trapping the π-allylic palladium complex with intermolecular nucleophiles to synthesize structurally novel spiro-compounds are currently underway. The results will be reported in due course.

Acknowledgment. This work was support by the Fundamental Research Funds for the Central Universities (2012ZZ043), the National Natural Science Foundation of China (No. 21072062), and the Natural Science Foundation of Guangdong Province, China (10351064101000000).

Supporting Information Available. Details on general experimental methods, and copies of ^{1}H and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(14) For a similar synthesis of functionalized indoles using aryl iodide under microwave irradiation, see: Kaim, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887.