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

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

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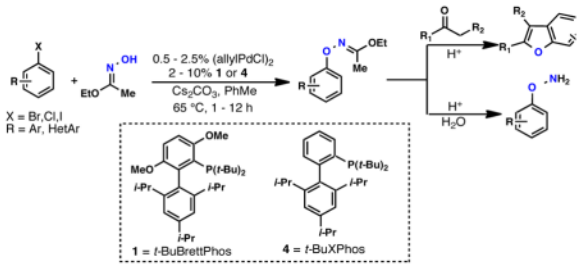
Abstract



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, allows 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] as well as serving 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

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SUPPORTING INFORMATION AVAILABLE: Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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 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-*i*-propyl groups, as well as ligands **2** and **5** which do not contain the di-*t*-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] as well as the ability of Pd(0) to oxidatively add into this bond at elevated temperatures.[12]

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 hour 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 *i*-propyl 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 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 makes this an attractive method to prepare highly substituted *O*-arylhydroxylamines and benzofurans from simple aryl halides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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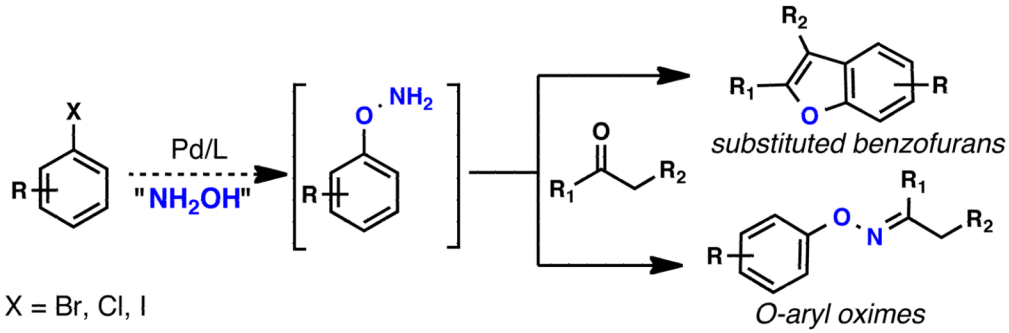
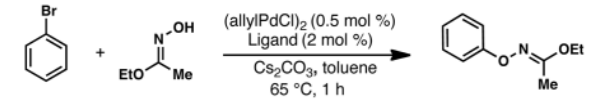


Figure 1.
Desired Transformation.

Table 1

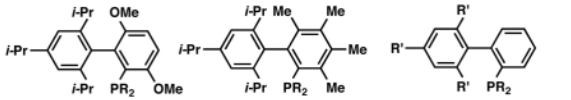
Ligand Evaluation.[a]



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



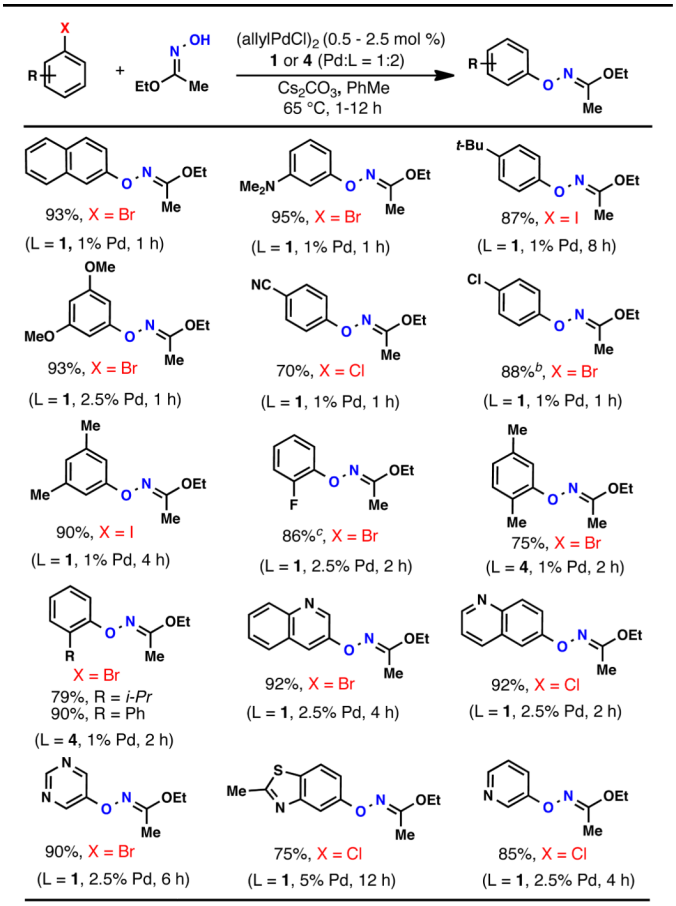
1: R = *t*-Bu (*t*-BuBrettPhos)
2: R = Cy (BrettPhos)

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)

Table 2

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



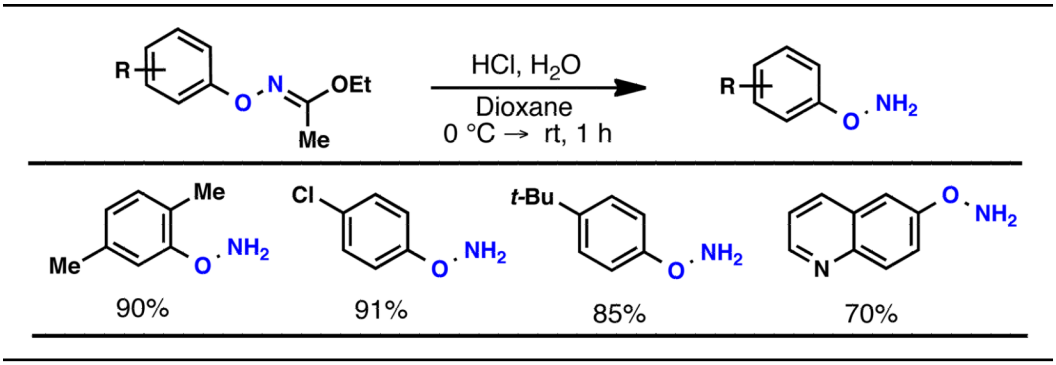
[a] ArX (1 mmol), Ethyl Acetohydroximate (1.25 mmol), Cs_2CO_3 (1.5 mmol), $(allylPdCl)_2$ (0.5 – 2.5 mol %), **1** or **4** (2 – 10 mol %), PhMe (2 ml), 65 °C, 1–12 h; isolated yields, average of 2 or more runs.

[b] yield on a 10 mmol scale = 87%.

[c] yield on a 5 mmol scale = 88%.

Table 3

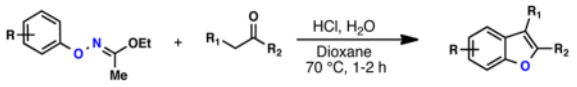
Oxime Hydrolysis.[a]

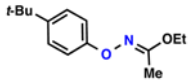
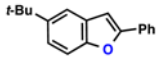
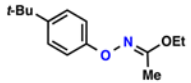
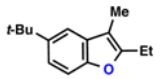
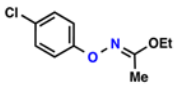
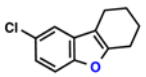
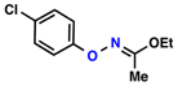
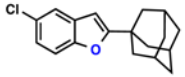
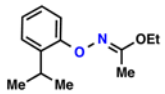
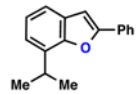
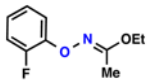
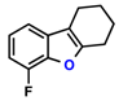


[a]Oxime (1 equiv), HCl (6 M in H_2O, 2 equiv), 1,4-dioxane (0.5 M), 0 °C → rt, 1 h; isolated yields, average of 2 runs on a 0.5 – 1.0 mmol scale.

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 2 runs on a 0.5 – 1.0 mmol scale.