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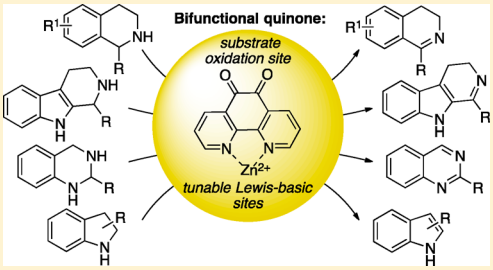
Bioinspired Aerobic Oxidation of Secondary Amines and Nitrogen Heterocycles with a Bifunctional Quinone Catalyst

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: Copper amine oxidases are a family of enzymes with quinone cofactors that oxidize primary amines to aldehydes. The native mechanism proceeds via an iminoquinone intermediate that promotes high selectivity for reactions with primary amines, thereby constraining the scope of potential biomimetic synthetic applications. Here we report a novel bioinspired quinone catalyst system consisting of 1,10-phenanthroline-5,6-dione/ZnI_2 that bypasses these constraints via an abiological pathway involving a hemiaminal intermediate. Efficient aerobic dehydrogenation of non-native secondary amine substrates, including pharmaceutically relevant nitrogen heterocycles, is demonstrated. The ZnI_2 cocatalyst activates the quinone toward amine oxidation and provides a source of iodide, which plays an important redox-mediator role to promote aerobic catalytic turnover. These findings provide a valuable foundation for broader development of aerobic oxidation reactions employing quinone-based catalysts.



INTRODUCTION

Enzymatic transformations have provided the inspiration for numerous advances in synthetic chemistry and catalysis. In connection with the widespread interest in the development of aerobic oxidation reactions, numerous researchers have turned to metalloenzymes as a starting point for the development of small-molecule transition-metal catalysts. Organic cofactors are also common in naturally occurring oxidases and oxygenases, but these have been less extensively developed for use in synthetic applications. Copper amine oxidases promote aerobic oxidation of primary amines to aldehydes in nature (Figure 1).[1] Copper is present in the enzyme, but substrate oxidation is promoted exclusively by a quinone cofactor in the active site. The mechanism of the reaction was the subject of considerable historical debate that focused on two possible pathways:[2,3] a "transamination" pathway involving the formation and oxidation of an iminoquinone intermediate (Figure 1A) and an "addition−elimination" pathway involving substrate oxidation via a hemiaminal intermediate (Figure 1B). Extensive mechanistic studies of the enzyme and model systems by Klinman, Sayre, and others convincingly demonstrated that the reaction proceeds via the transamination pathway.[4,5]

Recently, several groups have begun to explore quinone-based catalysts[6−9] as alternatives to metal-based catalysts for amine dehydrogenation.[10−12] The use of quinones **Q1**[6] and **Q2**[7] (Scheme 1) enables efficient and selective production of homo- and heterocoupled imines under mild reaction conditions (Scheme 1). These catalysts show exquisite selectivity for primary amines, similar to the native enzymes. Secondary amines are not compatible with the transamination mechanism, and they often serve as inhibitors via the formation of irreversible covalent adducts.[13,14]

The function of quinone cofactors in nature is not limited to primary amine oxidation. For example, pyrroloquinoline quinone (PQQ)-dependent alcohol dehydrogenases (Figure 2) mediate alcohol oxidation via a mechanism that involves a hemiacetal intermediate, resembling the addition−elimination mechanism in Figure 1B.[15−17] Identification of new quinone-based catalysts that operate via an addition−elimination mechanism could significantly enhance the synthetic scope of such oxidation reactions. Kobayashi proposed the involvement of hemiaminal intermediates in diverse amine oxidation reactions that use Pt/Ir nanoclusters and 4-*tert*-butylcatechol as cocatalysts.[8] In this work, we have expanded this concept by showing that 1,10-phenanthroline-5,6-dione (phd) (Figure 2) is an effective catalyst for secondary amine oxidation. Fundamental studies have provided direct evidence for the addition−elimination pathway, including spectroscopic characterization of the hemiaminal intermediate. We further show that coordination of the distal nitrogen atoms to Zn^{2+} enhances the amine oxidation activity of phd and that a catalyst system composed of phd and ZnI_2 promotes efficient aerobic oxidation of a variety of secondary amines and nitrogen heterocycles.

RESULTS AND DISCUSSION

Stoichiometric Secondary Amine Oxidation and Characterization of a Hemiaminal Adduct. In an effort to expand upon our earlier studies of quinone-mediated amine oxidation,[6] we were drawn to the structure of phd as a potential catalyst because of its bifunctional character associated with the *o*-quinone moiety and the distal chelating nitrogen atoms

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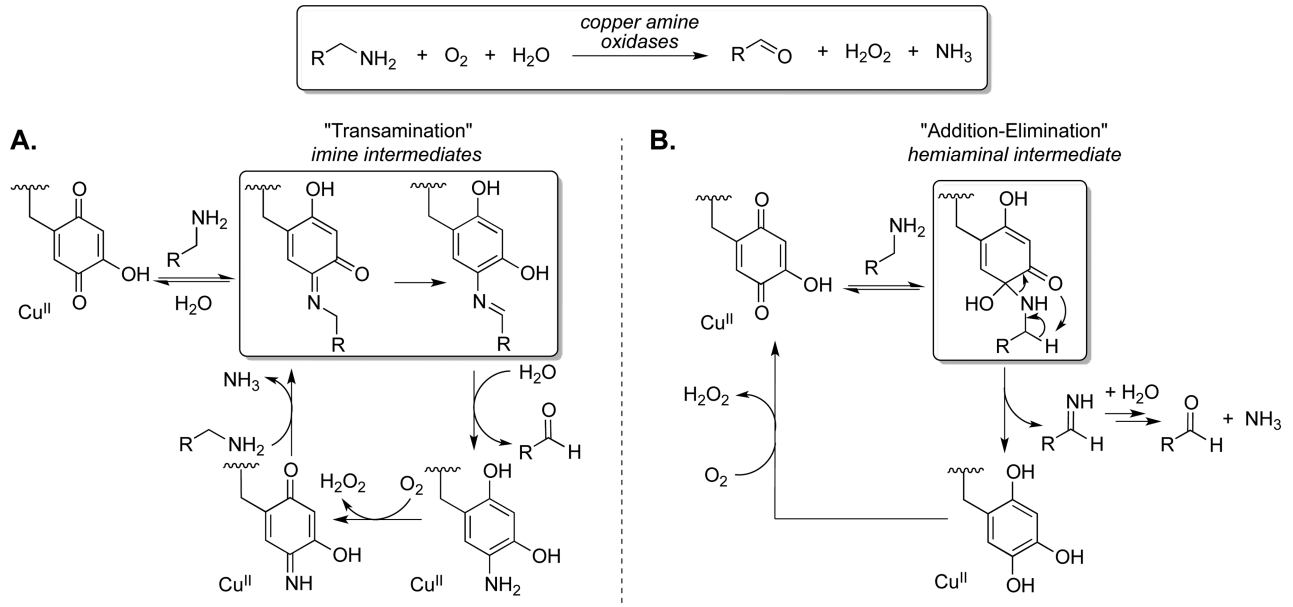
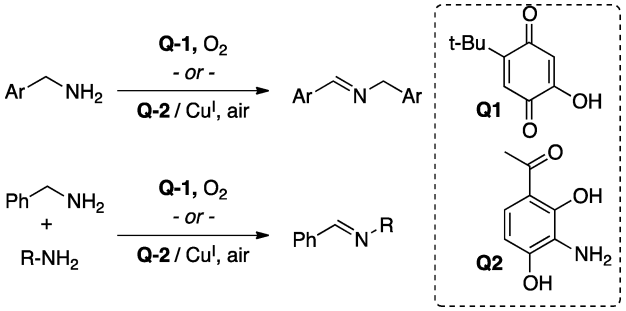


Figure 1. Mechanism of aerobic amine oxidation mediated by copper amine oxidase enzymes. (A) "Transamination" mechanism involving covalent imine intermediates. (B) "Addition–elimination" mechanism involving a hemiaminal intermediate.

Scheme 1. Biomimetic Precatalysts Q1 and Q2 and Their Synthetic Application to Oxidative Homo- and Cross-Coupling of Primary Amines



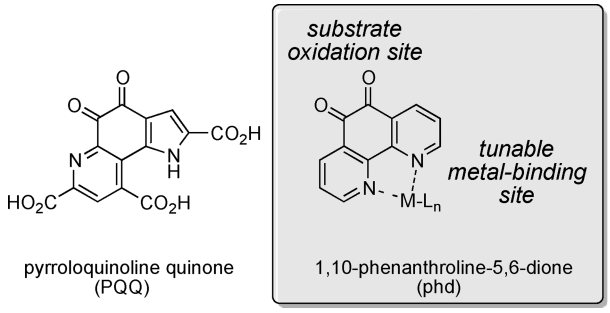
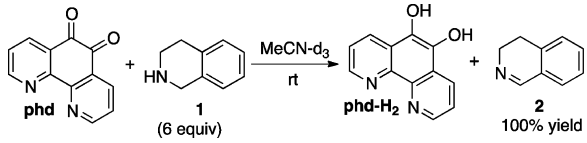


Figure 2. (left) Pyrroloquinoline quinone (PQQ) and (right) phd, a modular, bifunctional catalyst for amine oxidation. The *o*-quinone moiety is responsible for substrate oxidation, while the remote metal-binding sites can be used to tune the quinone reactivity.

(Figure 2). Independently, the coordination chemistry of phd with a number of different metals has been investigated.[18−20] We speculated that these two features could be combined to achieve unique amine oxidation reactivity.[21] The dehydrogenation of cyclic secondary amines was targeted because these substrates have been ineffective with traditional amine oxidase mimics. For example, Bruice and co-workers studied isomeric phenanthroline-derived *o*-quinones as models of the cofactor PQQ, and they observed stoichiometric oxidation of various amines, including the secondary amine morpholine. No catalytic reactivity was observed, however, and the reaction with morpholine led to the formation of an irreversible covalent adduct.[14,22] Catalytic dehydrogenation of secondary amines is also an important target because the unsaturated heterocyclic products are prevalent in pharmaceuticals and other biologically active molecules.[23]

Our initial studies probed the stoichiometric reaction of 1,2,3,4-tetrahydroisoquinoline (**1**) with phd in MeCN. The reaction proceeded quantitatively at room temperature within 18 h to afford 3,4-dihydroisoquinoline (**2**) and 1,10-phenanthroline-5,6-diol (phd-H_2) as a yellow-green precipitate (eq 1). The effectiveness of this reaction was better than



(1)

expected in light of Bruice's precedent showing that secondary amines could form irreversible covalent adducts with phd analogues.[14]

The reaction of **1** with phd was monitored by ^{1}H NMR spectroscopy to determine whether intermediates could be observed. Upon addition of 6 equiv of **1** in MeCN-d_3 at room temperature, the characteristic phd resonances disappeared with the concomitant formation of new broad peaks. Variable-temperature studies demonstrated these broad peaks to be associated with an equilibrium exchange process occurring on the NMR time scale. The broad peaks were resolved at lower temperature (Figure 3 and Figure S1 in the Supporting Information) to reveal the presence of a new species, and the chemical exchange process was sufficiently slow at −40 °C to enable full characterization of this intermediate by NMR spectroscopy.[24] It was identified as hemiaminal A (Figure 3A) on the basis of ^{1}H−^{13}C and ^{1}H−^{15}N gradient heteronuclear single-quantum coherence (gHSQC) and gradient hetero-

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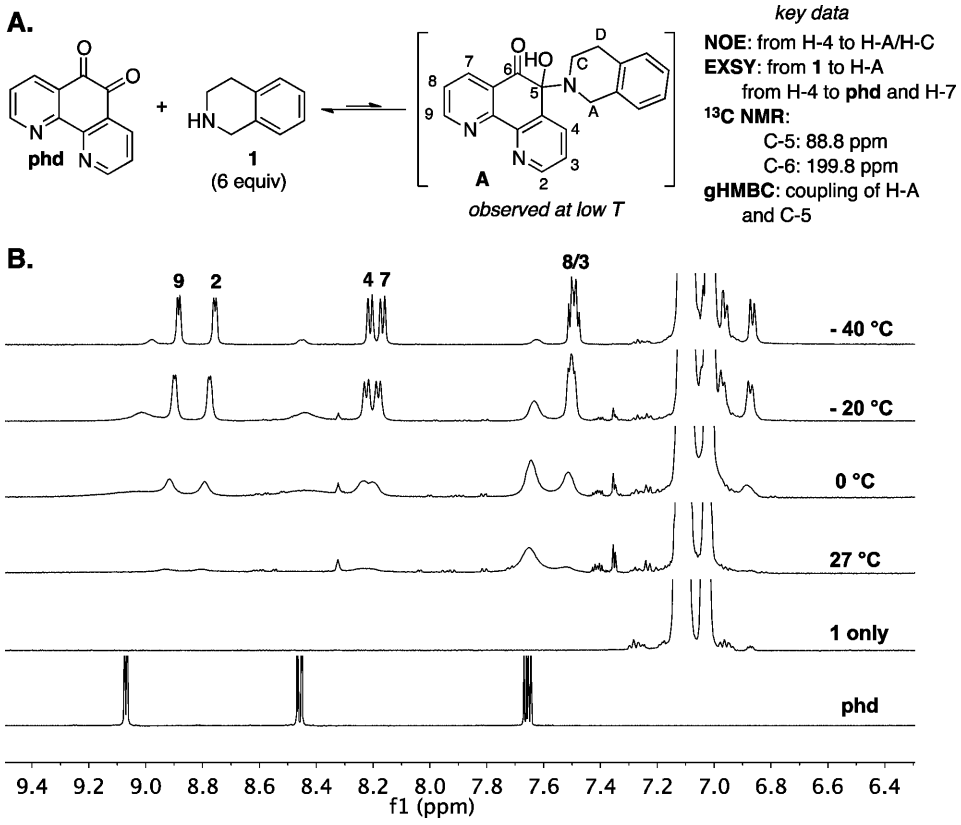

Figure 3. Observation of hemiaminal intermediate **A** by variable-temperature ^{1}H NMR spectroscopy.

nuclear multiple-bond correlation (gHMBC) data as well as 1D nuclear Overhauser effect spectroscopy (NOESY) data (see Figures S2–S6 in the Supporting Information).

NMR titration studies of phd with **1** in MeCN-d_3 (Figure S7 in the Supporting Information) were used to establish the equilibrium constant for hemiaminal formation as K = 0.10 mM^{-1} at −40 °C. Exchange spectroscopy (EXSY) experiments carried out with 6 equiv of **1** revealed exchange between **1** and the hemiaminal and between the hemiaminal and free phd (Figures S8 and S9 in the Supporting Information).

Zn^{2+}-Promoted Amine Oxidation and Characterization of Zn–phd Complexes. The prospect that metal ions could promote phd-mediated amine oxidation was tested by adding various quantities of $Zn(OTf)_2$ to the reaction mixture. The most significant rate enhancement was observed with 0.5 equiv of $Zn(OTf)_2$ (i.e., phd/Zn^{2+} = 2:1), which led to an 11-fold increase in the initial rate of the oxidation of **1** by phd (Figure 4). The formation of large quantities of a precipitate, presumably corresponding to a Zn^{2+}/phd-H_2 coordination polymer, slowed the reaction after approximately 40–50% conversion under these conditions.

NMR titration studies of $Zn(OTf)_2$ and phd in MeCN-d_3 revealed the sequential formation of three discrete species in solution, corresponding to $[Zn(phd)_3]^{2+}$, $[Zn(phd)_2]^{2+}$, and $[Zn(phd)]^{2+}$ (Figure 5 and Figure S10 in the Supporting Information). ^{1}H–^{15}N HMBC experiments revealed that the phd ^{15}N resonances shifted from 313 to 251 ppm in the presence of $Zn(OTf)_2$ (Figures S11 and S12 in the Supporting Information), consistent with coordination of the pyridyl nitrogen atoms to Zn. X-ray-quality crystals of a $[Zn(phd)_2]^{2+}$ species were obtained from a 2:1 phd/$Zn(OTf)_2$ mixture in MeCN, confirming the coordination of phd to Zn (Figure 6).

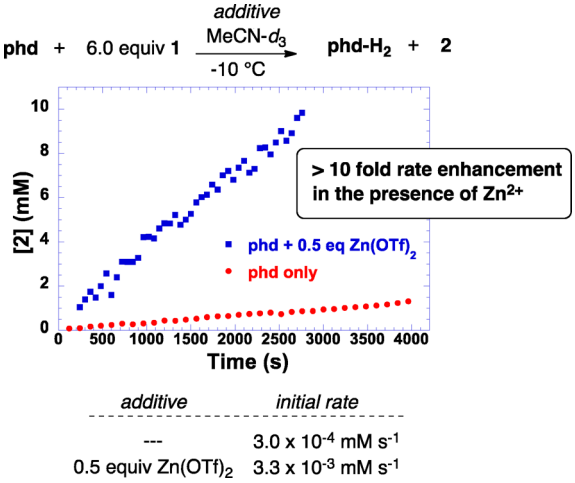

Figure 4. Rates of the stoichiometric reaction of **1** with phd at −10 °C in acetonitrile with and without 0.5 equiv of $Zn(OTf)_2$. Reaction conditions: [phd] = 19 mM (0.019 mmol), [**1**] = 114 mM (0.114 mmol), [$Zn(OTf)_2$] = 9.5 mM (0.095 mmol), MeCN (1 mL), −10 °C.

Catalytic Aerobic Oxidation of Secondary Amines. The oxidation of tetrahydroisoquinoline **1** to dihydroisoquinoline **2** was then tested with catalytic quantities of phd (5 mol %) and different Zn^{2+} sources (2.5 mol %) under O_2 (1 atm) (Table 1). Negligible catalytic turnover was observed in the oxidation of **1** by phd in the absence of Zn^{2+} ions (7% yield), and little improvement was achieved by including $Zn(OTf)_2$, $Zn(OAc)_2$, $ZnCl_2$, or $ZnBr_2$ (Table 1, entries 1–5). Use of ZnI_2, however, resulted in significant catalytic turnover (55% yield; entry 6). The yield further improved upon the addition of

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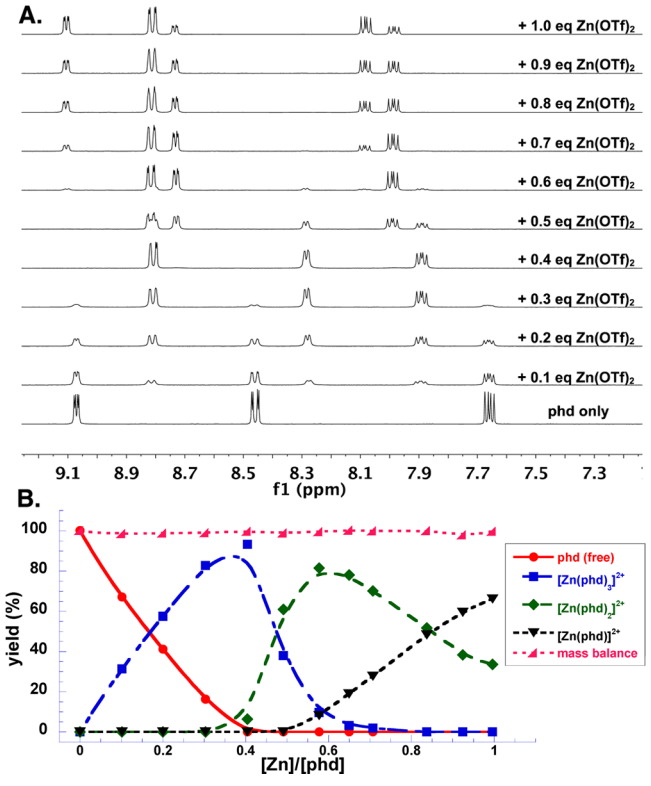


Figure 5. (A) ^{1}H NMR titration data and (B) speciation plot at different $Zn(OTf)_2$/phd ratios. Lines in (B) do not represent fits but are included to guide the eye.

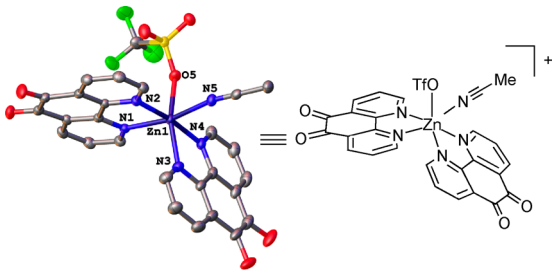
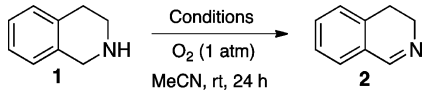


Figure 6. X-ray crystal structure of $[Zn(phd)_2(MeCN)(OTf)]^+$ shown with 50% probability ellipsoids. All H atoms and disorder have been omitted for clarity (see the Supporting Information for details).

catalytic quantities of a Brønsted acid [75% yield with 15 mol % pyridinium *p*-toluenesulfonic acid (PPTS); entry 7]. Control experiments showed that no amine oxidation occurred in the absence of phd under these conditions (entry 8), and removal of the ZnI_2 led to only stoichiometric oxidation (7%; entry 9). Replacement of phd with 1,10-phenanthroline also resulted in no substrate oxidation (entry 10).

Further studies of the oxidation of **1** to **2**, as well as the oxidation of dibenzylamine (**3**) to *N*-benzylidene benzylamine (**4**), revealed that both Zn^{2+} and iodide are important to the success of the catalytic reactions. Oxidation of **3** under the optimized reaction conditions resulted in an 80% yield of **4** (Table 2, entry 1). Upon replacement of ZnI_2 with tetrabutylammonium iodide (Bu_4NI), significant catalytic activity was retained in the oxidation of **1**, but only stoichiometric reactivity was observed in the oxidation of **3** (entry 2). A similar observation was made when ZnI_2 was replaced with molecular iodine (entry 3). Use of catalytic I_2 in

Table 1. Optimization of the Reaction Conditions for the Catalytic Aerobic Oxidation of Tetrahydroisoquinoline (1)[a]



entry	quinone	additive	additive	yield of **2** (%)
1	5% phd	—	—	7
2	5% phd	2.5% $ZnOTf_2$	—	7
3	5% phd	2.5% $ZnOAc_2$	—	7
4	5% phd	2.5% $ZnCl_2$	—	7
5	5% phd	2.5% $ZnBr_2$	—	10
6	5% phd	2.5% ZnI_2	—	55
7	**5% phd**	**2.5% ZnI_2**	**15% PPTS**	**75**
8	—	2.5% ZnI_2	15% PPTS	NR
9	5% phd	—	15% PPTS	7
10	5% phen	2.5% ZnI_2	15% PPTS	NR

[a]Reaction conditions: **1** (0.130 mmol), MeCN (0.5 mL), O_2 atmosphere, 24 h. PPTS, pyridinium *p*-toluenesulfonic acid, phen, 1,10-phenanthroline. Yields were determined by ^{1}H NMR spectroscopy.

Table 2. Beneficial Effect of Zn^{2+} and Iodide on Catalytic Aerobic Amine Oxidation[a]

				yield (%)	
entry	quinone	additive	additive	**2**	**4**
1	5% phd	2.5% ZnI_2	15% PPTS	75	80
2	5% phd	5% Bu_4NI	15% PPTS	61	6
3	5% phd	2.5% I_2	15% PPTS	52	8
4	—	2.5% I_2	15% PPTS	2	3

[a]Reaction conditions: amine (0.130 mmol), MeCN (0.5 mL), O_2 atmosphere, 24 h. PPTS, Pyridinium *p*-toluenesulfonic acid. Yields were determined by ^{1}H NMR spectroscopy.

the absence of phd led to negligible reactivity, even in the reaction of **1** (entry 4).

The unique beneficial effect of iodide counterions raised the possibility of a catalytic redox role for iodide, and the use of a starch–iodine test provided evidence for the formation of I_3^- in the absence of substrate under the standard reaction conditions. On the basis of this result, at least two reasonable mechanisms could be considered for the amine oxidation reactions (Scheme 2). Mechanism A involves phd-mediated amine oxidation, similar to the stoichiometric reactivity shown in eq 1 and Figure 4. Catalytic turnover involves an iodide/triiodide cycle[25] that mediates aerobic reoxidation of phd-H_2 (Scheme 2A). Mechanism B reflects literature precedents for stoichiometric oxidation of certain amines by molecular iodine,[26] and the catalytic cycle involves I_2/I_3^--promoted amine oxidation coupled to a phd-based redox cycle that mediates aerobic reoxidation of iodide (Scheme 2B). The latter pathway resembles metal-catalyzed oxidation reactions in which quinones have been used to facilitate aerobic oxidation of the reduced catalyst.[27]

Kinetic isotope effect (KIE) experiments were carried out in order to distinguish between these possibilities (Scheme 3).

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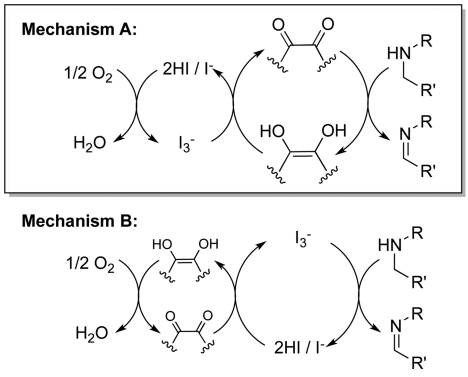
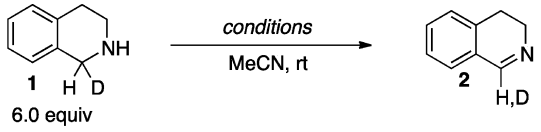
Scheme 2. Two Proposed Reaction Mechanisms



Scheme 3. Intramolecular Competition Kinetic Isotope Effect Experiments



stoichiometric reactions:

(a) 1.0 equiv phd, 0.5 equiv $Zn(OTf)_2$, 3.0 equiv PPTS
KIE = **6.4 ± 0.2**, 80% yield

(b) 1.0 equiv I_2, 0.5 equiv ZnI_2, 3.0 equiv PPTS
KIE = **3.8 ± 0.2**, 45% yield

catalytic reaction:

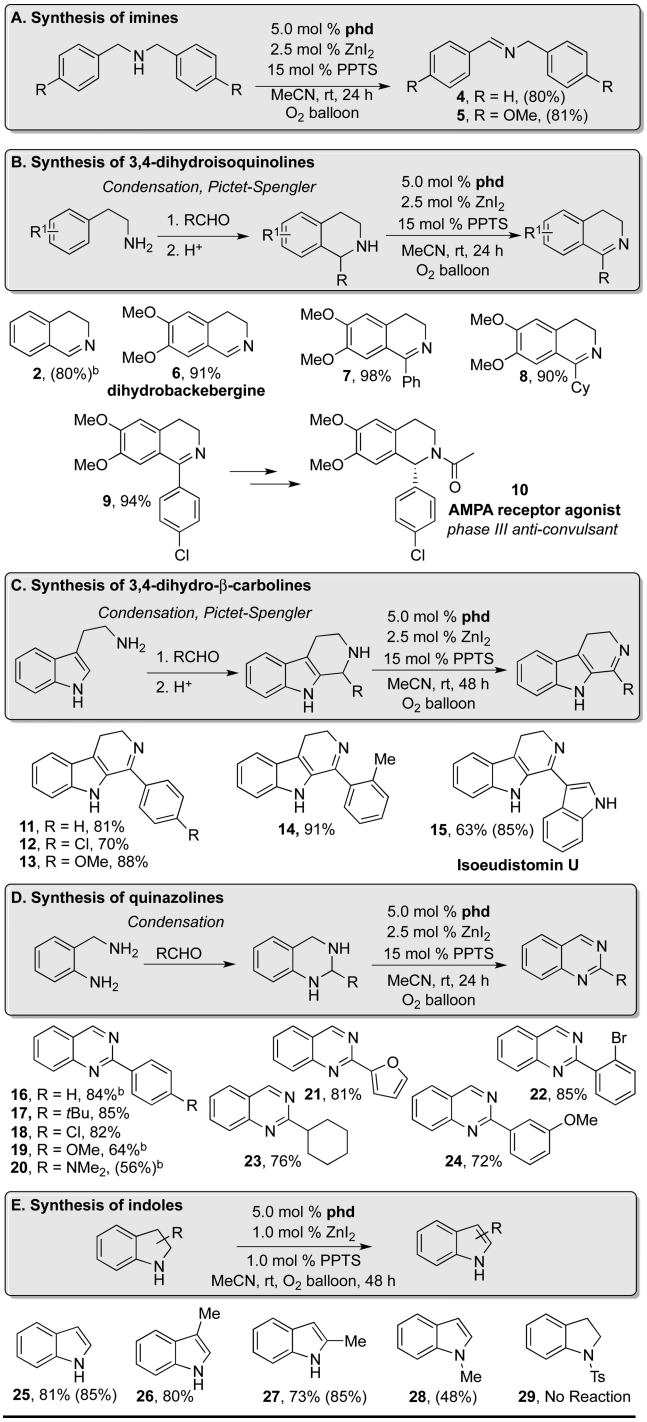
(c) 5 mol % phd, 2.5 mol % ZnI_2, 15 mol % PPTS, 1 atm O_2
KIE = **6.4 ± 0.2**, 52% yield

The reaction of **1**-d_1 was performed under three different sets of reaction conditions: (a) use of stoichiometric phd as the oxidant under anaerobic conditions; (b) use of stoichiometric iodine as the oxidant under anaerobic conditions; and (c) the optimized catalytic conditions with 5 mol % phd/2.5 mol % ZnI_2 under aerobic conditions. Comparison of the KIEs from these experiments showed that the KIE obtained under catalytic conditions matched that obtained with stoichiometric phd (KIE = 6.4 in both cases) and differed from that observed with I_2 as the oxidant (KIE = 3.8). These results provide strong support for the quinone-mediated amine oxidation pathway associated with mechanism A in Scheme 2.

Substrate Scope and Synthetic Applications. The optimized catalytic conditions were tested with a number of different substrates (Table 3), ranging from simple dibenzyl amines (A) to various nitrogen heterocycles such as tetrahydroisoquinolines (B), tetrahydro-β-carbolines (C), and tetrahydroquinazolines (D), as well as indolines (E). Substrate classes B–D are particularly appealing because the saturated heterocycles may be accessed readily via simple condensation and Pictet–Spengler reactions (Table 3B–D).

Substituted tetrahydroisoquinolines were smoothly converted to 3,4-dihydroisoquinolines under these conditions (Table 3B). Electron-donating groups improved the reaction yield and diminished the reaction time. 6,7-Dimethoxytetrahydroisoquinoline was oxidized to dihydrobackebergine (**6**) in 91% isolated yield, and the reaction proceeded more rapidly than that of the parent substrate **1**. Aryl and alkyl substitution at the 1-position was well-tolerated: 1-phenyl- and 1-cyclohexyl-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines were isolated in excellent yields (98% yield of **7** and 90% yield of **8**,

Table 3. Substrate Scope and Synthetic Applications[a]



[a]Reaction conditions: substrate amine (1.0 mmol), phd (0.05 mmol), ZnI_2 (0.025 mmol), PPTS (0.15 mmol), MeCN (4.0 mL), O_2 balloon, 24–48 h. The reported yields are isolated yields; numbers in parentheses indicate NMR yields. [b]48 h reaction time.

respectively). The 3,4-dihydroisoquinoline products of these reactions have been widely used as precursors to chiral tetrahydroisoquinolines, which are widely represented in natural products and pharmaceuticals. For example, 1-(4-chlorophenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (**9**), which was obtained in 94% yield under our aerobic oxidation conditions, is an intermediate to the phase III antiepileptic AMPA receptor agonist **10**.[28]

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Substituted tetrahydro-β-carbolines were readily converted to 3,4-dihydro-β-carbolines using the same optimized conditions (Table 3C). Aryl substitution in the 1-position was again tolerated, with slightly improved yields for substrates containing electron-rich substituents (**13**, R = OMe, 88% yield) relative to those containing electron-deficient substituents (**11**, R = Cl, 70% yield). *o*-Methyl substitution was also well-tolerated (**14**, 91% yield), and the natural product isoeudistomin U (**15**) was obtained in 63% isolated yield (85% NMR yield).

Quinazolines were formed in good yields from tetrahydroquinazolines (Table 3D). Unlike other substrate classes, wherein electron-donating substituents improved the yield, quinazoline products containing electron-withdrawing substitution at the 2-position were better substrates. Ring−chain tautomerism in 2-substituted tetrahydroquinazolines could occur, and the improved yields for electron-deficient quinazolines may reflect the stabilization of the ring tautomer in the respective tetrahydroquinazoline substrates.

With a slight modification of the reaction conditions (5 mol % phd, 1.0 mol % ZnI_2, and 1.0 mol % PPTS), indoline could be converted to indole (**25**) in 81% isolated yield (Table 3E). 3-Methyl- and 2-methylindolines were also oxidized to the corresponding indoles in good yields (80% and 73% isolated yields for **26** and **27**, respectively). Even the tertiary amine substrate *N*-methylindoline afforded the indole product **28** in 48% yield (Table 3E); however, electron-deficient *N*-tosylindoline (**29**) was not oxidized under these conditions. Bruice previously demonstrated stoichiometric oxidation of tertiary amines with phenanthroline-derived *o*-quinones, and he proposed a mechanism analogous to the addition−elimination mechanism in Figure 1B involving an ammonium−hemiaminal intermediate.[14] Further studies to develop improved quinone-based catalysts for tertiary amine oxidation are ongoing.

CONCLUSION

In conclusion, we have identified a new strategy for aerobic oxidation of secondary amines that employs 1,10-phenanthroline-5,6-dione as a bifunctional *o*-quinone catalyst. The success of these reactions can be traced to the non-biomimetic reaction mechanism, which involves an addition−elimination pathway rather than the transamination pathway employed by copper amine oxidase enzymes and many quinone model systems. Direct spectroscopic evidence for the hemiaminal intermediate was obtained. The bifunctional character of the phd catalyst was exploited in the use of Zn^{2+} to promote amine oxidation, and iodide was fortuitously discovered to promote aerobic catalytic turnover. Control experiments and mechanistic studies revealed that iodide plays a critical redox role in mediating aerobic reoxidation of the reduced quinone catalyst. Collectively, these results provide a foundation for broader exploration of quinones and related redox-active organic catalysts in selective aerobic oxidation reactions.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

stahl@chem.wisc.edu

Notes

The authors declare no competing financial interest.

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