

Synthetic Methods

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Synthesis of Complex Phenols Enabled by a Rationally Designed Hydroxide Surrogate

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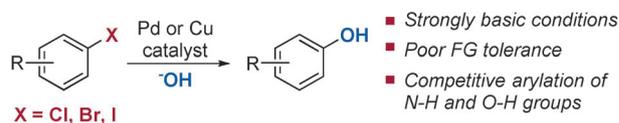
Abstract: The conversion of aryl halides to phenols under mild reaction conditions is a longstanding and formidable challenge in organic chemistry. Herein, we report the rational design of a broadly applicable Pd-catalyzed method to prepare phenols with benzaldehyde oxime as a hydroxide surrogate. These reactions occur under mildly basic conditions and enable the late-stage hydroxylation of several functionally-dense drug-like aryl halides.

Phenols and their derivatives are prevalent across many chemical disciplines, and are components of several pharmaceutical, agrochemical, and material products.^[1] Phenols are also versatile intermediates in organic chemistry for a multitude of transformations. Yet, few methods allow for the formation of Ar–OH bonds in the presence of sensitive functionality found in complex molecules.

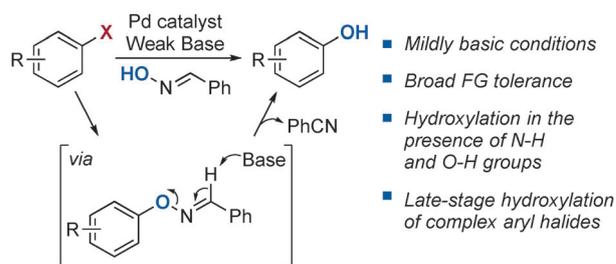
The hydroxylation of aryl halides is among the most attractive strategies to prepare phenols due to the ubiquity of haloarenes.^[2] Both copper- and palladium-catalyzed reactions have been developed to prepare phenols from unactivated aryl halides (Scheme 1 A).^[3,4] However, Cu-catalyzed hydroxylation reactions typically require high temperatures, strong bases, and are predominantly limited to aryl iodides and bromides. Palladium catalysts can promote the conversion of unactivated aryl bromides and chlorides to phenols; however the use of KOH, CsOH, or an organic superbases^[4,5] is still necessary for high yields. Due to the strongly basic conditions, these reactions are not applicable to substrates containing base-sensitive functionality.

Furthermore, a major drawback of reported Pd-catalyzed hydroxylation methods is the lack of hydroxide coupling in the presence of functional groups that can undergo *N*- or *O*-arylation, such as amides, amines, and alcohols. This problem is inherent in coupling reactions with hydroxide, as Ar–Pd–OH complexes react readily with functional groups containing N–H and O–H bonds to form water and the corresponding Ar–Pd–NR₂ or Ar–Pd–OR complexes faster than undergoing Ar–OH reductive elimination.^[6–9] Herein, we report the rational design of an enabling Pd-catalyzed method to prepare phenols that addresses the shortcomings of previous

A. Transition-Metal-Catalyzed Coupling of Hydroxide with Aryl Halides



B. Pd-Catalyzed Synthesis of Phenols with Benzaldehyde Oxime



Scheme 1. Synthesis of phenols from aryl halides.

hydroxylation reactions by avoiding strongly basic conditions and circumventing Ar–Pd–OH species as catalytic intermediates.

We proposed that the limitations of previously reported Pd-catalyzed hydroxylation reactions would be overcome with a suitable hydroxide surrogate in place of KOH or CsOH. The criteria in identifying a hydroxide replacement were that it would: 1) couple under mildly basic conditions, 2) form an intermediate that would liberate the phenol product in situ with an innocuous byproduct, 3) be tolerant of electrophilic and base-sensitive functionality, 4) react in the presence of the phenol products and nucleophilic sites in the substrates, and 5) be readily available, stable, and inexpensive.

With the above considerations in mind, benzaldoxime was identified as a mild hydroxide surrogate that would react to form *O*-aryl oxime intermediates (Scheme 1 B). Base-induced elimination in situ would reveal the phenol product with the concomitant generation of benzonitrile.^[10] It was presumed that benzaldoxime would react under mildly basic conditions due to its similar acidity to phenol (*pK_a* values in DMSO: benzaldoxime, 20; phenol, 18) and significantly reduced basicity compared to hydroxide (H₂O has a *pK_a* of 31 in DMSO). Furthermore, it was anticipated that the benzaldoxime anion, which has enhanced nucleophilicity from the alpha-effect and is sterically unencumbered, would couple to form phenols in the presence of pendant nucleophilic functionality.

Several challenges exist in developing the proposed reaction with benzaldoxime. First, there have been no reports on the Pd-catalyzed *O*-arylation of aldoximes to date, and it

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was unclear whether such a reaction could be developed.^[11] Second, the initially formed *O*-aryl oximes could participate in unproductive side-reactions, as Pd⁰ has been shown to oxidatively insert into the N–O bond of oximes.^[12] Finally, it was unclear how facile the *syn*-elimination would occur with unactivated aryloxy groups under mildly basic reaction conditions (Scheme 1 B).^[10]

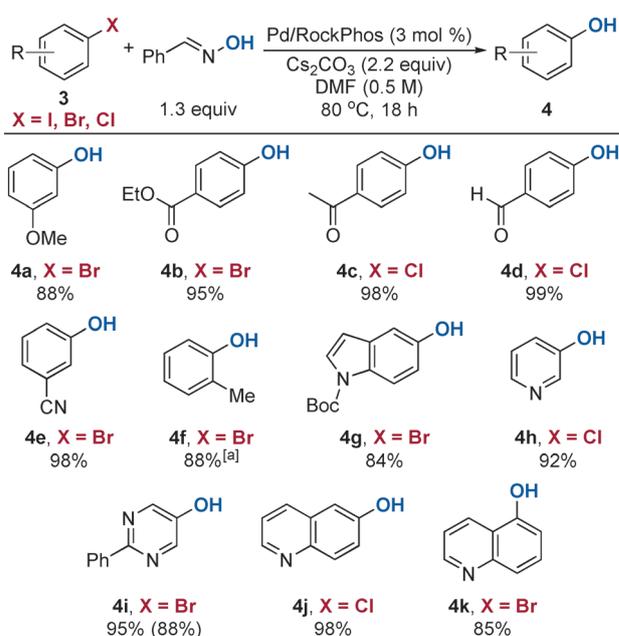
In order to develop the proposed reaction, we carried out several high-throughput experiments. We chose to investigate reactions with **1**, as this substrate contains a reactive aliphatic ester, and an aryl fluoride that can undergo S_NAr reactions. Of particular importance, this substrate underwent complete ester hydrolysis even under the mildest conditions^[4] reported for the Pd-catalyzed hydroxylation of aryl halides (CsOH, rt). After initial screening of solvents, bases, temperatures, and stoichiometries, we performed 96 experiments where we investigated the most promising leads of: two bases (Cs₂CO₃, K₃PO₄), two solvents (DMF, 2-MeTHF), along with 24 Pd G3 precatalysts (Scheme 2 and Supporting Information). The

	DMF Cs ₂ CO ₃	DMF K ₃ PO ₄	2-MeTHF Cs ₂ CO ₃	2-MeTHF K ₃ PO ₄
<i>t</i> Bu ₃ P	0	0	0	0
Mor-DalPhos	0	0	0	0
SPhos	0	0	0	0
BrettPhos	1	2	1	1
AdBippyPhos	2	31	2	2
<i>t</i> BuXPhos	30	13	32	12
Me ₄ <i>t</i> BuXPhos	81	43	60	30
<i>t</i> BuBrettPhos	67	80	76	69
AdBrettPhos	90	81	80	66
RockPhos	95	73	86	73

Scheme 2. High-throughput reaction development. Reaction conditions: 5.0 μmol of **1**, 1.3 equiv benzaldehyde oxime, 2.2 equiv of base, 5 mol% Pd G3 precatalyst, solvent (0.2 M), 80°C, 18 h. Structures of all 24 precatalysts investigated are illustrated in the Supporting Information. Yields were determined by HPLC against an authentic product standard.

combination of Pd/RockPhos, Cs₂CO₃, and DMF provided the product in 95% assay yield. Critically, less than 1% of ester hydrolysis or S_NAr displacement of the aryl fluoride was observed. Reactions performed with a combination of [(allyl)PdCl]₂ or Pd₂(dba)₃ with RockPhos provided similar results to those performed with RockPhos Pd G3 precatalyst. K₃PO₄ could be used in place of Cs₂CO₃ with a slight decrease in the yield of **2** (73% yield). RockPhos/Pd-catalyzed reactions conducted in 2-MeTHF also provided the phenol product in synthetically useful yields with either Cs₂CO₃ (86% yield) or K₃PO₄ (73% yield).

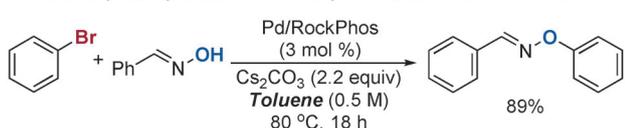
After lowering the catalyst loading and increasing the reaction concentration, we explored the generality of the reaction with respect to the inherent properties of the aryl halide, tolerance of common functional groups, and the ability



Scheme 3. General scope for the conversion of aryl halides to phenols with benzaldehyde oxime. Reactions were performed on 1.0 mmol scale with RockPhos Pd G3 as the precatalyst. [a] *t*BuBrettPhos Pd G3 was used as the precatalyst. Yields were determined by HPLC against authentic product standards. Isolated yield shown in parentheses. Catalyst loadings and reaction times were not optimized for each substrate.

to couple both aryl bromides and chlorides (Scheme 3). As shown, the reaction provides the phenol products in high yields in the presence of esters, ketones, aldehydes, nitriles, and common heterocycles. *Ortho*-alkyl substituted aryl halides coupled in modest yield (65%) with RockPhos as the ligand, however, switching to the less bulky *t*BuBrettPhos ligand allowed for the coupling of 2-bromotoluene in 88% yield.

Monitoring the catalytic reactions by HPLC revealed that intermediate species were present at 3–10% relative to the starting concentration of the aryl halide. The mass spectrum of the intermediate was obtained by LC/MS analysis of a reaction with bromobenzene, and was consistent with the proposed *O*-aryloxime species. To confirm the identity, *O*-phenyl benzaldehyde oxime was prepared from the condensation of *O*-phenylhydroxylamine with benzaldehyde (Scheme 4 A). This species was identical by HPLC and LC/MS analysis to the species observed during a reaction with bromobenzene as the substrate under our catalytic reaction conditions. The isolated oxime reacted with Cs₂CO₃ in DMF at 80°C over 30 minutes with the formation of equimolar amounts of PhOH and PhCN in quantitative yield. In all of our hydroxylation reactions, an equimolar amount of benzonitrile and the phenol product was observed. Control reactions confirmed that phenol is not formed in the absence of benzaldehyde or the Pd precatalyst. Taken together, these results are consistent with a mechanism proceeding via the Pd-catalyzed formation of *O*-aryl benzaldehyde oxime species, followed by Cs₂CO₃-mediated elimination to form the phenol product and benzonitrile. Performing the Pd-catalyzed reaction with toluene in place of DMF suppressed the

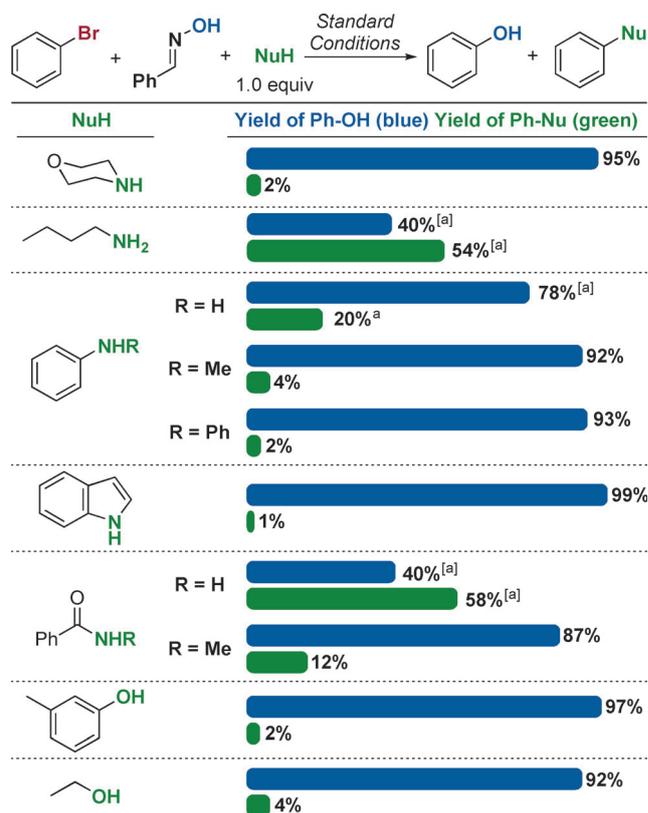
A. Independent Synthesis and Reactivity of *O*-Phenyl BenzaldoximeB. Pd-Catalyzed Synthesis of *O*-Phenyl Benzaldoxime in Toluene

Scheme 4. Studies on the reaction mechanism.

rate of the elimination reaction, and allowed for the synthesis of *O*-phenyl benzaldoxime in 89% yield (Scheme 4B). Notably, this is the first example of a Pd-catalyzed C–O coupling to prepare an *O*-aryl aldehyde oxime.^[11]

Having demonstrated the reaction on simple substrates with an understanding of the reaction mechanism, the reaction was then performed in the presence of functional groups that can undergo competitive *N*- or *O*-arylation reactions. The coupling reaction of bromobenzene was carried out with an equimolar amount of various additives (Nu-H) and the amounts of PhOH and Ph-Nu formed in the reactions were determined.^[13] This experimental design allows for the clear and unambiguous interpretation of the results, and avoids any biasing impact of the nucleophilic groups on the properties of the aryl halide. As shown in Scheme 5, benzaldoxime coupled in preference to common nucleophilic functionality present in drug-like molecules. It was found that primary amino groups couple competitively with benzaldoxime under the standard conditions, likely due to the low concentration of the oxime anion in solution in the presence of a weak heterogeneous base. Pre-forming the cesium salt of benzaldoxime in situ enabled synthetically useful yields of phenol in the presence of primary amino groups (see Supporting Information for details). Phenol was formed in high yield in the presence of secondary amines, anilines, and amides, and in >90% yield in the presence of indole, a phenol, and alcohols. The results from these experiments are significant, as these nucleophilic groups are known to couple under similar reaction conditions to those reported here,^[14] and showcase the utility of benzaldoxime over hydroxide salts^[15] for the synthesis of phenols from poly-functional aryl halides without the need for protecting groups.

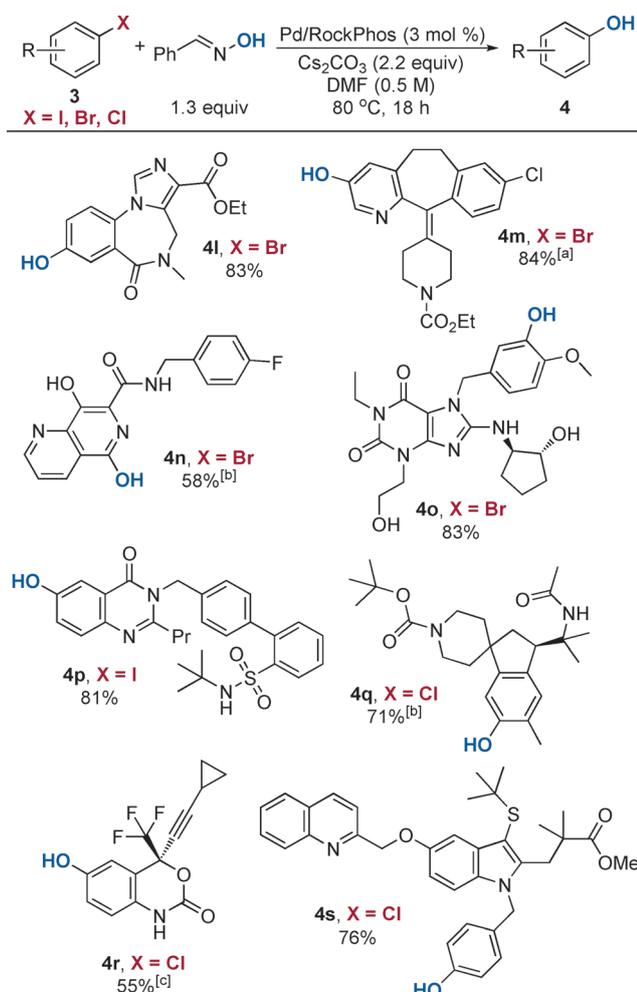
To supplement the results from the additive experiments, and to demonstrate this methodology on complex substrates, we carried out our new reaction on a chemistry informer library. The chemistry informer library consists of 18 poly-functional drug-like aryl halides that are representative of drug-like space designed to test reactions on challenging substrates (see Supporting Information for structures).^[16] With the reaction conditions reported here, the phenol products were formed in good yields with both *ortho*-substituted and electron-rich aryl halides (Scheme 6). Several common functional groups were tolerated, including esters,



Scheme 5. Coupling benzaldehyde oxime in the presence of common nucleophilic functional groups. Phenol is formed in 99% yield under the standard reaction conditions in the absence of any added nucleophiles. [a] Reactions were performed with 2.0 equiv of in situ formed benzaldoxime cesium salt. Yields were determined by HPLC against authentic product standards.

free O–H bonds of phenols and alcohols, free N–H bonds of amines, amides, and sulfonamides, and several basic heterocycles. The use of DMF as the reaction solvent allows for the conversion of several complex substrates (**3n**, **3p**, **3s**) that have negligible solubility in solvents that are more commonly used in cross-coupling, such as toluene and 1,4-dioxane. Across the informer library, the phenol products were formed in >20% yield in 11/18 cases, and in >50% isolated yield for 8/18 substrates (Scheme 6, and Supporting Information).^[17] To put these results in context, *N*-arylation of the 18 aryl halides with piperidine under the most advanced Pd-catalyzed C–N coupling conditions provided only 6/18 of the cross-coupled products in >20% yield, and only 4/18 in >50% yield.^[16] These results highlight the synthetic utility of the reaction reported here, as highly complex phenols bearing common functionality can be prepared without the need for protecting groups.

In summary, we have designed benzaldoxime as a synthetically useful hydroxide surrogate for the preparation of phenols from aryl halides. High-throughput experimentation identified conditions that allow for the synthesis of complex phenols bearing sensitive functional groups and pendant nucleophilic functionality. Mechanistic studies support a reaction pathway via initial Pd-catalyzed *O*-arylation of benzaldoxime, followed by base-induced elimination of the phenol



Scheme 6. Selected scope for the synthesis of complex drug-like phenols. Isolated yields for reactions performed on 0.5 mmol scale. [a] Reaction performed with 1.0 equiv of benzaldoxime. [b] *t*BuBrett-Phos Pd G3 was used as the precatalyst. [c] Reaction performed at 100 °C. See Supporting Information for additional substrates.

product and benzonitrile. We anticipate that this methodology will be rapidly adopted due to the mild conditions and the ability to perform the reaction on functionally-dense complex molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · hydroxylation · medicinal chemistry · palladium · phenols

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Communications

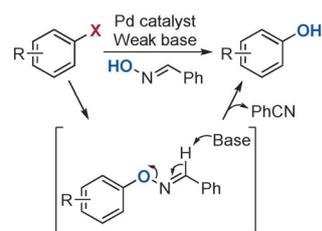


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Synthesis of Complex Phenols Enabled by
a Rationally Designed Hydroxide
Surrogate



- Mildly basic conditions
- Hydroxylation in the presence of N-H and O-H groups
- Broad FG tolerance
- Late-stage synthesis of complex phenols

The conversion of aryl halides to phenols under mild reaction conditions is a long-standing and formidable challenge in organic chemistry. The rational design of a broadly applicable Pd-catalyzed method to prepare phenols with benzaldehyde oxime as a hydroxide surrogate is now reported. These reactions occur under mildly basic conditions and enable the late-stage hydroxylation of functionally dense aryl halides.