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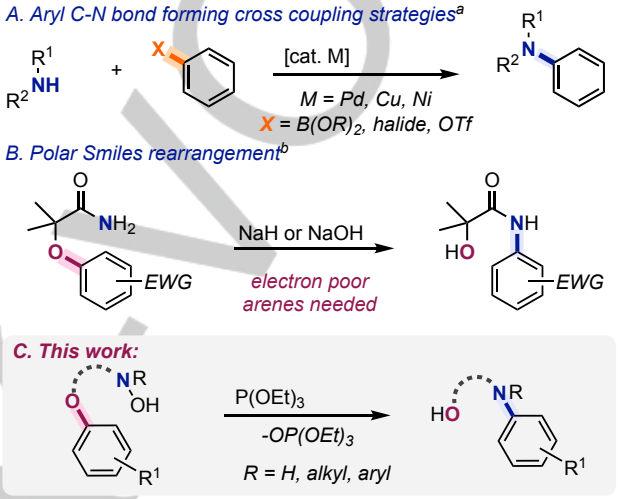
Formal Aniline Synthesis from Phenols via Deoxygenative N-Centered Radical Substitution

Samuel W. Lardy, Kristine C. Luong, and Valerie A. Schmidt*

Abstract: Phenolic, lignin derived substrates have emerged as desirable biorenewable chemical feedstocks for coupling reactions. Herein, we describe a radical-mediated conversion of phenol derivatives to anilines using unfunctionalized hydroxamic acids as the N-centered radical source. We demonstrate the applicability of this triethyl phosphite mediated O-atom transfer approach which tolerates a range of steric and electronic demands to naturally occurring phenols and lignin models to access the corresponding aniline derivatives.

Aromatic amines are highly valuable motifs in pharamaceuticals, natural products, materials, organic pigments, and agricultural chemicals.[1] Anilines can be prepared via a 2-step nitration-hydrogenation sequence, though this method often suffers from harsh reaction conditions and can result in mixtures of regioisomers.[2] Conversely, transition metal catalyzed coupling strategies developed by Ullman,[3] Buchwald,[4] Hartwig,[5] Chan,[6] and Lam[7] forge aryl C-N bonds from aryl halides, pseudo halides, or boronic esters using N-atom nucleophiles (Scheme 1A). While many recent examples offer mild reaction conditions and tolerate a range of functionality,[8] there are relatively few examples that obviate the need for a transition metal catalyst and the expensive, designer ligands often required.[9,10] Due to abundant phenolic, lignin-biomass derived starting materials,[11] recent efforts have shifted focus to the potential impact of aryl C-O bond activation.[12,13]

Base-mediated Smiles rearrangements achieve intramolecular N-nucleophile substitution at an aryl ether (Scheme 1B).[14] Electron poor arenes are typically needed to achieve good reaction efficiencies in these systems, though emerging evidence suggests that in certain cases, less activated aromatics may participate in S_NAr as well.[15] Radical-mediated approaches to aniline synthesis via Smiles-type rearrangements are comparatively unaffected by electronic demands of the aromatic ring,[16] though few examples using N-centered radicals analogous to the polar variants have been reported.[17] Recently, Guo and co-workers reported an electrochemically-mediated rearrangement of *O*-(2,4-dinitro)-phenyl hydroxamate esters, where the (2,4-dinitro)-phenyl unit proved essential, serving as a redox-active electrophore that accepts an electron and triggers the rearrangement.[18]



Scheme 1. Aryl amination strategies. [a] See refs. 3-8. [b] See refs. 14c-d.

We recently reported the utility of triethyl phosphite to access phthalimidyl radicals via deoxygenation of *N*-hydroxyphthalimide.[19] We envisioned that through an analogous pathway, amidyl radicals could be accessed from hydroxamic acids without further pre-functionalization and used to undergo arene addition to achieve a rearrangement to formally synthesize anilines from phenols.

We began our investigations by treating hydroxamic acid **1a** derived from phenol with dilauroyl peroxide ($(undecylCO_2)_2$, 0.1 equiv) and a slight excess of triethyl phosphite (1.5 equiv) in 1,2-dichloroethane for 12 h at 90 °C. The corresponding N-methyl-N-phenyl amide **2a** was formed in 83% yield as determined by gas chromatography (Table 1, entry 1). Notably, **1a** can be easily prepared from an Ullman coupling of phenol and 2-iodobenzoic acid followed by amide bond formation using *N*-methylhydroxylamine in essentially quantitative yield over 2 synthetic steps.[20] Though DCE proved to be an excellent solvent for this process, we found that non-halogenated solvents such as acetonitrile could also be used with comparable reaction efficiencies.

Replacing dilauroyl peroxide with other common thermal initiators such as benzoyl peroxide or 2,2'-azobis(2-methylpropionitrile) (AIBN) resulted in no detectable formation of **2a** (entries 2 and 3). However, using di-*tert*-butyl peroxide improved reaction efficiency to 95% isolated yield in 24 h (entry 4).[21] No detectable quantities of **2a** were observed in the absence of radical initiator or triethylphosphite (entries 5 and 6).

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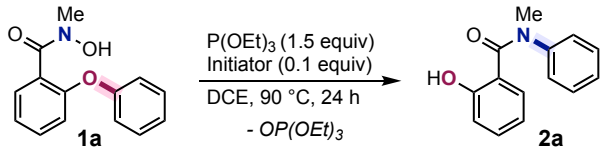
Table 1. Reaction optimization.



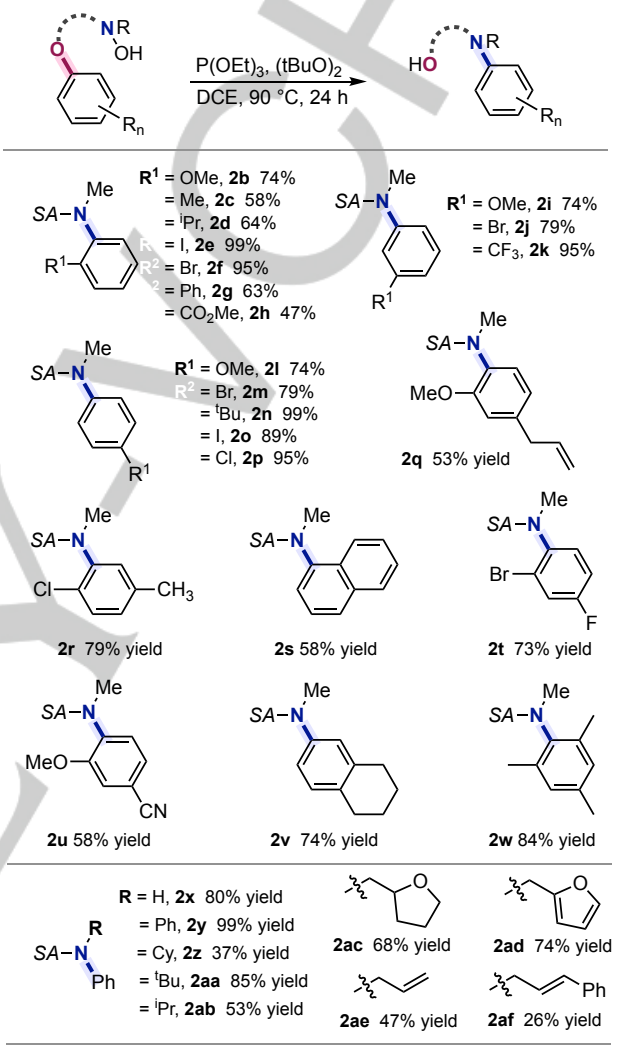
Entry	Initiator	Yield of **2a** [a]
1	$(undecylCO_2)_2$	83%
2	$(BzO)_2$	< 5%
3	AIBN	< 5%
4	$(^tBuO)_2$	95%[b]
5	*none*	< 5%
6	$(^tBuO)_2$ and *no P(OEt)3*	< 5%

Reactions carried out with **1a** (1 equiv), $P(OEt)_3$ (1.5 equiv), and initiator (0.1 equiv) in 0.16M 1,2-dichloroethane at 90 °C for 24 h; AIBN = 2,2'-azobis(2-methylpropionitrile). [a] Yields determined by gas chromatography using mesitylene as an internal standard. [b] Carried out with 0.5 equiv initiator; isolated yield following silica gel chromatography.

Subjecting the amide analog of **1a**, *N-tert*-butyl-2-phenoxybenzamide, to base-mediated Smiles rearrangement reaction conditions developed by Turner[14d] and Yamano[14c] resulted in isolation of unreacted starting material only. These experiments combined with the control experiments from entries 5 and 6 of Table 1, further support both the intermediacy of radicals and the necessity of a radical approach for this conversion.[22]

With these conditions in hand, we set out to identify other phenols that could be similarly converted to their corresponding anilines. Phenols with *ortho* substituents ranging from electron-donating methoxy (**2b**) and alkyl groups (methyl and isopropyl, **2c** and **2d**) to electron-withdrawing halides (I and Br, **2e** and **2f**) and methyl ester (**2h**) were efficiently converted to the *N*-methyl-*N*-aryl acetamides in good to excellent yields (58 – 99%). Even the inclusion of an *ortho*-phenyl group resulted in the corresponding anilide **2g** in 63% yield.

Similarly, *meta*- (**2i** – **2k**) and *para*-substituents (**2l** – **2p**) were well tolerated. The disposition of the methoxy group, relative to the aryl ether linkage reflected no change in reaction efficiency (**2b**, **2i**, **2l** all isolated in 74% yield). Multi-substituted aryl ethers were also examined with good results (**2q** – **2w**, 53 – 84% yields). Notably, aryl halides which are susceptible to nucleophilic aromatic substitution under strongly basic conditions remained unreacted, leaving these valuable functional handles present for subsequent derivatization. Allyl and nitrile substituents were tolerated though their presence did result in slightly diminished reaction efficiencies (**2q** and **2u** in 58 and 53% yield). Increased conjugation of 1-naphthol participated in this O-atom transfer amination in modest yield (**2s** in 58% yield). The sterically encumbered 2,4,6-trimethyl phenol derivative was converted to the corresponding *N*-methyl anilide **2w** in 84% yield, indicating that steric factors do not significantly diminish efficiency.



Scheme 2. Reaction scope. All reactions carried out with the corresponding hydroxamic acid (1 equiv), $P(OEt)_3$ (1.5 equiv), and $(^tBuO)_2$ (5 equiv) in 0.16M 1,2-dichloroethane at 90 °C. *SA* = 2-hydroxy benzoyl (salicylate).

We also surveyed the versatility of the amino group in this process. We opted to carry out the majority of our studies using *N*-methyl hydroxylamine to synthesize hydroxamic acids because of its commercial availability and favorable spectroscopic properties. Previous reports were limited to few groups outside of *N*-methyl hydroxamates,[18] but we found that a range of substituents were amenable to our approach (**2x** – **2af**).

More significantly, we found that the unsubstituted amino group derived from parent hydroxylamine resulted in highly efficient C-N bond formation, generating **2x** in 80% yield. This highlights the ability of our mild, deoxygenative approach to access primary as

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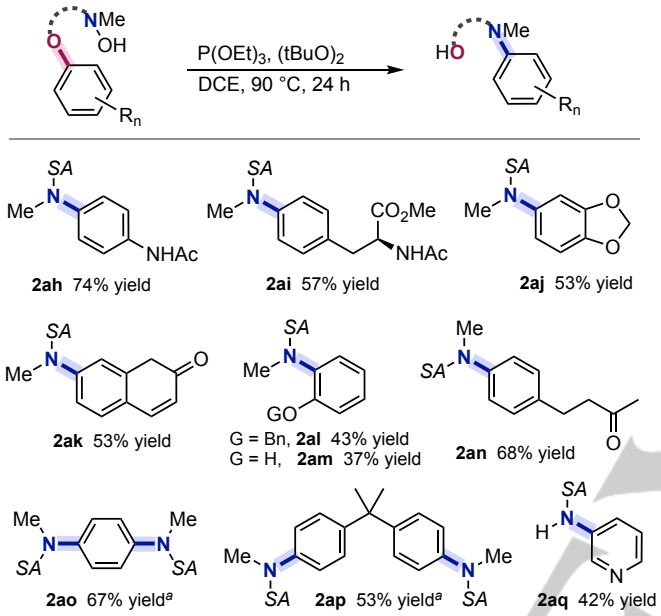
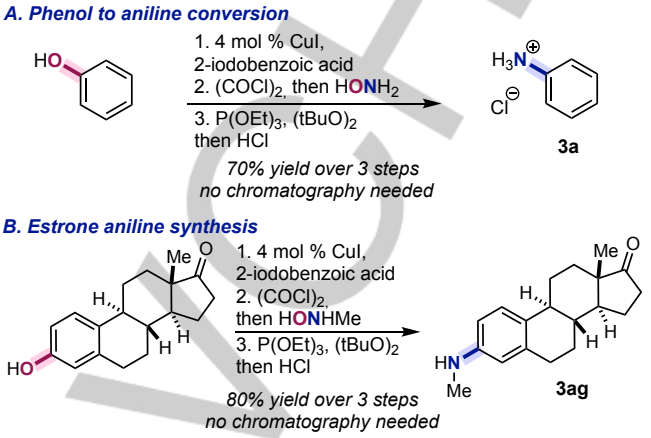
well as secondary amide products. Various other N-atom substituents similarly proved well tolerated including phenyl (**2y**, 99% yield), *tert*-butyl (**2aa**, 85% yield), furanyl (**2ad**, 74% yield), and tetrahydrofuranyl groups (**2ac**, 68% yield). Amino groups containing tertiary (cyclohexyl and iso-propyl) or allylic C-H bonds (*N*-allyl and *N*-cinnamyl, **2ae** and **2af**) adjacent to the amidyl N-atom were among the least efficient to undergo this aryl substitution. We attribute this to the relative ease of H-atom abstraction from the position adjacent to nitrogen which lead to reduction without rearrangement.



Scheme 3. Amination of complex phenols. All reactions carried out with the corresponding hydroxamic acid (1 equiv), $P(OEt)_3$ (1.5 equiv), and $(^tBuO)_2$ (5 equiv) in 0.16M 1,2-dichloroethane at 90 °C for 24 h. Yields reported are of isolated materials following silica gel chromatography. *SA* = 2-hydrox benzoyl (salicylate). [a] Reaction performed using 3 equiv $P(OEt)_3$.

We next explored the ability of phenols present in more complex, biologically relevant compounds to undergo this phosphite-mediated O-atom transfer rearrangement to produce the corresponding anilines (Scheme 3). Acetaminophen, a common over-the-counter analgesic was successful under these conditions (**2ah**) resulting in the differentiated 1,4-bisaniline. The conversion of *N*-acetyl-L-tyrosine methyl ester to the corresponding amide proceeded well (**2ai**, 57% yield), as did sesamol, a naturally occurring suspected antioxidant and anti-fungal phenol (**2aj**, 53% yield) and umbilliferone, a member of the coumarin family (**2ak**, 53% yield). We also surveyed 2-benzyloxyphenol as a model of the α-O-4 linkage of lignin and found it was converted to the corresponding *N*-methyl aniline, as was the free hydroxy congener in 43% (**2al)** and 37% (**2am**) yield, respectively. Similarly, raspberry ketone, the compound responsible for the pleasant smell of raspberries was converted to the corresponding anilide in 68% yield (**2an**). Polyphenolic substrates such as those derived from *para*-hydroquinone and bisphenol A also underwent this transformation in 67% (**2ao**) and 53% yield (**2ap**), respectively. The substrate derived from 3-hydroxypyridine was similarly transformed with modest efficiency (**2aq**, 42% yield), revealing the ability of this method to be used on hydroxylated heterocycles.



Scheme 4. Facile conversion of phenols to anilines. Detailed experimental procedures can be found in the SI.

In order to demonstrate the synthetic utility of this method toward the synthesis of anilines, we carried out the conversion of phenol to aniline hydrochloride in 70% isolated yield over 3 synthetic steps with no chromatographic purifications needed (Scheme 4A). Despite the stepwise approach used, each synthetic step proceeded in very high reaction efficiency and the final product was purified through recrystallization. We additionally performed the conversion of phenol to *N*-methyl aniline hydrochloride on a gram-scale and obtained a 77% yield over the 3 synthetic steps used, also without the need for intermediary or final chromatographic purification. Estrone was similarly converted to its *N*-methyl aniline analog in only 3 steps with an overall 80% yield, also without intermediate purifications (Scheme 4B).

Mechanistically, this process likely proceeds by radical initiation to generate an amidoxyl radical followed by O-atom transfer to triethyl phosphite (Scheme 5). The amidyl radical produced from this exchange then undergoes *ispo* addition to the aryl ether, producing a resonance stabilized arene-radical. Rearomatization through cleavage of the weaker aryl ether C-O bond is favored to generate a phenoxy radical. Hydrogen-atom transfer from another equivalent of hydroxamic acid can formally regenerate amidoxyl radical and provide the initial amide product. This H-atom transfer process is nearly thermoneutral as the O-H bond dissociation energies of the hydroxamic acid (~88 kcal/mol) and of the phenol group (85-95 kcal/mol) are similar.[23] Upon complete consumption of the starting material, a solvent swap and addition of a 6M hydrochloric acid solution in dioxane allowed for the facile removal of the *ortho*-hydroxy benzoyl tether to afford the aniline analog of the initial phenol and liberate salicylic acid.

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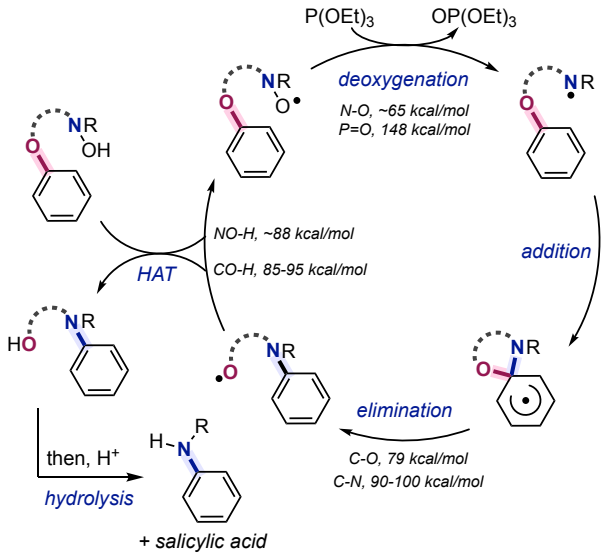

Scheme 5. Mechanistic proposal. See ref. 23 for bond dissociation energies.

Anilines are essential motifs found in a variety of organic compounds and synthesizing them from phenols is a particularly promising pursuit due to the push to use biorenewable compounds such as aryl ethers as chemical feedstocks. The application of our mild, deoxygenative approach allows for phenol to aniline conversion in only 3 synthetic steps without the need for intermediate purifications using inexpensive triethyl phosphite reagent. The use of N-centered radicalophiles allows for a broad range of sterically and electronically varied phenols to participate in this process.

Experimental Section

General rearrangement procedure: To a 1-dram vial charged with a magnetic stir bar was added hydroxamic acid (20 mg, 1 equiv), di-*tert*-butyl peroxide (5 equiv), triethyl phosphite (1.5 equiv), and 1,2-dichloroethane (0.5 mL). The reaction mixture was heated to 90 °C for 24 h or until consumption of starting material as determined by thin layer chromatography (5% ethyl acetate in hexanes). The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (5-10% ethyl acetate in hexanes).

3-Step sequence of *N*-methylaniline hydrochloride: **Step 1**: To a 100 mL round-bottomed flask charged with a magnetic stir bar and *N,N*-dimethylformamide (50 mL) was added 2-iodobenzoic acid (1.00 g, 1 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.8 mL, 3 equiv), phenol (0.76 g, 2 equiv), pyridine (63 μL, 0.20 equiv), Cu powder (11 mg, 0.04 equiv), and CuI (32 mg, 0.04 equiv). The reaction mixture was sparged with N_2 for 10 mins prior to heating to 140 °C for 12 h. The mixture was cooled to ambient temperature and then poured into 200 mL of ice cold 1M HCl solution. The mixture was then filtered to furnish the crude diaryl ether (0.85 g, quantitative yield). Crude carboxylic acid from Step 1 was immediately carried forward to **Step 2**: In a 100 mL round-bottomed flask charged with the carboxylic acid from Step 1 (0.85 g, 1 equiv) with dichloromethane (20 mL) and *N,N*-dimethylformamide (310 μL). Oxalyl chloride (1.8 mL, 5 equiv) was added and the reaction mixture was stirred at ambient temperature for 1 h after which a solution of *N*-methylhydroxylamine hydrochloride (2.0 g, 6 equiv) and triethylamine (4.5 mL, 8 equiv) in a 9:1 tetrahydrofuran:water mixture (20 mL) was added. The reaction mixture was allowed to stir for 1 h before transferring to a separatory funnel, washed once with 1M aqueous HCl, dried over Na_2SO_4, and concentrated under reduced pressure. The crude hydroxamic acid was then recrystallized from hexanes to give **1a** (1.01 g, quantitative yield) which was used immediately in **Step 3**: To a 100 mL round-bottomed flask equipped with a reflux condenser and charged with a magnetic stir bar was added **1a** (1.01 g, 1 equiv), di-*tert*-butyl peroxide (3.7 mL, 5 equiv), triethyl phosphite (1.0 mL, 1.5 equiv), and 1,2-dichloroethane (25 mL). The flask was heated to 90 °C under an air atmosphere for 24 h. Upon consumption of 1a as determined by TLC (25% ethyl acetate in hexanes), the reaction mixture was concentrated under reduced pressure before the addition of 6M aqueous HCl (7 mL) and dioxane (7 mL). The mixture was then heated to 100 °C for 48 h before cooling to ambient temperature, extracted 3 times with ethyl acetate to remove salicylic acid. The remaining fraction was concentrated to provide *N*-methylaniline hydrochloride as an off-white crystalline solid (447 mg, 77% yield).

Acknowledgements

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Keywords: aniline • phenol • radicals • deoxygenation • phosphite

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[20] **1a** can be alternatively prepared from 2-fluorobenzonitrile and phenol. See the SI for additional experimental details.

[21] Reaction time can be decreased significantly to 0.17 h if the reaction temperature was increased to 140 °C.

[22] See Scheme S2 in the Supporting Information for details.

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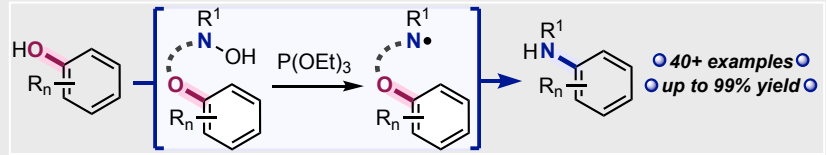

Triethyl phosphite mediated radical deoxygenation of 2-aryloxy hydroxamic acids allows for the transformation of phenols to their corresponding anilines. This approach has been applied to the conversion of a tyrosine derivative, sesamol, estrone, acetaminophen, 3-hydroxypyridine, and bisphenol A.

*Samuel W. Lardy, Kristine C. Luong, and Valerie A. Schmidt**

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Formal Aniline Synthesis from Phenols via Deoxygenative N-Centered Radical Substitution