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Synthesis of *ortho*-Azophenols by Formal Dehydrogenative Coupling of Phenols and Hydrazines or Hydrazides

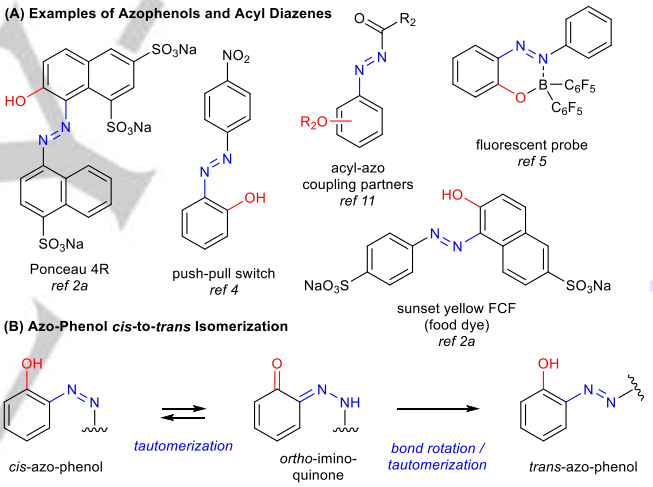
Kenneth Virgel N. Esguerra, [a] and Jean-Philip Lumb* [a]

Dedication ((optional))

Abstract: Azophenols are important chromophores and reagents in organic synthesis, with applications as pigments and molecular switches. Herein, we describe a catalytic aerobic process that couples phenols and hydrazines or hydrazides for their synthesis. The key aromatic C-N bond is formed via condensation between the hydrazine or hydrazide and an *ortho*-quinone, which triggers a redox-isomerization to install the azo functionality. Notable features include rapid access to highly functionalized azophenols with a range of electronic configurations, including "push-pull" systems, under conditions that employ simple, un-activated substrates, occur at room temperature using an earth-abundant and commercially available copper-catalyst, and produce water as the only stoichiometric byproduct.

Azophenols are an important class of azobenzene dyes,[1] with applications as pigments,[2] ligands for transition metals,[3] molecular switches,[4] fluorescent probes[5] and sensors (Scheme 1A).[6] Relative to non-phenolic azobenzenes, they possess red-shifted absorption spectra, and exhibit rapid rates of *cis*-to-*trans* thermal relaxation, made possible by a facile tautomerization to the *ortho*-imino-quinone (Scheme 1B). These are important properties for fast information transmission in biologically relevant contexts,[7] which can be further fine-tuned by the degree of polarization across the azo-linkage.[1a,4,8] Azophenols possessing a polarized or "push-pull" electronic configuration are noted for their fast rates of switching, which is attenuated for less-polarized derivatives possessing neutral or electron-rich aromatic rings.[4] Structurally related 2-aryl-azo-carboxylates (Scheme 1A) are widely used as electrophilic reagents,[9-10] in heterocycle synthesis,[11] and also as versatile synthetic intermediates.[12] The unique properties of these two classes of azo-compounds creates a need for new methodologies that can efficiently provide non-symmetrical azophenols with a palette of electron releasing and withdrawing substituents on the non-phenolic substituent.

In contrast to the synthesis of azobenzenes, for which a number of recent methodologies have been reported,[7c,13] the synthesis of azophenols remains complicated by issues of selectivity and reactivity.[14] Their classical preparation from an aryl diazonium salt and a phenol is not regioselective (Scheme 2A),[14a] and can be difficult to apply to azo-phenols containing heterocycles. Heterocyclic azophenols are a particularly interesting class of azo-switches,[15] which display exceptionally fast and quantitative thermal isomerization.[3] Transition metal-catalyzed *ortho*-oxygenation of symmetric azobenzenes has been reported (Scheme 2A),[14b-d] but suffers from poor regio- and chemoselectivity in non-symmetrical substrates, complicating the synthesis of "push-pull" azophenols. A mechanistically distinct, but undeveloped transformation that leads selectively to *ortho*-azophenols, occurs by a condensation and redox isomerization cascade between *ortho*-quinones and hydrazines.[16] This process has been used to probe the chemistry of the quinone co-factor pyrroloquinoline quinone (PQQ),[16a-c] but it has not been developed as a synthetic methodology. This stems, in part, from the limited availability of *ortho*-quinones, which are electrophilic, redox-sensitive, and often difficult to prepare and store.



Scheme 1. (A) Selected examples of azophenols. (B) Mechanism of isomerization for *ortho*-azophenols.[17]

Recognizing these challenges, we envisioned that a catalytic aerobic *ortho*-oxygenation of phenols could allow entry to this transformation.[18] Phenols are readily available staring materials, but their *ortho*-oxygenation has historically required a multi-step sequence,[19] or a synthetic oxidant that can be difficult to use in sequential transformations.[19d] In the current context, we questioned whether our aerobic *ortho*-oxygenation could be interfaced with a hydrazine / hydrazide coupling reaction to provide *ortho*-azophenols in a 1-pot, sequential process from phenols. To our knowledge, the cross-coupling of these two nucleophilic reagents is unknown. Hydrazines and hydrazides benefit from widespread commercial availability, but they are underdeveloped for the synthesis of azobenzenes.[20] Herein we demonstrate their utility in a formal dehydrogenative C_{sp^2}-N_{sp^2} coupling reaction, providing valuable *ortho*-azophenols with a range of electronically distinct functional groups

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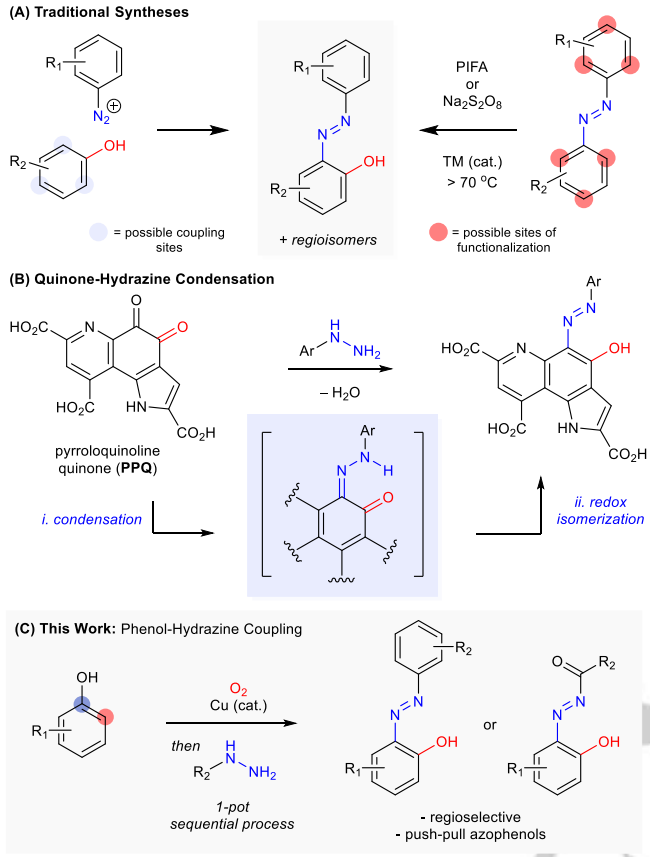
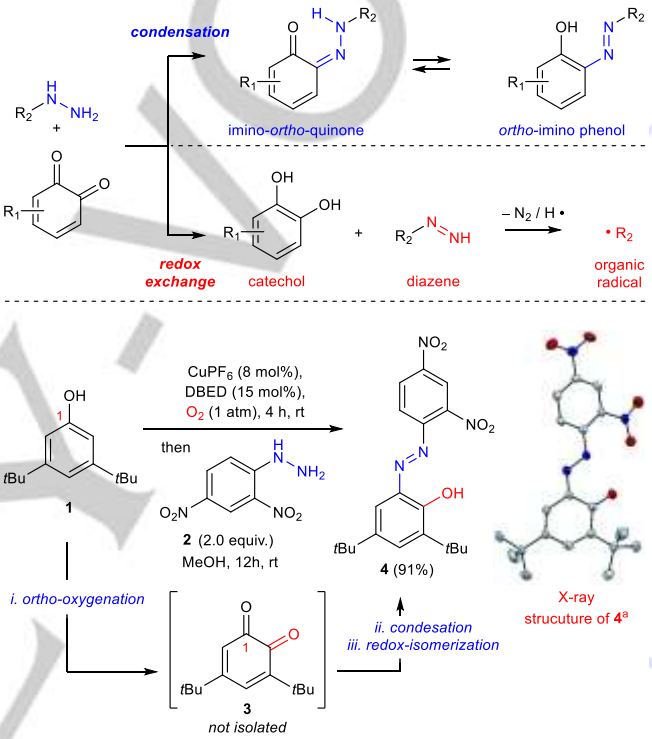
directly from phenols under mild and regioselective conditions (Scheme 2C).



Scheme 2. (A) Classical syntheses by diazo coupling, and transition metal catalyzed hydroxylation. (B) PQQ and hydrazine condensation. (C) Work described therein.

At the outset of our work, we discovered two competitive pathways for the reaction of *ortho*-quinones with hydrazines (Scheme 3). For constructive C-N bond formation to occur, condensation must out-compete a redox exchange, in which the quinone is reduced to the corresponding catechol, and the hydrazine is ultimately oxidized to an organic radical. The latter pathway provides an interesting entry into arene radical chemistry, which is discussed later in Scheme 4. To develop the desired C-N coupling, we employed 3,5-di-*tert*-butyl-phenol (**1**) and 2,4-di-nitrophenylhydrazine (**2**), which could be coupled in a 1-pot, sequential process involving aerobic oxygenation of **1** to *ortho*-quinone **3** with 8 mol% of $Cu(CH_3CN)_4(PF_6)$ (abbreviated as $CuPF_6$) and 15 mol% of di-*tert*-butyl-ethylenediamine (DBED).[18] After 4 hours at room temperature, **3** is produced in > 95 % yield (see Tables S1 and S2 in the Supporting Information for optimization studies). The direct addition of **2** (1 equiv) then triggers the condensation / redox-isomerization to provide **4**, but only in 13% yield after 4 h. We observed dramatic improvements to the efficiency and selectivity of C-N coupling upon the addition of MeOH, under the premise that a more protic environment would facilitate condensation. Reaction parameters that were optimized include the equivalents of **2** (2 equiv), its addition as a homogeneous solution in MeOH (0.7 M), and the time for C-N coupling (12 h), which led to yields of ~ 90% on scales that range from 1 to 20 mmol. An x-ray structure of **4** confirms the regioselectivity of C-N bond formation at the more sterically accessible C_1-carbonyl of **3**, defining the overall transformation as a formal transposition of the C_1 oxygen of the phenol to C_2 with concomitant formation of the azo at C_1.



Scheme 3. Initial studies on aerobic coupling of phenol **1** and hydrazine **2**. [a] Hydrogens are omitted for clarity. Blue = N, Red = O, Teal = C.

The scope of the nitrogen coupling partner was evaluated using these optimized conditions (Table 1). Azophenols with a push-pull electronic configuration are prepared in generally high yields from the coupling of aryl or heteroaryl hydrazines bearing a range of electron-withdrawing substituents. These include fluorine, chlorine, trifluoromethyl and sulfonate groups (entries 1-5). We highlight entries 2 and 3, as azophenols possessing *ortho*-chloro substituents, and entry 5 as a heterocyclic "push-pull" azophenol, which are two substrate classes that have attracted recent attention for their red-shifted optical properties and their fast thermal isomerization.[4,7c] The use of hydrazides as nitrogen coupling partners is equally efficient (entries 6-11), and establishes a new C_{sp^2}-N_{sp^2} coupling reaction that is selective for the terminal nitrogen of the hydrazide. This complements the regioselectivity of more traditional metal-catalyzed coupling reactions, which are typically selective for the internal

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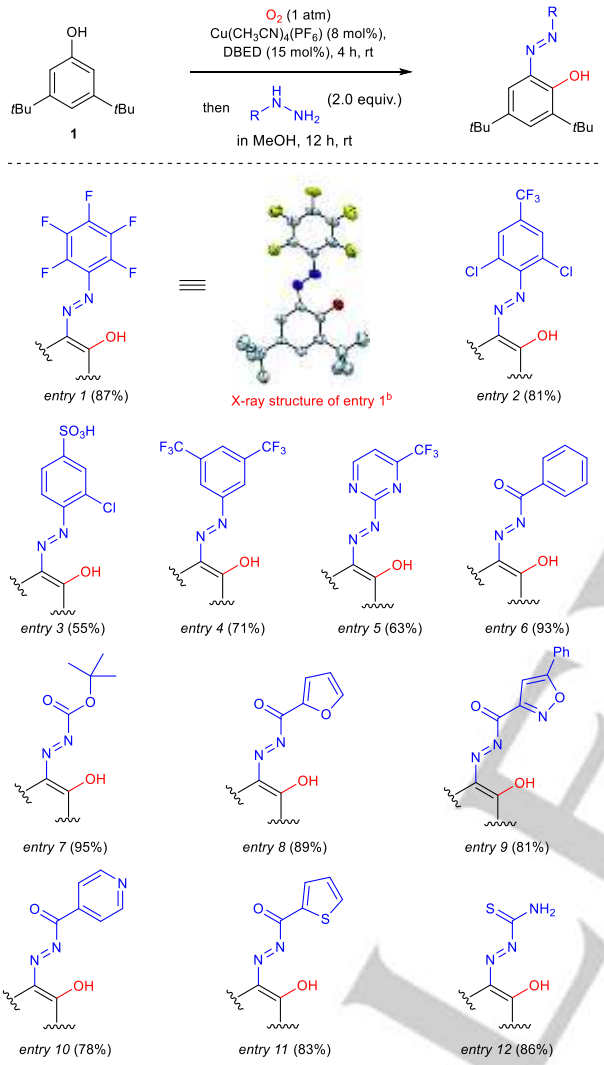
nitrogen.[21] Aryl (entry 6) and carbamate (entry 7) substituents on the hydrazide are tolerated, as are furan (entry 8), isoxazole (entry 9), pyridine (entry 10), and thiophene (entry 12) heterocycles. Likewise, thiosemicarbazides (entry 12) function well.

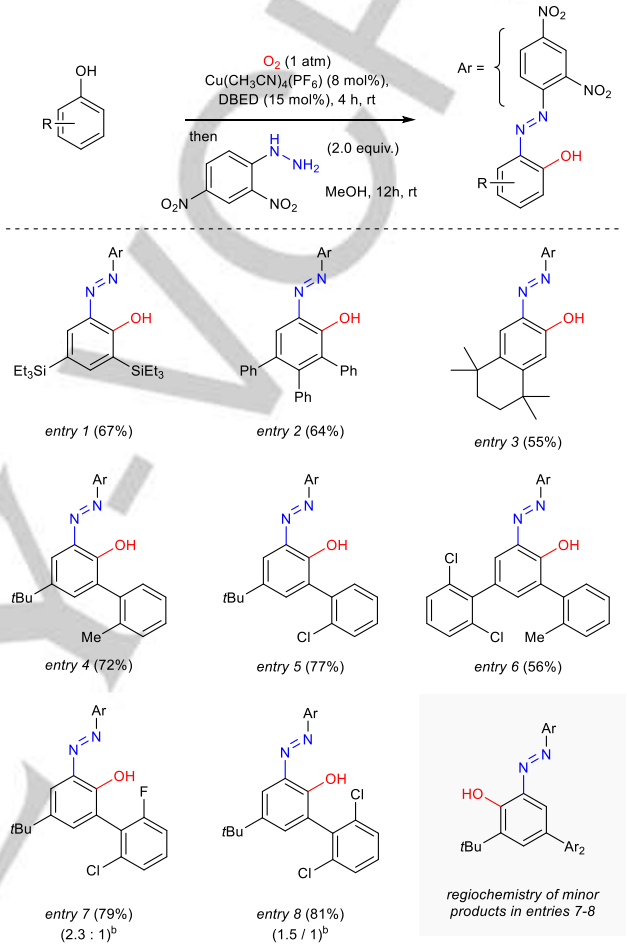
Table 1. Scope of Hydrazines and Hydrazides



[a] *Reaction conditions*: **1** (1.0 mmol), $CuPF_6$ (8 mol%), DBED (15 mol%), O_2 (1 atm), CH_2Cl_2 (0.1 M), rt, 4 h; then, hydrazine/hydrazide (2 equiv.) in MeOH (3 mL), rt, 12 h. Isolated yields are reported for each entry. [b] Hydrogens are removed for clarity. Red = O, Blue = N, Yellow = F and Teal = C.

Our conditions also tolerate phenols bearing 3,5-di-silyl groups, to provide azophenols with attractive functional handles (Table 2, entry 1). Likewise, 3,4,5-tri-phenyl phenol provides the corresponding penta-substituted azophenol in good yield (entry 2). The coupling of unsymmetrical phenols is also possible, in spite notorious difficulties of controlling the regioselectivity of C-H oxygenation when O_2 is the atom-transfer agent.[22] Under our conditions,[23] oxygenation occurs within a dinuclear Cu(III)-μ-oxo phenolate (see Scheme S2 and S3 in the Supporting Information),[24] such that oxygenation is regioselective for the sterically least demanding *ortho*-position of phenols possessing differentiated substituents at C3 and C5 (entries 3-6).[25] The subsequent amination occurs exclusively at the less encumbered carbonyl of the *ortho*-quinone to provide single regioisomers of "push-pull" azophenols in good yields. In cases where selectivity during *ortho*-oxygenation is diminished, C-N coupling remains selective, to provide a mixture of only two, separable azophenols, in synthetically useful yields (entries 7 and 8).

Table 2. Scope of Di- and Tri-Substituted Phenols [a]



[a] Conducted with 1.0 mmol of **1**. Isolated yields are reported for each entry. [b] Ratio of regioisomers.

The balance between condensation and redox exhange sways to the latter for hydrazines that are more electron-rich, such that the attempted coupling of phenyl hydrazine with **1** returns catechol **5** at complete conversion, without evidence of C-N coupling (Scheme 4A). While the fate of the hydrazine is difficult to discern under these conditions, control experiments between quinone **2** and hydrazine **6** suggest the intermediacy of arene radical **10**, which can be intercepted either by the quinone to provide aryl ether **7**,[26] or by benzene to provide biaryl **8** (Scheme 4B). Despite extensive investigations into the oxidation of hydrazines,[27] little is known about their redox-exchange with *ortho*-quinones. The plausibility of a 2 electron / 2 proton exchange to provide aryl diazene **9** is supported by literature precedent, in so far as related diazenes are known to serve as precursors to arene radicals.[28]

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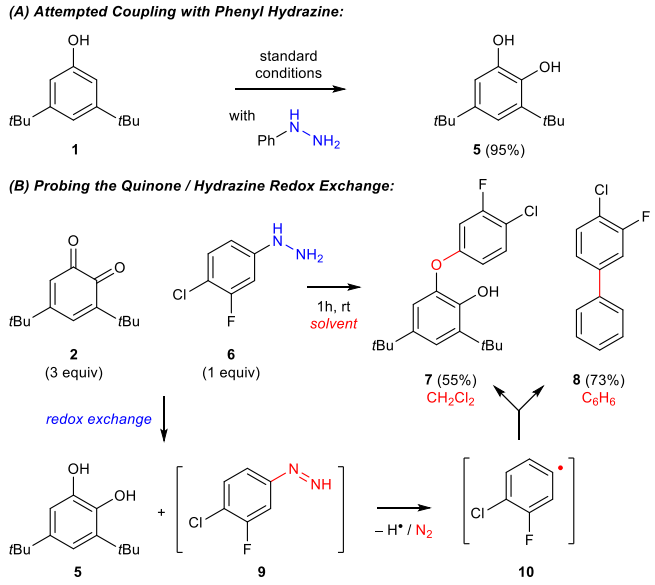
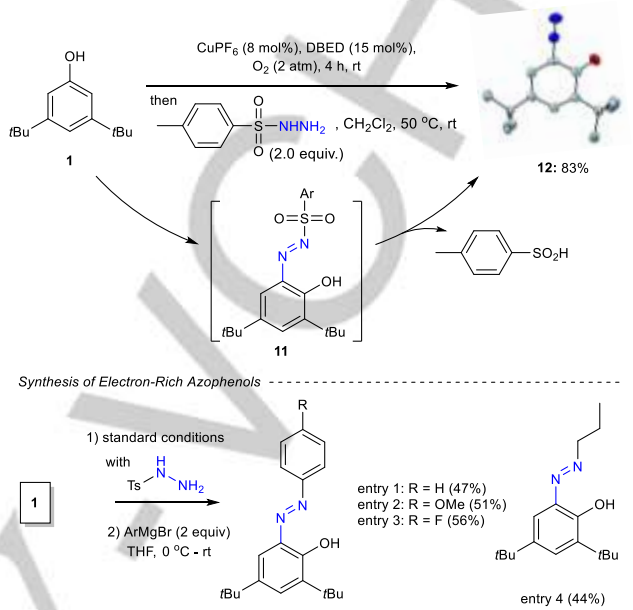


Scheme 4. (A) Redox reaction of **1** with phenylhydrazine. (B) Mechanistic studies on quinone / hydrazine redox exchange.

While the redox chemistry of hydrazines and *ortho*-quinones presents an interesting entry into arene radical chemistry, it also creates a practical limitation for the synthesis of more electron rich azophenols, which we sought to overcome by exploiting a coupling reaction with *para*-toluenesulfonyl hydrazide (Scheme 5). This provides diazobenzoquinone **12**, following the spontaneous elimination of toluene sulfinic acid from *N*-tosyl-azo phenol **11**.[29] The *ortho*-azo-quinone structure of **12** was confirmed by x-ray crystallography, and is consistent with previously reported structures of azo-naphthoquinones[29a,29b] and azo-*para*-quinones,[30] which have been synthesized from the corresponding aminophenol by diazotization.[30c-f] Diazobenzoquinones have applications in photolithography[31] and as precursors to carbenes.[30c,32] In the current context, we explored the reactivity of **12** towards Grignard reagents, with the hope of accessing less-polarized azophenols by nucleophilic addition to the terminal nitrogen.[33] Gratifyingly, this provides a two-step alternative for the synthesis of azophenols possessing aromatic rings (entries 1-3), or even an alkyl substituent (entry 4), that cannot be incorporated using our standard phenol / hydrazine coupling conditions. We anticipate a number of opportunities to exploit *ortho*-azobenzoquinones, which, unlike their *para*-isomers or naphthalene / phenanthrene analogues, have not previously been synthesized.

In this work, we have explored an unconventional approach for the synthesis of azophenols that hinges on a formal dehydrogenative coupling of phenols and hydrazines or hydrazides. The unification of these two, nucleophilic reagents is made possible by an aerobic dearomatization of phenols that harnesses the potential energy stored in O_2 in the form of an electrophilic *ortho*-quinone. As a consequence, aromatic C-N bond formation can occur at room temperature, using an earth-abundant and commercially available Cu-catalyst, with the added benefit of generating H_2O as the sole stoichiometric byproduct.



Scheme 5. Synthesis of electron-rich azophenols from diazobenzoquinones.

Acknowledgements

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Keywords: Azophenol • Aerobic Copper Catalysis • Phenol • Hydrazine • C-H Functionalization

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[25] Di-substituted phenols, such as 3-*tert*-butyl at C3 and 5-para-OMe-phenyl at C5, with less sterically encumbered substituents undergo a sequential *ortho*-oxygenation / oxidative coupling (see Scheme S2 and S3 in the supporting information). For discussion, see ref. 18.

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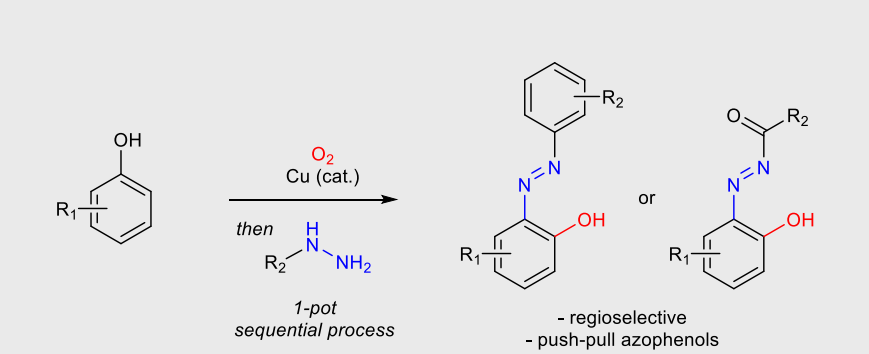

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