

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*-BuBrettPhos⁹ (**1**) was highly active in the cross-coupling of

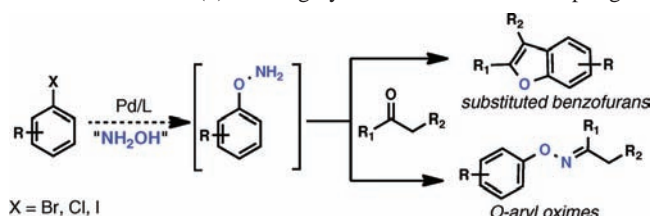


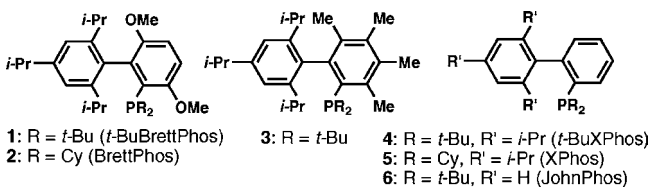
Figure 1. Desired transformation.

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%

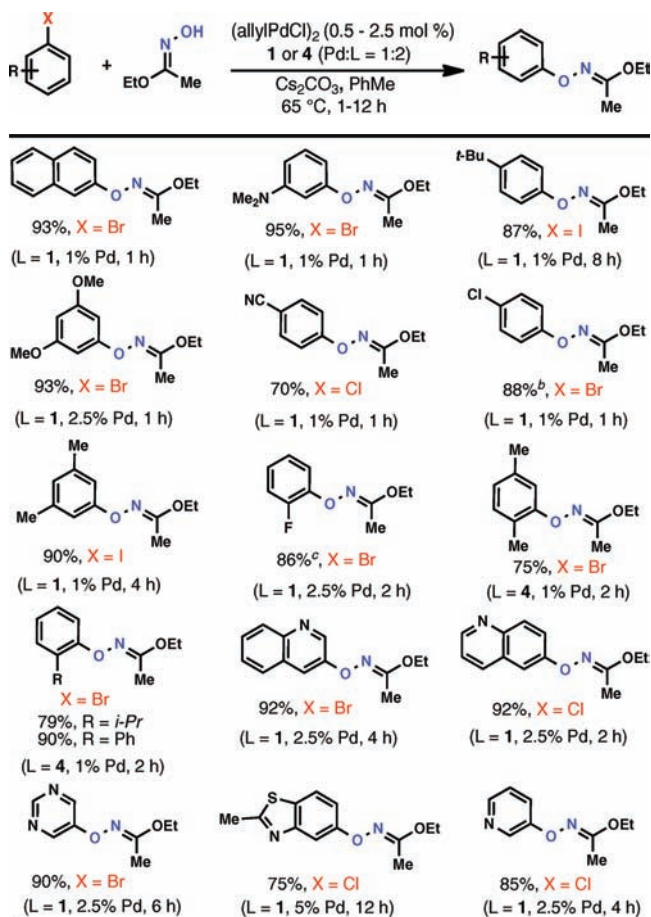
^a PhBr (1.5 mmol), ethyl acetohydroximate (1.9 mmol), Cs₂CO₃ (2.3 mmol), (allylPdCl)₂ (0.5 mol %), Ligand (2 mol %), toluene (3 mL), 65 °C, 1 h. ^b Determined by GC.

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

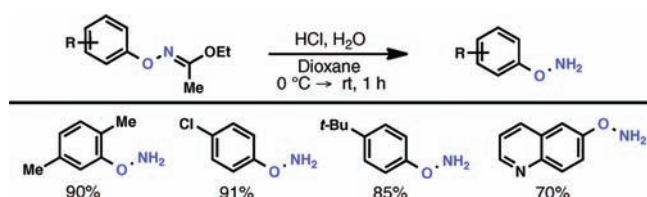


The generality of the coupling process is shown by the examples in Table 2. Aryl chlorides, bromides, and iodides could all be employed, with aryl bromides being optimal and electron-rich aryl chlorides being most problematic.¹³ Using 1% Pd,¹⁴ 2% **1**, and Cs₂CO₃ as base, many electron-neutral or -deficient 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

Table 2. Palladium-Catalyzed O-Arylation of Ethyl Acetohydroximate^a

^a ArX (1 mmol), Ethyl Acetohydroximate (1.25 mmol), Cs₂CO₃ (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%.

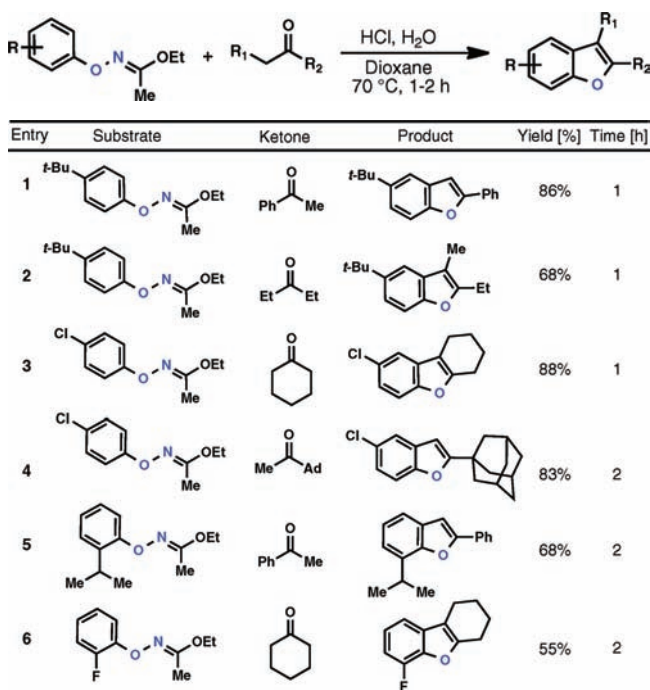
Table 3. Oxime Hydrolysis^a

^a Oxime (1 equiv), HCl (6 M in H₂O, 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 H₂O 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

^a Oxime (1 equiv), ketone (2 equiv), H₂O (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.

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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>.

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