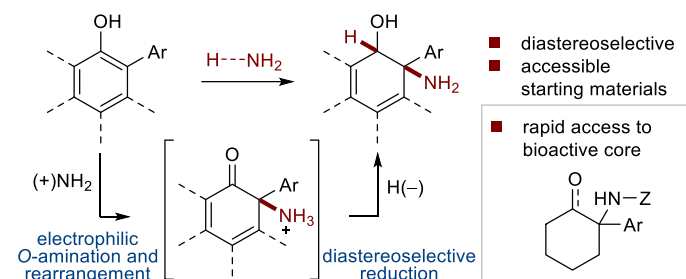


Formal Dearomative Hydroamination of 2-Arylphenols

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Supporting Information Placeholder



ABSTRACT: An acid-promoted dearomative rearrangement of *O*-arylhydroxylamines affords 2-aminocyclohexadien-1-ones, which can in turn be reductively quenched for the synthesis of trans-aminoalcohols on a cyclohexadiene core. This method serves as an efficient entry to the pharmaceutically relevant 1-arylcyclohexylamine scaffold in two steps (one purification) from commercially available or readily prepared 2-arylphenols.

Phenol dearomatization is a powerful method for the synthesis of “value-added” compounds with three-dimensional complexity from planar arenes,^{1–3} rendering myriad oxidized carbocycles quickly and efficiently accessible. Many phenol dearomatizations take advantage of phenol’s nucleophilicity through reaction with an activated electrophile at a substituted position.^{3–6} Other dearomatizations use stoichiometric hypervalent iodine or transition metal oxidants to oxidize the phenol to an arenium and allow for the incorporation of a nucleophile, often an alcohol or acetate.^{1,7–9} These methodologies often produce stoichiometric quantities of byproducts that may have associated environmental and health hazards and may be difficult to separate from dearomatized products. A “greener” method for oxidative dearomatization might rely on the pre-installation of a weak bond to a phenolic oxygen: through activation with a suitable promoter (e.g. an acid), heterolytic cleavage of the weak bond and recombination with the nucleofuge to the arenium could allow for an atom efficient dearomatization reaction (**Figure 1a**).¹⁰

Methods for the dearomative *ortho*-amination of phenols have recently been reported for systems containing 2,6-disubstitutions or tethered hydroxylamines (**Figure 1b**).^{11–14} These methods are valuable, but are limited to the substitution patterns required for reactivity and by the inability to directly produce primary amines. Multiple systems have been reported for the dearomative *ortho*-amination of naphthols, or a dearomative *para*-amination of phenols, but such a reaction remains elusive for *ortho*-amination of mono-substituted phenols.^{13,15,16} Herein, we endeavor to address this gap in the literature through the

exploration of a dearomative *ortho*-amination of 2-arylphenols that proceeds by intramolecular delivery of an –NH₂ fragment.

A key study supporting the feasibility of this reaction described an acid-promoted amine 1,3-migration of *O*-arylhydroxylamines proceeding through an ion pair and forming 2-aminophenols.¹⁷ *Ortho*-substituted phenols were observed to afford dearomatized cyclohexadienones that dimerized through a [4+2]-cycloaddition (**Figure 1c**), or at elevated temperatures rearranged to the derived dihydroazepinones.¹⁸ In connection with our prior work, we hypothesized that the unwanted dimerization could be avoided through an *in situ* ketone reduction upon workup.¹⁰ This overall process, the conversion of a 2-arylphenol to a dearomatized aminocyclohexadienol, represents a formal dearomative hydroamination of 2-arylphenols.^{19–22} A fully realized reaction would provide rapid access to the 1-arylcyclohexylamine core (**Figure 1d**).²³ This class of compounds is prominent in the pharmaceutical sciences as anesthetics and antidepressants, and there is value in expanding the scope of their synthetically available analogues.

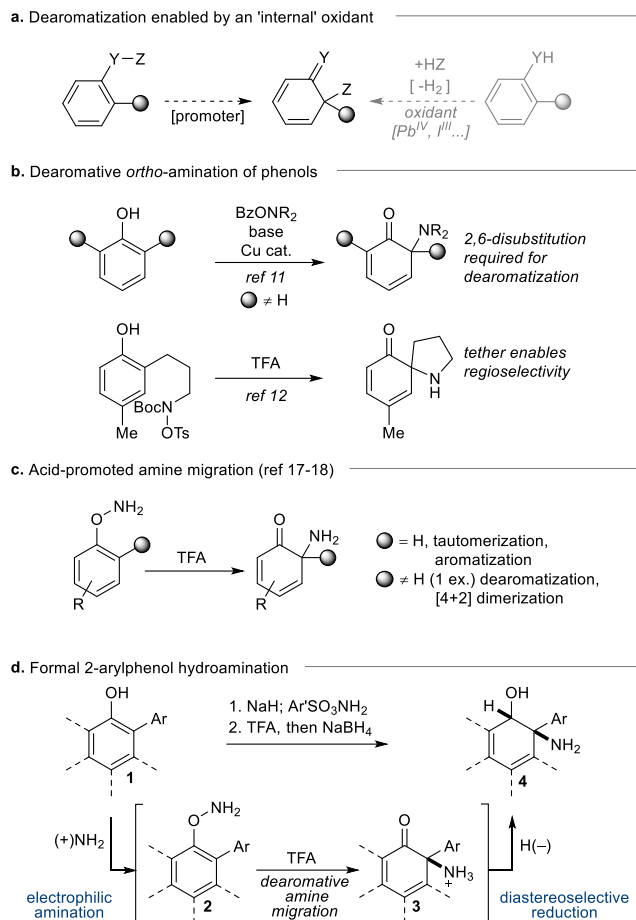


Figure 1. Background and project conception. (a) Dearomatization enabled by weak bond-cleavage. (b) Precedent for dearomative phenol *ortho*-amination. (c) Acid-promoted amine migration of *O*-arylhydroxylamines. (d) Proposed reaction: dearomative hydroamination of 2-arylphenols.

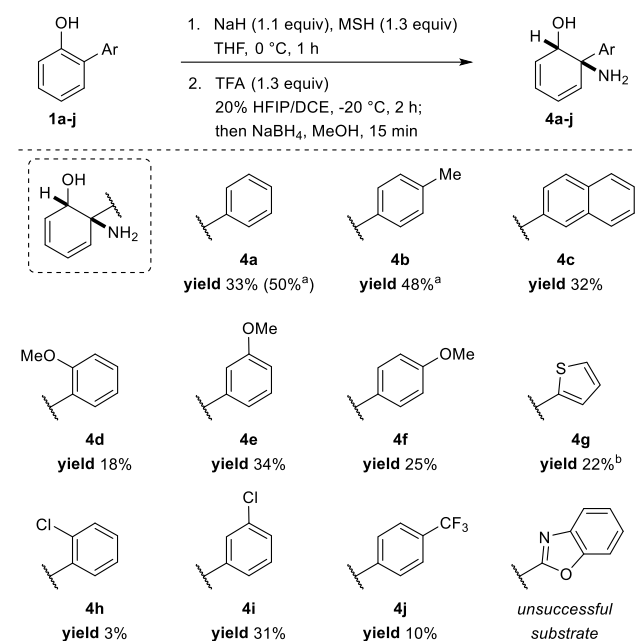
Of the reported syntheses of *O*-arylhydroxylamines **2**,²⁴⁻²⁶ amination of *ortho*-substituted phenols using the easily synthesized mesitylenesulfonyl hydroxylamine (MSH) was determined to be an optimal and general pathway to the desired hydroxylamines. While MSH is known to be unstable for long term storage, the Boc-protected analogue can be made in one step and readily deprotected as needed to yield the crystalline MSH.²⁷ *Ortho*-aryl phenols were accessible through cross-coupling reactions and/or electrophilic aromatic substitution of commercially available phenols. Through the development of a modified amination procedure, *O*-arylhydroxylamines **2** were available reproducibly in yields between 40% and 70% with the remaining mass mainly comprised of returned phenol **2** (see supplemental information for more details).²⁴

Under the rearrangement conditions reported by Endo, treating hydroxylamine **2a** with trifluoroacetic acid (TFA, 10 equiv) in halogenated solvents at room temperature yielded cyclohexadienone ammonium salt **3a** (observed by ¹H NMR spectroscopy in CDCl₃). A reductive quench of the reaction with methanol and sodium borohydride afforded aminoalcohol **4a** in moderate yield (41% by ¹H NMR spectroscopy). After screening various solvents and reaction conditions, a slight increase in overall yield was realized when performing the rearrangement at -20 °C in a solution of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in 1,2-dichloroethane (DCE) before a reductive quench.²⁸ Under

these conditions amino alcohol **4a** was isolated in 53% yield (58% ¹H NMR yield) as a single diastereomer. Attempts to perform the dearomative rearrangement with catalytic quantities of acid were unsuccessful. The efficiency of the dearomative rearrangement suffered from the formation of unwanted side products, such as *ortho* amine migration and rearomatization or *para*-hydroxylation, as described and characterized in the original reports.^{17,18} We did not isolate or characterize the side-products of the dearomative hydroamination reactions in these studies.

At the onset of our investigations, we encountered significant issues with the stability of *O*-arylhydroxylamines **2**. In many instances, the purification of these compounds was hindered by significant decomposition to the original 2-arylphenol **1** upon exposure to silica gel during flash column chromatography; therefore, we generally did not attempt purification of hydroxylamines **2** and used the unpurified residue of the amination reaction directly in the dearomative rearrangement. This semi-telecoped process did not affect the overall (two-step) yield of aminoalcohols **4** and increased the overall efficiency by removing a purification step (Scheme 1).

Scheme 1. Scope of 2-aryl substituent.



All reactions were carried out using 2.00 mmol phenol **1**. Yields shown represent the average isolated yield from two experiments.

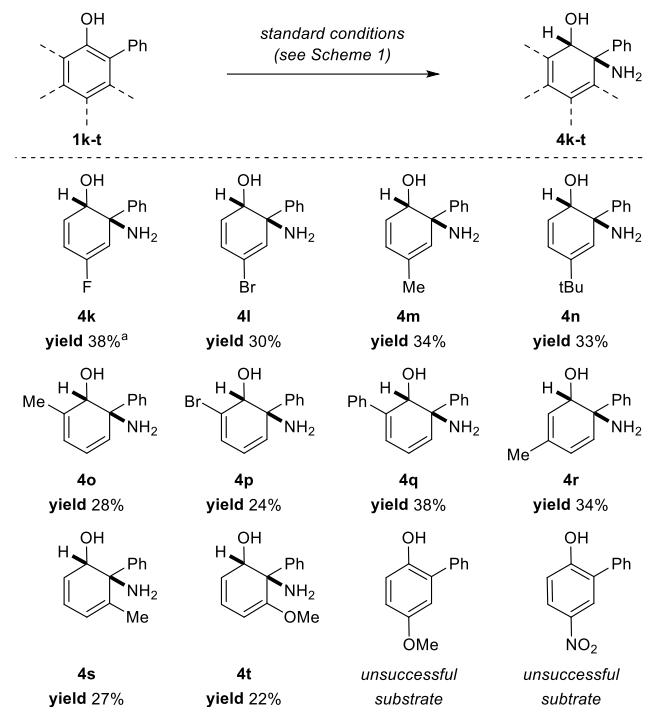
^a Reaction performed with 0.200 mmol hydroxylamine **2**, yield refers to only step 2. ^b ¹H NMR yield of aminoalcohol **4g**.

The two-step dearomative hydroamination afforded aminoalcohols **4** across a variety of substituents at the 2-aryl position (Scheme 1). The reaction saw little change in overall yield with *para*-tolyl-substituted aminoalcohol **4b**, naphthyl substituted **4c**, *meta*-methoxy **4e**, and *meta*-chloro **4i**. More significant decreases in overall yield were observed in the reaction of 2-arylphenols with electron rich arenes (**4d**, **4f**) or thiophene (**4g**). The reaction was the least efficient with strongly electron-withdrawing groups in the case of trifluoromethyl-substituted **4j**, and *meta*-chlorinated **4h**. A hydroxylamine with benzoxazole at the 2-position was successfully prepared, but the rearrangement did not proceed. ¹H NMR spectroscopic analysis of a mixture

of the hydroxylamine treated with TFA suggested protonation of the Lewis basic amine, but no N–O bond cleavage.

The dearomative hydroamination could similarly be carried out with a range of substitution patterns on the dearomatized phenol (**Scheme 2**). Consistent results were realized with 2-phenylphenols containing substitution at each carbon in the phenol ring, demonstrating the effectiveness of the dearomative hydroamination on diverse phenolic starting materials. As would be expected, the best performing reaction occurred in the synthesis of aminoalcohol **4q**, where aromatic byproducts resulting from amine migration to C6 are not an issue.

Scheme 2. Scope of phenol substitutions.



All reactions were carried out using 2.00 mmol phenol **1**. Yields shown represent the average isolated yields from two experiments.

^a Reaction performed with 0.200 mmol hydroxylamine **2k**, yield refers to only step 2.

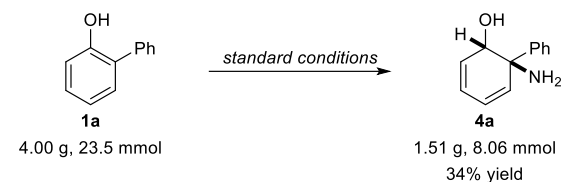
No desired product formation was observed when the reaction sequence was tested with 4-methoxy-2-phenylphenol. The hydroxylamine was found to be highly unstable and decomposed under rearrangement conditions. This lack of stability can be hypothesized to result from resonance stabilization in the arenium intermediate, making N–O bond cleavage favorable but N–C bond formation less so. Additionally, the rearrangement of the hydroxylamine of 4-nitro-2-phenylphenol was not observed. These results can be attributed to inverse electronic effects of the *para*-substituent on the hydroxylamine and the ease of ionization to form a cationic arenium intermediate during the dearomative amine migration.¹⁷ This methodology was limited to dearomative aminations that form primary amines, as *N*-alkyl substituted O-arylhydroxylamines have been reported to be highly unstable and we were similarly unable to prepare one for testing in a dearomatization reaction.²⁹

The dearomative hydroamination was performed on multigram scale with no decrease in efficiency (**Figure 2a**). With substantial amounts of aminoalcohol **4a** in hand, we wished to study further functionalizations of the novel aminoalcohols. Amino cyclohexadienol **4a** was readily converted to

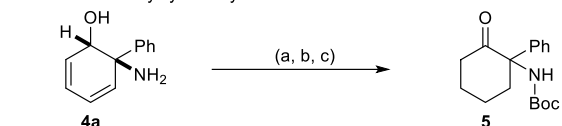
aminocyclohexanone **5** in high yield over three steps (1. carbamate protection; 2. olefin reduction; 3. alcohol oxidation). Due to the efficiency of each reaction, the unpurified products of each reaction could be used directly in the next step, giving expeditious access to the pharmaceutically relevant ring system (**Figure 2b**). Under different carbamate-protection conditions, bicyclic oxazolidinone **6** was produced in moderate yields (**Figure 2c**).

Figure 2. Scale-up and secondary transformations

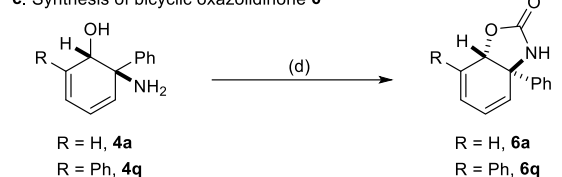
a. Gram scale synthesis of **4a**



b. Access to 1-arylcylohexylamine scaffold



c. Synthesis of bicyclic oxazolidinone **6**

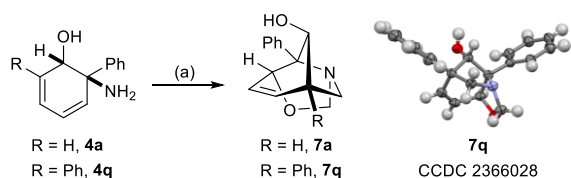


Reaction conditions: (a) **4a** (1.00 mmol) Boc₂O (1.3 equiv), K₂CO₃ (aq.), EtOAc, 23 °C, 3 h; (b) H₂ (1 atm), Pd/C (10 wt%, 5 mol %), EtOH, 23 °C, 16 h; (c) DMP (1.3 equiv), DCM, 23 °C, 3 h; **5**: 71%. (d) **4a** or **4q** (0.200 mmol), Boc₂O (3 equiv), N₂ (4 equiv), DCM, 35 °C, **6a**: 47%; **6q**: 51%.

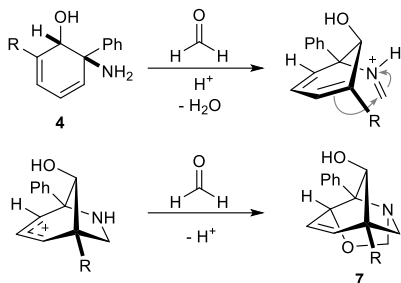
We were next interested in exploring the reactivity of the *p*-system of aminoalcohol **4**. Reacting **4a** and **4q** with excess formaldehyde and acid led to caged animals **7a** and **7q** (**Figure 3a**). In the case of **7q**, a significant amount of phenol **1q** (70%) was isolated as well. The structure of **7q** was proven unambiguously through X-ray diffraction crystallography (**Figure 3a**). Mechanistically, these compounds likely arise from formaldehyde condensation to the primary amine and aza-Prins addition of the diene to the iminium.³⁰ The resultant allylic cation is then trapped with an additional equivalent of formaldehyde (**Figure 3b**).

Figure 3. Observed aza-prins reactivity and proposed mechanism.

a. Synthesis of caged aminal **7**



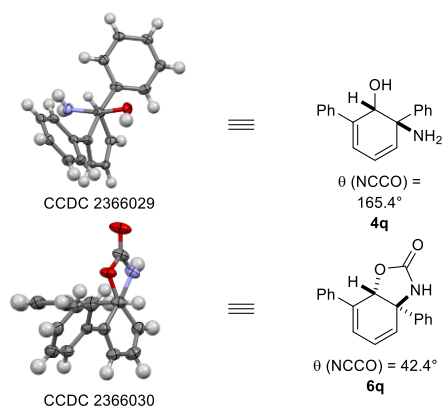
b. Proposed mechanism for the formation of caged aminal **7**



Reaction conditions: (a) **4** (0.100 mmol), CH₂O (37% in H₂O, 10 equiv), (+)-CSA (1 equiv), MeCN ([**4**]₀ = 0.1 M), 23 °C, 18 h. **7a**: 80%, **7q**: 20%. X-ray structure of aminal **7q** shown at 50% thermal ellipsoids.

In all examples of the dearomative hydroamination reaction, only a single diastereomer of aminoalcohol **4** was observed or isolated. The relative stereochemistry of aminoalcohols **4** was determined by an X-ray diffraction study of aminoalcohol **4q**. The diastereoselectivity observed in these reactions, with hydride addition to the same face as the amine, is consistent with prior observations of α -amino carbonyl reductions.¹⁰ The X-ray crystal structures of aminoalcohol **4q** and cyclic carbamate **6q** underscore the conformational changes in the cyclohexadiene: the NCCO dihedral angle in aminoalcohol **4q** is 165°, almost completely antiperiplanar, compared to the NCCO dihedral angle of 42° in the bicyclic oxazolidinone (**Figure 4**). These crystal structures provide uncommon examples of conformational dynamics in 1,3-cyclohexadienes.^{31,32}

Figure 4. X-ray structures of aminoalcohol **4q and oxazolidinone **6q****

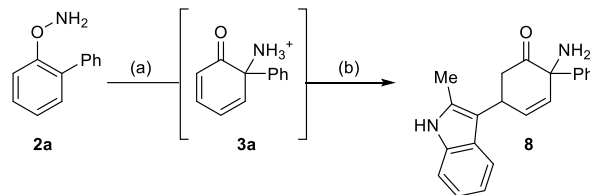


X-ray structures are shown at 50% thermal ellipsoids and facing down the OCCN dihedral angle.

Finally, we were interested in exploring *in situ* functionalization of dearomatized cyclohexadienone **3a** rather than a reduction to the corresponding aminoalcohol **4a**. We investigated a Friedel-Crafts type conjugate arylation of dienone **3a** with 2-

methylindole (**Scheme 3**).³³ Arylation to cyclohexenone **8** proceeded in high diastereoselectivity and in moderate yield.

Scheme 3. Rearrangement and *in situ* nucleophilic arylation



Reaction conditions: (a) TFA (1.3 equiv), 20% HFIP/DCE, -20 °C, 1.5 h. (b) 2-methylindole (1.5 equiv), 23 °C, 18 h. **8**: 20%.

Through these studies we have exemplified the strategy of dearomatization with an internal oxidant for the preparation of previously inaccessible compounds through a formal dearomative hydroamination of 2-arylphenols. The reaction is scalable and allows for expeditious entry to the arylcyclohexylamine scaffold. Further transformations effectively functionalize the π -system of synthesized cyclohexadienes to yield novel tricyclic aminals **7**. Finally, the electrophilicity of cyclohexadienone **3a** was demonstrated with a Friedel-Crafts type arylation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, materials, methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, and information on X-ray diffraction experiments (PDF).

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Notes

The authors declare no competing financial interest.

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