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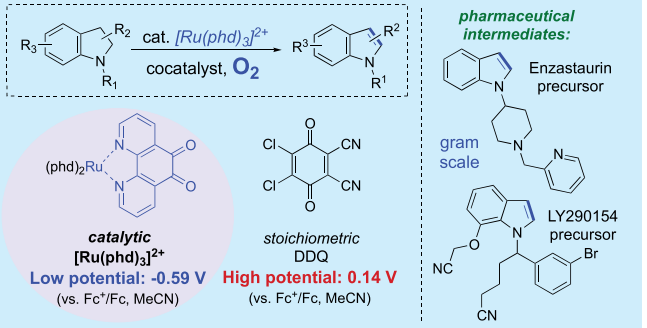
Replacement of Stoichiometric DDQ with a Low Potential *o*-Quinone Catalyst Enabling Aerobic Dehydrogenation of Tertiary Indolines in Pharmaceutical Intermediates

Bao Li, Alison E. Wendlandt,[†] and Shannon S. Stahl*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

Supporting Information

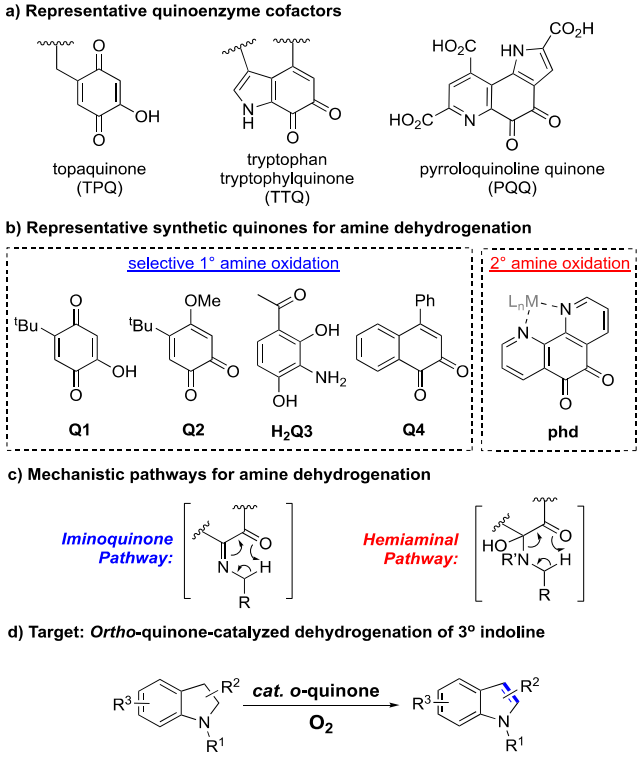
ABSTRACT: A transition-metal/quinone complex, [Ru(phd)$_3$]$^{2+}$ (phd = 1,10-phenanthroline-5,6-dione), is shown to be effective for aerobic dehydrogenation of 3° indolines to the corresponding indoles. The results show how low potential quinones may be tailored to provide a catalytic alternative to stoichiometric DDQ, due to their ability to mediate efficient substrate dehydrogenation while also being compatible with facile reoxidation by O_2. The utility of the method is demonstrated in the synthesis of key intermediates to pharmaceutically important molecules.



Quinone cofactors present in copper amine oxidases (CAOs) and other "quinoenzymes" (Scheme 1a) have inspired numerous efforts to mimic their reactivity with synthetic catalysts.[1,2] Early efforts used *ortho*-quinones to probe enzymatic mechanisms,[3−12] while recent studies have expanded on synthetic applications.[13−31] These studies show that *o*-quinones are effective catalysts for aerobic dehydrogenation of primary and secondary amines (Scheme 1b). Primary amines are the native substrates for CAO enzymes, and mechanistic data support a pathway in which amine condensation with the quinone affords an iminoquinone intermediate that undergoes an internal redox reaction via hydride transfer to generate the oxidized substrate (Scheme 1c).[3−11] Consistent with this mechanism, biomimetic *o*-quinones often support selective dehydrogenation of 1° amines, without reacting with 2° and 3° amines.[16,21,22,24] In complementary efforts, we showed that 1,10-phenanthroline-5,6-dione (phd, Scheme 1b), in the presence of ZnI_2, can effect catalytic dehydrogenation of 2° amines with O_2 as the terminal oxidant.[17] This reactivity arises from a different mechanism involving a hemiaminal intermediate (Scheme 1c).

Quinone-catalyzed aerobic oxidation of 3° amines has not yet been reported and remains a challenge. For example, the phd/ZnI_2 catalyst system showed poor reactivity in the attempted dehydrogenation of a 3° indoline.[17] The latter reaction is a valuable target owing to the prevalence of *N*-substituted indoles in bioactive natural products and pharmaceuticals.[32−34] Dehydrogenation of indolines provides a strategic route to these compounds,[35−38] often overcoming limitations of other synthetic routes to indoles.[39−44] Indoline dehydrogenation is typically accomplished with (super)-stoichiometric oxidants, such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), $KMnO_4$, or MnO_2.[39,45−47] DDQ has found especially broad use, including application in

Scheme 1. Quinone-Catalyzed Dehydrogenation of Amines



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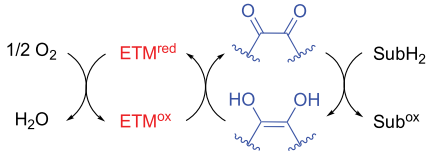
process-scale pharmaceutical synthesis.[38] The cost, toxicity, and waste disposal associated with DDQ have motivated efforts to identify catalytic alternatives.[13,48−52] Herein, we pursue this goal and report the first 3° amine dehydrogenation reactions with CAO-inspired *o*-quinone catalysts, showing that a phd-ligated Ru complex,[18] $[Ru(phd)_3](PF_6)_2$, enables efficient conversion of 3° indolines to indoles (Scheme 1d). This low-potential *o*-quinone catalyst system is shown to have broader functional group compatibility than DDQ and outperforms stoichiometric DDQ in the preparation of important pharmaceutical intermediates.

The enthalpy of indoline dehydrogenation is ∼12 kcal/mol, and assuming typical entropic contributions, the $\Delta G°$ for this reaction is estimated to be ≤5 kcal/mol.[53] DDQ is a high-potential quinone that provides an unnecessarily strong driving force for dehydrogenation (>40 kcal/mol).[54] We postulated that a lower-potential quinone for indoline dehydrogenation could exhibit broader functional-group compatibility, while also enabling efficient aerobic catalytic turnover (Scheme 2).

Scheme 2. Quinone-Catalyzed Aerobic Dehydrogenation Process Using Electron-Transfer Mediators (ETMs)[56]



Several of the *o*-quinones in Scheme 1b were analyzed by cyclic voltammetry.[55] **Q2**, phd, and $[Ru(phd)_3]^{2+}$ exhibit reduction potentials of −0.93, −0.88, and −0.59 V, respectively, vs Fc^+/Fc in MeCN. These potentials are 0.73−1.07 V lower than that of DDQ (0.14 V vs Fc^+/Fc) under the same conditions. Tertiary amines are unlikely to be capable of generating stable covalent adducts similar to those observed with 1° and 2° amines (cf. Scheme 1c).[3−11] Nevertheless, we reasoned that transient adduct formation could lead to kinetically efficient dehydrogenation, even in the absence of the strong thermodynamic driving force available from DDQ.

To test our hypothesis, we assessed the reactivity of **Q1**, **Q2**, and phd, in combination with various electron-transfer mediators (ETMs), as catalysts for dehydrogenation of 1-methylindoline **1a** and the more electron-deficient derivative **2a**. Two complementary catalyst systems/reaction conditions were identified from these efforts: $[Ru(phd)_3]^{2+}/Bu_4NI/CH_3CN$ (**A**) and $[Ru(phd)_3]^{2+}$/Co(salophen)/MeOH[57] (**B**), respectively, for **1a** and **1b** (see Supporting Information for full screening data). Catalytic conditions **A** and **B** were then evaluated with a number of other indoline substrates (Figure 1). The $[Ru(phd)_3]^{2+}/Bu_4NI$ catalyst system **A** appears to fare best with electronically neutral substrates. Good yields of indole product were obtained with 1-methylindoline **1a**, in addition to derivatives **7a**, **8a**, **11a**, **12a**, and **13a** bearing modified *N*-substituents and/or small substituents on the indoline core. More electron-rich substrates, such as 1-methyl-5-methoxyindoline **3a** and 1-methyl-7-benzyloxyindoline **10a**, and more electron-poor derivatives, such as 1-methyl-5-bromoindoline **2a** and 5-formylindoline **5a**, afforded lower yields with this catalyst system. In each of these cases, the $[Ru(phd)_3]^{2+}$/Co(salophen) catalyst system **B** proved more effective, enabling higher product yields and shorter reaction time. In a few cases, such as the chloro- and cyano-substituted

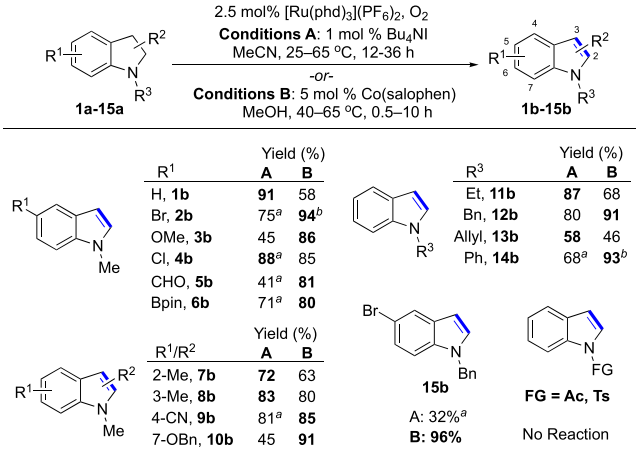


Figure 1. Substrate scope of aerobic dehydrogenation of N-substituted indolines to indoles. Conditions (A): 1.0 mmol scale, 2.5 mol % $[Ru(phd)_3](PF_6)_2$, 1 mol % Bu_4NI, MeCN (0.1 M), O_2, room temperature. Conditions (B): 1.0 mmol scale, 2.5 mol % $[Ru(phd)_3](PF_6)_2$, 5 mol % Co(salophen), MeOH (0.1 M), O_2, 65 °C. Isolated yields. [a]Reactions were run at 65 °C. [b]Reactions were run at 40 °C.

derivatives **4a** and **9a**, good product yields were obtained with both catalyst systems. Catalyst system **B** occasionally led to substrate decomposition and poor yield (e.g., with **1a**), but it appears to be the more broadly effective of the two catalyst systems.

Simple indoles such as those in Figure 1 are often accessible by other methods, and therefore, the utility of dehydrogenation methods is more evident in complex molecule synthesis. The lower redox potential of the present quinone catalyst relative to DDQ should enable broader functional group compatibility. Substrate **6a**, for example, features an oxidatively sensitive pinacolboronate. This substrate underwent dehydrogenation in 80% yield with catalyst system **B**, while a significantly reduced yield was obtained with stoichiometric DDQ (47% yield, with complete substrate conversion). More extensive testing was conducted by evaluating the dehydrogenation of **2a** under catalytic conditions **B** (cf. Figure 1) and with stoichiometric DDQ in the presence of oxidatively sensitive molecules (Figure 2). Examples include those known to react with DDQ, such as diphenylmethane,[58] isochroman,[59] and allylic alcohol.[60] In each case, **2b** was generated in excellent yield under the

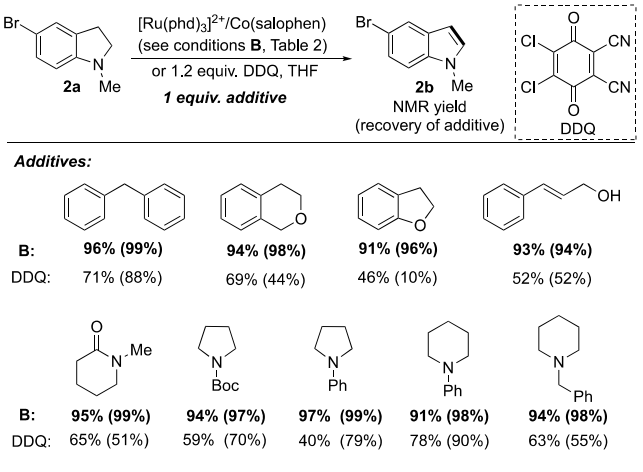


Figure 2. Competition studies with oxidatively sensitive molecules.

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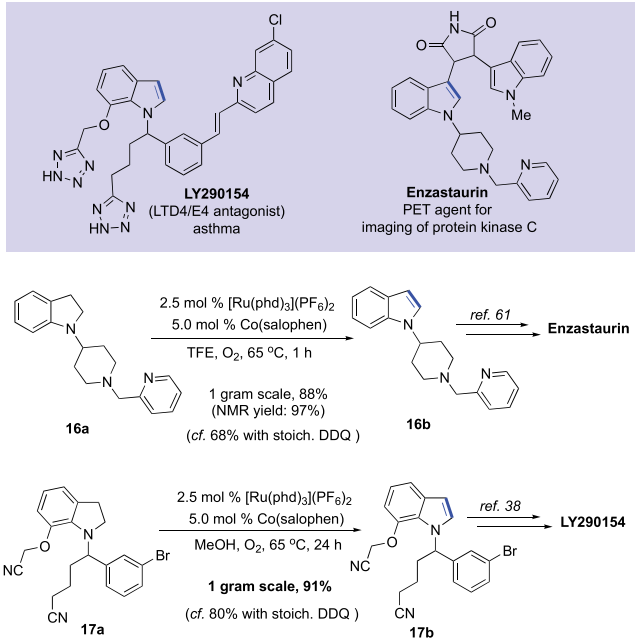
catalytic aerobic conditions (91−97% yield), with virtually no decomposition of the additive (≥94% recovery). Meanwhile, the reactions with DDQ led to moderate yields of **2b** (40−78% yield) and often resulted in significant decomposition of the additive (up to 90%). The preferred reactivity of indoline **2a** over *N*-phenyl pyrrolidine and *N*-phenyl piperidine may be rationalized by the conformational constraints of the indoline ring, which enforce conjugation with the arene ring and should enhance the hydride donor ability of the substrate.

The catalytic conditions obtained here were then evaluated in the preparation of pharmaceutical intermediates (Scheme 3). Indole **16b** is an intermediate en route to the natural

Scheme 3. Quinone-Catalyzed Dehydrogenation of Pharmaceutical Intermediates



product Enzastaurin (Scheme 3), which has been targeted as a PET reagent for imaging of protein kinase C.[61] Gram-scale dehydrogenation of indoline **16a** with the $[Ru(phd)_3]^{2+}$/Co(salophen) catalyst system provided **17b** in near-quantitative NMR yield (97%; 88% isolated yield), reflecting the excellent chemoselectivity for dehydrogenation of the indoline rather than the tertiary piperidine and also demonstrating compatibility with a pyridine substituent. This result may be compared with a previously reported protocol, which employed 1.1 equiv of DDQ and generated **16b** in 68% yield.[43] Preparation of the asthma drug candidate LY290154 (Scheme 3) proceeds via the indole intermediate **17b**. Reported efforts to carry out *N*-alkylation of the substituted indole with a secondary alkyl halide were complicated by competing elimination reactions. Therefore, the synthesis of **17b** was conducted by sequential alkylation and dehydrogenation of the corresponding indoline with DDQ.[38] Use of the $[Ru(phd)_3]^{2+}$/Co(salophen) catalyst system in a gram-scale aerobic dehydrogenation of **17a** afforded **17b** in 91% isolated yield, again surpassing the reported outcome with stoichiometric DDQ (80% yield).

The good reactivity of the low-potential quinone catalyst may be rationalized by a mechanistic variant of the "hemiaminal" mechanism in Scheme 1c, involving transient formation of an adduct between the tertiary amine and the phd *o*-quinone. As expected, however, the 3° amine substrate does not form a resting state adduct with the quinone, as revealed by variable-temperature NMR analysis of a solution of $[Ru(phd)_3]^{2+}$ and **2a**.[62]

To further probe the mechanism of the reaction, deuterium kinetic isotope effects (KIEs) were obtained by independently comparing the rate of dehydrogenation of **2a**, **2a**-C2-d_2, **2a**-C3-d_2, and **2a**-d_4 (Figure 3a). The data revealed a significant

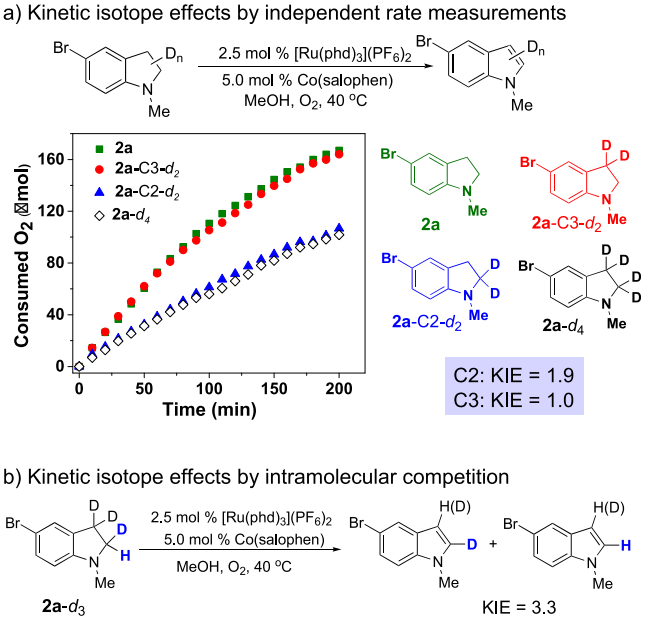


Figure 3. Kinetic isotope effect data from $Ru(phd)_3]^{2+}$/Co(salophen)-catalyzed dehydrogenation of **2a** and its isotopologues. (Note: The deuterium labels in the C3 position of **2a**-d_3 are a byproduct of the synthetic protocol; $NaBD_3CN$/DOAc-mediated reduction of the indole leads to full H/D exchange at the C3 position. Then, partial H incorporation from MeOH occurs at the C3 position during the dehydrogenation reaction.)

deuterium KIE at C2 (KIE = 1.9) but no KIE at the C3 position. An intramolecular competition deuterium KIE of 3.3 was observed at C2, obtained by probing the reaction of **2a**-d_3 (Figure 3b).[63] The higher magnitude of the latter KIE relative to the independent rate KIE suggests that the reaction does not proceed by a single-step bimolecular hydride-transfer pathway, and it is consistent with pre-equilibrium formation of a transient covalent adduct prior to hydride transfer from the C2 position of the indoline. This pathway is consistent with the lack of reactivity exhibited by substrates bearing *N*-carbonyl or -sulfonyl substituents (e.g., Ac, Ts; cf. last entry in Figure 1). The latter results could also be rationalized by a single-electron transfer pathway; however, such a pathway is unlikely, considering the oxidative peak potentials of *N*-methylindolines **1a** and **2a** are nearly 1 V higher than the potential of $[Ru(phd)_3]^{2+}$ (approximately +0.40 V vs −0.59 V, respectively).

The catalyst system described here should find application in other tertiary amine dehydrogenation reactions. An important example is cross-dehydrogenative coupling (CDC) for functionalization adjacent to the nitrogen atom.[64,65] As a preliminary test of this application, we evaluated the $[Ru(phd)_3]^{2+}$/Co(salophen) catalyst system in the reaction of *N*-phenyltetrahydroisoquinoline with a series of different

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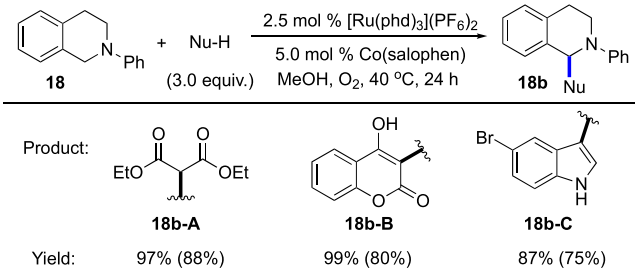
nucleophiles (Scheme 4). Excellent yields were obtained in C–C bond forming reactions with diethylmalonate, 4-hydroxy-

Scheme 4. Quinone-Catalyzed Cross-Dehydrogenative Coupling (CDC) Reactions of *N*-Phenyltetrahydroisoquinoline[a]



[a]1.0 mmol scale. Yields were determined by ^{1}H NMR. Isolated yields in parentheses.

coumarin, and indole. These results set the stage for future studies to explore other aerobic oxidative coupling reactions with CAO-inspired quinone catalyst systems.

In summary, here we have demonstrated that a CAO-inspired *o*-quinone catalyst, $[Ru(phd)_3]^{2+}$, is effective for the aerobic dehydrogenation of 3° indolines. These observations represent an important advance beyond the established reactivity of CAO catalyst systems with 1° and 2° amines. The low-potential nature of quinone catalyst systems of this type provides the basis for excellent functional-group compatibility and establishes a foundation for the development of other catalytic alternatives to stoichiometric DDQ and related high-potential oxidants, with applications including dehydrogenation and oxidative coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00111.

Experimental procedures and characterization data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stahl@chem.wisc.edu.

ORCID

Alison E. Wendlandt: 0000-0003-2970-9817
Shannon S. Stahl: 0000-0002-9000-7665

Present Address

†Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139, USA. E-mail: awendlan@mit.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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