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Pd-Catalyzed O-Arylation of Ethyl Acetohydroximate: Synthesis of *O*-Arylhydroxylamines and Substituted Benzofurans

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Abstract: An efficient Pd catalyst for the O-arylation of ethyl acetohydroximate with aryl chlorides, bromides, and iodides has been developed. Ethyl acetohydroximate serves as an efficient hydroxylamine equivalent for C−O cross-coupling, thereby allowing for the preparation of *O*-arylhydroxylamines from simple aryl halides. Short reaction times and broad substrate scope, including heteroaryl coupling partners, allow access to *O*-arylhydroxylamines that would be difficult to prepare in a single step by traditional methods. Moreover, the O-arylated products so formed can be directly transformed into substituted benzofurans in a single operation.

Owing to their facile incorporation into a variety of bioactive oxime linkages,[1] use as tagging elements for library synthesis,[2] and function as key starting materials for the synthesis of benzofurans,[3] *O*-arylhydroxylamines (aryloxyamines) represent valuable synthetic building blocks. Historically, this motif has been constructed via S_NAr-type processes of various hydroxylamine equivalents (e.g., *N*-hydroxyphthalimide, ethyl acetohydroximate) with highly electron-deficient aromatic systems, including arene−metal complexes.[4] In addition, *N*-transfer reagents have also been employed to form the N−O linkage from the corresponding phenol.[5] Given the limited generality in these processes, recent emphasis has been placed on the copper-mediated construction of Ar−ON(R) bonds. Maitra and Wailes have reported the coupling of oximes with aryl iodides catalyzed by a CuI/1,10-Phenanthroline system.[6] In addition, both Huang and Meyer have reported the coupling of oximes with arylboronic acids utilizing Cu(II) salts.[7] To date, however, it is perhaps the copper-mediated coupling of aryl boronic acids with *N*-hydroxyphthalimide, reported by Sharpless and Kelly, that represents the most general route to *O*-arylhydroxylamines.[8] We envisioned that a Pd-catalyzed coupling of simple aryl halides with a suitable hydroxylamine equivalent (Figure 1) could potentially address many of the shortcomings of the aforementioned Cu-based methodologies—namely low to moderate yields, long reaction times, difficulty with substrates containing *ortho*-substituents, lack of heterocyclic substrates, and the necessity to employ aryl iodides or arylboronic acids as coupling partners. Herein, we report a Pd-catalyzed method that utilizes commercially available ethyl acetohydroximate as the hydroxylamine equivalent. The O-arylated products so formed can easily be cleaved with aqueous acid to produce *O*-arylhydroxylamines or directly processed to substituted benzofurans.

A survey of biarylphosphine ligands revealed that a catalyst based on *t*-BuBrettPhos[9] (**1**) was highly active in the cross-coupling of

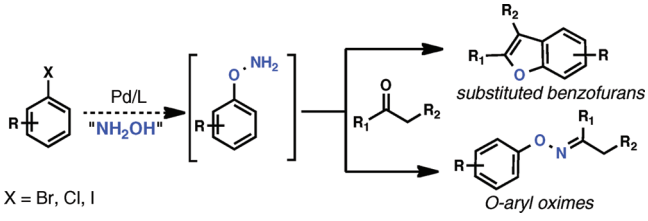
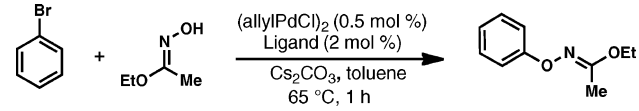


Figure 1. Desired transformation.

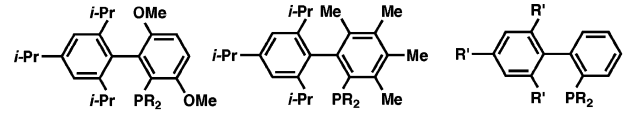
Table 1. Ligand Evaluation[a]



Entry	Ligand	Conversion[b]	Entry	Ligand	Conversion[b]
1	**1**	100%	4	**2**	0%
2	**3**	70%	5	**5**	0%
3	**4**	51%	6	**6**	0%

[a] PhBr (1.5 mmol), ethyl acetohydroximate (1.9 mmol), Cs_2CO_3 (2.3 mmol), $(allylPdCl)_2$ (0.5 mol %), Ligand (2 mol %), toluene (3 mL), 65 °C, 1 h. [b] Determined by GC.

PhBr with ethyl acetohydroximate (Table 1). Ligands **3** and **4** which have previously been employed in Pd-catalyzed C−O coupling processes between aryl halides and alcohols or phenols could be employed for this transformation, albeit with diminished efficiency.[10] Ligand **6**, which lacks the tri-isopropyl groups, as well as ligands **2** and **5** which do not contain the di-*tert*-butyl phosphine moiety, were all ineffective under these conditions. The high activity displayed with **1** was crucial due to both the thermal sensitivity of the product N−O linkage,[11] and the ability of Pd(0) to oxidatively add into this bond at elevated temperatures.[12]



1: R = *t*-Bu (*t*-BuBrettPhos)
2: R = Cy (BrettPhos)

3: R = *t*-Bu

4: R = *t*-Bu, R' = *i*-Pr (*t*-BuXPhos)
5: R = Cy, R' = *i*-Pr (XPhos)
6: R = *t*-Bu, R' = H (JohnPhos)

The generality of the coupling process is shown by the examples in Table 2. Aryl chlorides, bromides, and iodides could all be employed, with aryl bromides being optimal and electron-rich aryl chlorides being most problematic.[13] Using 1% Pd,[14] 2% **1**, and Cs_2CO_3 as base, many electron-neutral or -deficient aryl bromides were found to undergo complete conversion within 1 h at 65 °C in toluene. The couplings of 1,4-bromochlorobenzene and 1,2-bromofluorobenzene were performed on scales of 5 and 10 mmol, respectively. In addition, a variety of heteroaryl halides including pyridinyl, quinolinyl, pyrimidinyl, and benzothiazolyl were found to readily undergo coupling. Heterocycles containing acidic *N*-H groups, such as indoles and imidazoles, have proven problematic to date. We have found that for aryl bromides containing *ortho*-alkyl substituents, the use of ligand **4** gives superior results to that with **1**, presumably due to its smaller size. Using this system even hindered substrates with an isopropyl or phenyl group in the *ortho* position undergo efficient coupling (Table 2). The O-arylated products can be easily hydrolyzed to the free oxyamines by exposure to aqueous HCl (Table 3).

O-Arylketoximes bearing acidic α-hydrogens are known to rearrange to benzofurans via a [3,3] sigmatropic process, closely paralleling the venerable Fischer indole synthesis.[3] Of interest to us was the

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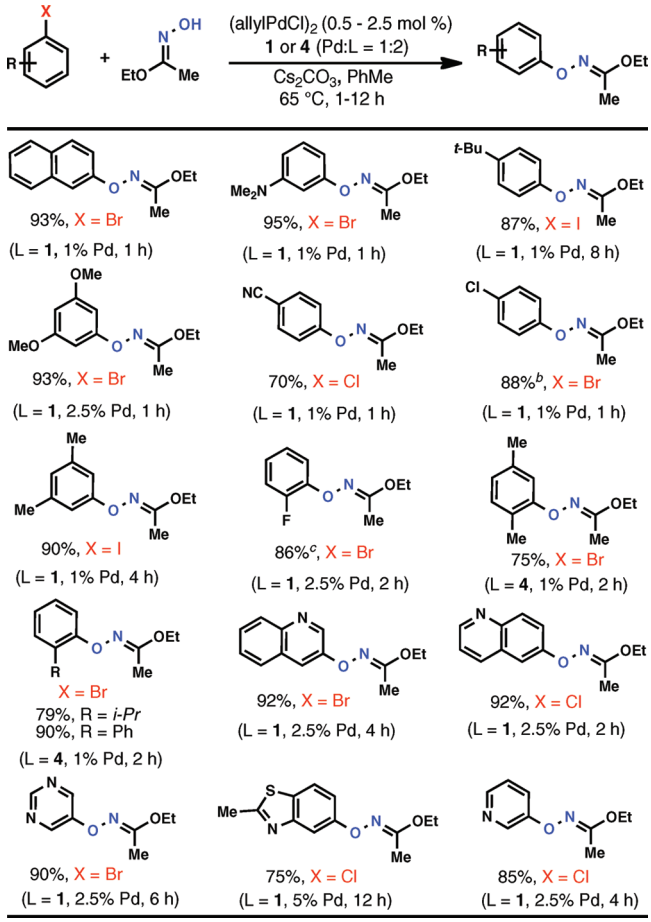
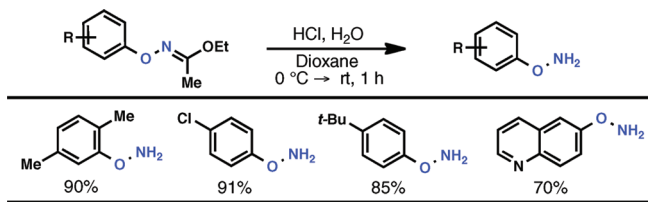
Table 2. Palladium-Catalzyed O-Arylation of Ethyl Acetohydroximate[a]



[a] ArX (1 mmol), Ethyl Acetohydroximate (1.25 mmol), Cs_2CO_3 (1.5 mmol), $(allylPdCl)_2$ (0.5−2.5 mol %), **1** or **4** (2−10 mol %), PhMe (2 mL), 65 °C, 1−12 h; isolated yields, average of two or more runs. [b] Yield on a 10 mmol scale = 87%. [c] Yield on a 5 mmol scale = 88%.

Table 3. Oxime Hydrolysis[a]



[a] Oxime (1 equiv), HCl (6 M in H_2O, 2 equiv), 1,4-dioxane (0.5 M), 0 °C → rt, 1 h; isolated yields, average of two runs on a 0.5−1.0 mmol scale.

prospect of directly converting the products of the Pd-coupling into benzofurans in a process reminiscent of our prior work in the Fischer indolization.[15] After significant experimentation, we found that exposure of the O-arylated ethyl acetohydroximate product to an exogenous ketone and H_2O in HCl/dioxane at 70 °C produces the corresponding benzofuran in synthetically useful yields (Table 4).

In summary, a hydroxylamine equivalent has been developed for Pd-catalyzed C−O cross-coupling. Key to the success of this reaction was the use of bulky biarylphosphine ligands **1** and **4**, which promote C−O reductive elimination under relatively mild conditions. Broad substrate scope and short reaction times make this an attractive method to prepare highly substituted *O*-arylhydroxylamines and benzofurans from simple aryl halides.

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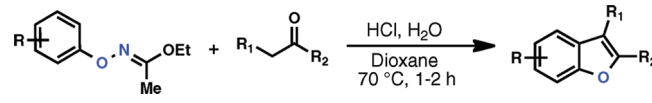
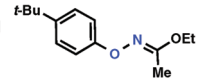
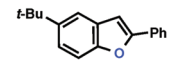
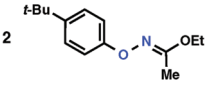
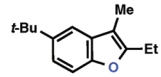
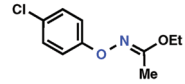
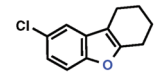
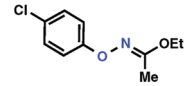
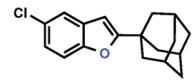
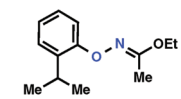
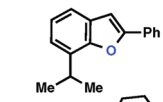
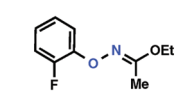
Table 4. One-Pot Synthesis of Benzofurans[a]



Entry	Substrate	Ketone	Product	Yield [%]	Time [h]
1				86%	1
2				68%	1
3				88%	1
4				83%	2
5				68%	2
6				55%	2

[a] Oxime (1 equiv), ketone (2 equiv), H_2O (5 equiv), HCl (4 M in dioxane, 5 equiv), 1,4-dioxane (0.2 M), 70 °C, 1−2 h; isolated yield, average of two runs on a 0.5−1.0 mmol scale.

Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamedmohaideen, N. N.; Purkey, H. E.; Nichols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K. B.; Kelly, J. W. *J. Med. Chem.* **2005**, *48*, 1576.
(2) Nazarpack-Kandlousy, N.; Chernushevich, I. V.; Meng, L.; Yang, Y.; Eliseev, A. V. *J. Am. Chem. Soc.* **2000**, *122*, 3358.
(3) (a) Sheradsky, T. *Tetrahedron Lett.* **1966**, *7*, 5225. (b) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 4399. (c) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 1491.
(4) (a) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 594. (b) Cadogan, J. I. G.; Rowley, A. G. *Synth. Commun.* **1977**, *7*, 365. (c) Baldoni, C.; Del Bettero, P.; Licandro, E.; Maiorana, S. *Synthesis* **1988**, 344.
(5) (a) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1348. (b) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *Synthesis* **1977**, 1. (c) Foot, O. F.; Knight, D. W. *Chem. Commun.* **2000**, 975.
(6) Prithwiraj, D.; Nonappa; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, 2767.
(7) (a) Feng, X.-H.; Zhang, G.-Z.; Chen, C.-Q.; Yang, M.-Y.; Xu, X.-Y.; Huang, G.-S. *Synth. Commun.* **2009**, *39*, 1768. (b) Abdelselam, A.; Meyer, A. G.; Tuck, K. L. *Synlett* **2009**, 955. A polymer supported Cu-catalyst has also been shown to couple oximes with aryl boronic acids, see Wang, L.; Huang, C.; Cai, C. *Catalysis Comm.* **2010**, *11*, 532.
(8) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139.
(9) For use of **1** see: (a) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576. (b) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (c) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898.
(10) (a) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. (b) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321.
(11) Blake, J. A.; Pratt, D. A.; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 3112.
(12) For many examples of oxidative addition of Pd(0) into polarized oxime N-O bonds see:Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505.
(13) We have observed the following trend in rate of C-O coupling: PhBr > PhI > PhCl.
(14) The use of $Pd_2(dba)_3$ gives similar results to $(allylPdCl)_2$.
(15) (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

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