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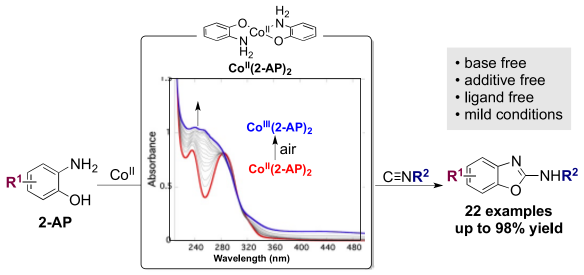
# Cobalt-Catalyzed Aerobic Oxidative Cyclization of 2-Aminophenols with Isonitriles: 2-Aminophenol Enabled $O_2$ Activation by Cobalt(II)

Jiaqi Liu and Jessica M. Hoover*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

*Supporting Information*

**ABSTRACT:** An aerobic cobalt-catalyzed oxidative cyclization of 2-aminophenols and isonitriles is reported. These additive-free conditions furnish a variety of substituted 2-aminobenzoxazoles in moderate to excellent yields. A series of control experiments and spectroscopic studies point to the importance of 2-aminophenol coordination in enabling the aerobic oxidation of cobalt(II).



- base free
- additive free
- ligand free
- mild conditions

Homogeneous transition-metal-catalyzed aerobic oxidation reactions have received considerable attention due to the benign and atom economic nature of $O_2$ as an oxidant. Significant advances have been made in the development of Pd-[1] and Cu-[2]catalyzed aerobic oxidation reactions, whereas recent efforts seek efficient catalysis utilizing alternative first-row transition-metal catalysts such as Co. Redox-active mediators or ligands, such as BQ,[3] NHPI,[4] and salen ligands,[5] are often employed to enable the utilization of $O_2$ as the terminal oxidant under Co catalysis (BQ = benzoquinone, NHPI = *N*-hydroxyphthalimide) (Scheme 1a,b). In addition, Co/BQ and Co/NHPI cocatalytic systems have been used to facilitate the use of $O_2$ as the terminal oxidant in Pd-catalyzed organic oxidation reactions.[6]

Despite the widespread utilization of Co-catalyzed aerobic oxidation reactions exploiting redox-active mediators, there are fewer examples of Co-catalyzed aerobic oxidation reactions that operate efficiently in the absence of an external redox-mediator.[7] Achieving such mediator-free oxidation reactions may be particularly challenging because these cofactors have recently been shown to assist in the prevention of undesired oxygenation side products by preventing the accumulation of

**Scheme 1. Redox-Active Cofactors Paired with Cobalt To Enable Aerobic Oxidation Reactions in Prior Studies and This Work**

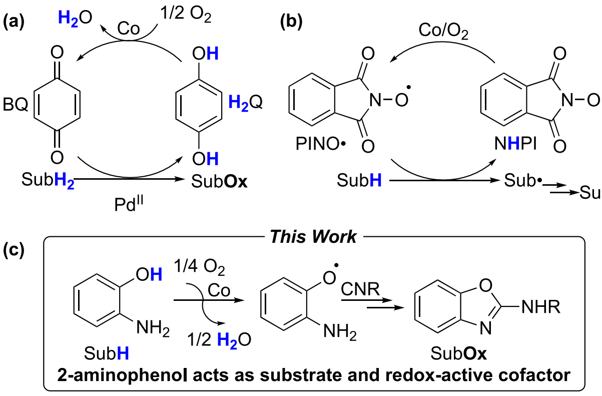
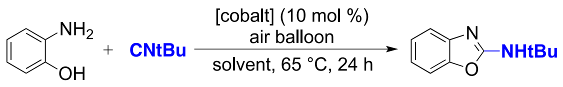


**Table 1. Optimization of the Reaction Conditions**[a]



1a 2a 3a

| entry | [cobalt] | solvent | time (h) | % yield[b] |
|---|---|---|---|---|
| 1 | Co(acac)$_2$ | THF | 24 | 58[c] |
| 2 | Co(acac)$_2$·$H_2O$ | THF | 24 | 67[c] |
| 3 | $CoCO_3$ | THF | 24 | 51 |
| 4 | $CoCO_3$·$H_2O$ | THF | 24 | trace |
| 5 | $CoCl_2$ | THF | 24 | 46 |
| 6 | Co(OAc)$_2$ | THF | 24 | 86 |
| 7 | Co(OAc)$_2$ | 1,4-dioxane | 24 | 89 |
| 8 | Co(OAc)$_2$ | 2-Me-THF | 24 | 54 |
| 9 | Co(OAc)$_2$ | DMF | 24 | 86 |
| 10 | Co(OAc)$_2$ | DMSO | 24 | 78 |
| **11** | **Co(OAc)$_2$** | **$CH_3CN$** | **24** | **93(90)**[c] |
| 12 | Co(OAc)$_2$ | $CH_3CN$ | 12 | 85 |
| 13 | Co(OAc)$_2$ | $CH_3CN$ | 6 | 79 |
| 14 |  | $CH_3CN$ | 24 | 0 |
| 15[d] | Co(OAc)$_2$ | $CH_3CN$ | 24 | 14 |

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), cobalt(II) catalyst (10 mol %), solvent (3 mL), at 65 °C with an air balloon for 24 h. [b]Yield of **3a** was determined by $^1H$ NMR spectroscopy with dimethylsulfone as internal standard (0.03 mmol). [c]Isolated yield. [d]Reaction was conducted under $N_2$.

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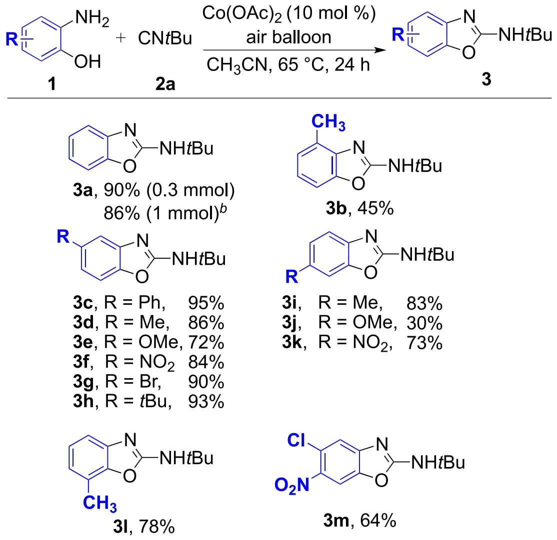
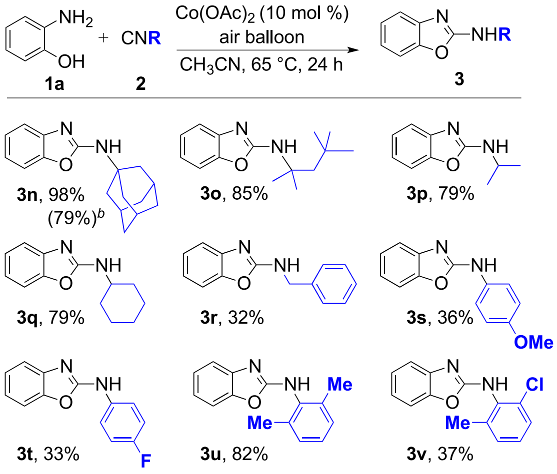
**Scheme 2. Scope of Substituted 2-Aminophenols**[a]



[a]Isolated yields. Reaction conditions: **1** (0.3 mmol), **2a** (0.3 mmol), and $Co(OAc)_2$ (10 mol %) in 3 mL of $CH_3CN$ at 65 °C with an air balloon for 24 h. [b]1 mmol scale reaction.

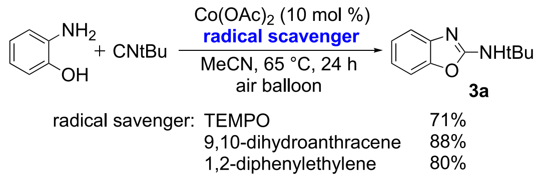
**Scheme 3. Scope of Isonitriles**[a]



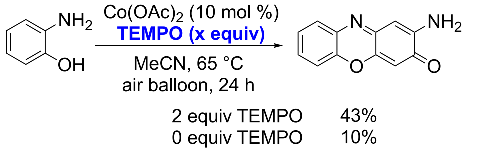
[a]Isolated yields. Reaction conditions: **1a** (0.3 mmol), **2** (0.3 mmol), and $Co(OAc)_2$ (10 mol %) in 3 mL of $CH_3CN$ at 65 °C with an air balloon for 24 h. [b]1 mmol scale reaction.

**Scheme 4. Oxidative Cyclization Conducted in the Presence of Radical Trapping Agents**

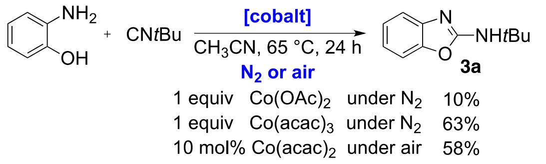
**(a) Control Reactions with Radical Scavengers**



**(b) Control Reactions with TEMPO in the Absence of Isonitrile**



**Scheme 5. Oxidative Cyclization of 2-Aminophenol and *tert*-Butylisonitrile Mediated by Cobalt under $N_2$**



superoxide and peroxide intermediates.[3] We hypothesized that the use of a substrate that can also act as a H-atom donor might enable the activation of $O_2$ and therefore allow the selective oxidation of organic substrates (Scheme 1c).

To explore this possibility we selected 2-aminophenol as a coupling partner due, in part, to its relevance to enzymatic systems. Cobalt-containing catecholase mimics enable the oxidation of catechol to *ortho*-quinone with the concomitant reduction of $O_2$ to $H_2O$,[8] and the related aminophenol-based scaffolds serve as common redox-active ligands.[9] Furthermore, the coupling of 2-aminophenols with isonitriles generates 2-aminobenzoxazoles, heterocyclic targets of biological and pharmaceutical importance. Whereas a $Pd/O_2$[10] catalyst and a Co/*t*BuOOH[11] system have been developed for this and related transformations (Scheme S1), $Co/O_2$ catalyst systems have not yet been reported.

We began our studies by evaluating the coupling reaction of 2-aminophenol (**1a**) and *tert*-butylisonitrile (**2a**) under aerobic conditions in the presence of cobalt salts (Table 1). In early reactions, air proved to be an efficient oxidant to promote this oxidative cyclization reaction. Of the $Co^{II}$ salts studied, $Co(OAc)_2$ gave the highest yield of **3a** (entry 6). When $CH_3CN$ was employed as the solvent, **3a** was obtained in 93% yield (entry 11). Shorter reaction times led to reduced yields (entries 12 and 13). The optimized reaction conditions employ a simple $Co(OAc)_2$ salt with an air balloon in $CH_3CN$ at 65 °C for 24 h. Control reactions conducted in the absence of $Co(OAc)_2$ (entry 14) or air (entry 15) resulted in 0 and 14% yield of **3a** respectively, highlighting the importance of both the cobalt catalyst and air in this oxidative transformation.

We next explored the scope of substituted 2-aminophenol coupling partners (**1**, Scheme 2). This protocol showed good tolerance of a variety of functional groups including both electron-rich (**3d**, **3e**, **3h**, and **3i**) and electron-deficient substituents (**3f**, **3g**, and **3k**). The influence of a methyl group in each of the four aromatic positions (**3b**, **3d**, **3i**, and **3l**) reveals only a small steric effect, as the yield of **3b** bearing the 3-methyl group showed a slightly decreased yield. The 4-, 5-, and 6-methyl aminophenols all resulted in high yields of the corresponding 2-aminobenzoxazoles. Similarly, the large phenyl and *tert*-butyl groups afforded the desired cyclized products in good yields (**3c** and **3h**). Finally, the disubstituted electron-deficient 5-nitro-4-chloro-2-aminophenol **1m** afforded the desired benzoxazole product in 64% yield.

To further evaluate the performance of this cyclization reaction, we investigated the scope of isonitriles (Scheme 3). Whereas *tert*-butylisonitrile is the most commonly employed isonitrile in related coupling protocols,[12] other bulky aliphatic isonitriles are also excellent coupling partners under our reaction conditions, furnishing the corresponding products in high yields (**3n**−**q**). Surprisingly, the isopropyl- and cyclohexyl-substituted isonitriles also generated high yields of the corresponding 2-aminobenzoxazole products (**3p** and **3q**). These products are expected to contain weak C−H bonds

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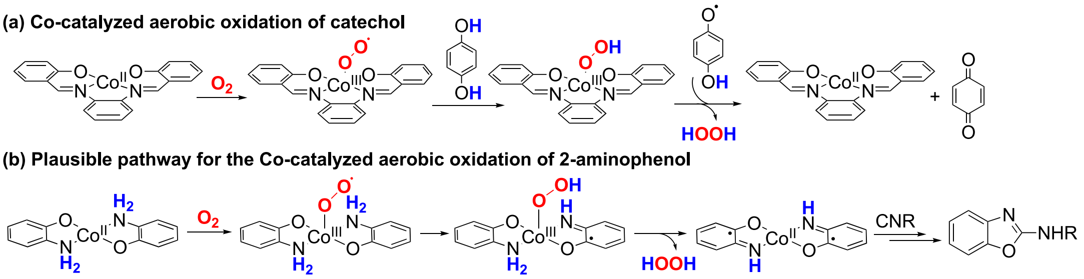
**Scheme 6. (a) Proposed Pathway in Literature for Aerobic Co-Catalyzed Catechol Oxidation and (b) Proposed Pathway for the Related Oxidation of 2-Aminophenol**



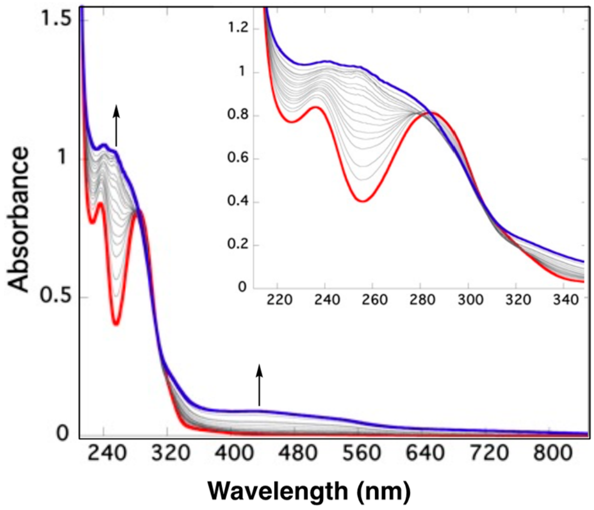


**Figure 1.** Absorption spectrum of Co(acac)$_2$ with 2-aminophenol under $N_2$ (red trace) exposed to air and monitored over the course of 12 h at rt. The final spectrum (blue trace) is similar to that of Co(acac)$_3$ treated with 2-aminophenol under $N_2$ after 24 h.

(BDE = ~86 kcal mol$^{-1}$)[13] and are plausible substrates for further oxidation. The benzylic isonitrile **2r**, however, did not undergo efficient coupling and instead resulted in only a moderate yield of the coupling product (**3r**, 32%). Also observed was the 3-aminobenzoxazine byproduct (16% yield) that results from the insertion of 2 equiv of isonitrile.[14] Surprisingly, no oxygenation byproducts[15] were observed in this reaction, despite the weak C−H bond (~72 kcal mol$^{-1}$)[13] and the precedent for Co/$O_2$ enabled benzylic oxygenation.[4c] Finally, aryl isonitriles also underwent coupling to yield the corresponding 2-aminobenzoxazole products, with the bulkier aromatic ring of **1u** resulting in the highest product yield (82%).

The efficient coupling of isonitriles bearing weak C−H bonds suggested that a free-radical intermediate is unlikely. Consistent with this hypothesis, efforts to trap free-radical intermediates with common radical scavengers, such as TEMPO, 9,10-dihydroanthracene, and 1,1-diphenylethylene, showed no evidence of trappable radical intermediates. Instead, when these reagents were included under the standard reaction conditions, high yields of **3a** were still observed (Scheme 4a).[16] The absence of trappable free radicals may suggest the stabilization of a ligand radical through coordination to Co. When the same reactions were conducted in the absence of isonitrile, oxidative dimerization of 2-aminophenol occurred to form 2-aminophenoxazine-3-one in both the presence and the absence of TEMPO (43 and 10% yield, respectively) (Scheme 4b),[17] consistent with the presence of aminophenol radicals.[8b,18] The elevated yield in the presence of TEMPO could be a result of a TEMPO-mediated H-atom abstraction pathway to form the aminophenol radical.[19]

A large series of Co$^{II}$ complexes of aminophenol-, aminothiophenol-, and diamine-derived ligands have been characterized,[9b,20] and Wieghardt and coworkers have shown the aerobic oxidation of these species to form stabilized iminobenzosemiquinonato-type species bearing $\pi$-radical ligands (AP$^{SQ}$).[20b] In all of these cases, highly substituted aminophenol ligands are used to avoid ligand dimerization and enable the isolation of the oxidized complexes. We believe that a related stabilized ligand radical may be formed under our reaction conditions from Co$^{II}$, $O_2$, and 2-aminophenol. When CNR is present, it is a sufficient trap for the aminophenol radical,[12] whereas in its absence, aminophenol dimerization occurs.

To determine if $O_2$ is required for the formation of **3** or if it is only responsible for regenerating Co$^{II}$ after product formation, we conducted a series of control experiments in the absence of $O_2$. When the standard reaction is conducted with 1 equiv of Co(OAc)$_2$ under $N_2$, only 10% yield of **3a** is obtained, indicating the need for oxygen to efficiently form product, not simply to regenerate Co$^{II}$ (Scheme 5). Additionally, when the same reaction is conducted with stoichiometric loadings of the Co$^{III}$ salt, Co(acac)$_3$, under $N_2$, **3a** is formed in 63% yield (Scheme 5). The reduced yield obtained with Co(acac)$_3$ relative to the standard catalytic conditions with Co(OAc)$_2$ are attributed to the slow exchange of the acac ligand. Consistent with this hypothesis, the standard catalytic reaction conducted with Co(acac)$_2$ leads to 58% yield of **3a**, compared with the 93% yield obtained when Co(OAc)$_2$ is used (Table 1, entry 11). These combined data suggest that $O_2$ is responsible for the oxidation of Co$^{II}$ to generate an active Co$^{III}$ or ligand oxidized semiquinonato Co$^{II}$AP$^{SQ}$ intermediate.

Given the importance of oxidation for product formation, we sought to better understand the aerobic oxidation step. The oxidation of Co$^{II}$ by $O_2$ is typically proposed to generate a Co$^{III}$−superoxide intermediate. In a recent study by Stahl, Hammes-Schiffer, and coworkers utilizing salophen-bound cobalt complexes, the Co$^{III}$−superoxide species is responsible for H-atom abstraction (HAA) from $H_2Q$ to generate a Co$^{III}$−hydroperoxide intermediate (Scheme 6a).[3] A second HAA step then generates the quinone and Co$^{II}$ with the release of $H_2O_2$. Under these conditions, $H_2O_2$ undergoes disproportionation to form $O_2$ and $H_2O$. Similarly, the reoxidation of NHPI is proposed to proceed through an analogous HAA step.[4a] Thus we imagined that a Co$^{III}$−superoxide species may be responsible for the HAA of 2-aminophenol under our oxidative cyclization conditions (Scheme 6b).

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We conducted a series of UV−visible experiments to probe this oxidation step and, in particular, the ligand environment that enables aerobic oxidation. First, when Co(acac)$_2$ in $CH_3CN$ is exposed to air for 12 h, no changes in the absorption spectrum are observed (Figure S3). Similarly, a mixture of Co(acac)$_2$ and CN*t*Bu in $CH_3CN$ showed no significant changes in the spectroscopic features after exposure to air (Figure S4). In contrast, when a solution of Co(acac)$_2$ and 2-aminophenol is exposed to air, a color change from light pink to orange-brown occurs within minutes. This rapid color change is accompanied by an increase in the absorption around 260 nm (Figure 1). This spectroscopic band is similar to that observed when Co(acac)$_3$ is combined with 2-aminophenol under $N_2$ ($\lambda_{max}$ = 233 nm, Figure S7). In related Co systems bearing catechol ligands, the semiquinonato species can be obtained when Co$^{III}$ starting materials are treated with catechol,[21] and a related redox equilibrium to access Co$^{II}$(AP$^{SQ}$) from Co$^{III}$ may be operative in these aminophenol systems. Overall, these spectroscopic changes suggest that the aerobic oxidation of Co$^{II}$ is facilitated by the presence of 2-aminophenol.

Although our work here has focused on the aerobic oxidation of Co$^{II}$, the subsequent coupling of the oxidized intermediate with isonitrile is also of interest. In related Pd-catalyzed cyclization reactions of aminophenols with isonitriles, the C−N bond-forming step is proposed to proceed via the migratory insertion of the CNR ligand.[14] Alternatively, a radical-based addition to CNR may be operative given the presence of the proposed semiquinonato radical intermediates.[12]

In summary, we have developed a convenient and atom economical route to 2-aminobenzoxazoles utilizing an additive-free cobalt-catalyst system under aerobic conditions. A broad scope of substituted 2-aminophenols and isonitriles is tolerated by this catalyst system. Finally, the importance of 2-aminophenol acting as a ligand to facilitate the aerobic oxidation of Co$^{II}$ was confirmed with a series of UV−visible studies. Ongoing work is directed toward the isolation and characterization of the relevant aminophenol-ligated cobalt intermediates.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01384.

> Details of reaction development, characterization data for starting materials and products, and $^1H$ and $^{13}C$ NMR spectra (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: Jessica.Hoover@mail.wvu.edu.

### ORCID

Jessica M. Hoover: 0000-0003-0254-5090

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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