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Bioinspired Organocatalytic Aerobic C−H Oxidation of Amines with an *ortho*-Quinone Catalyst

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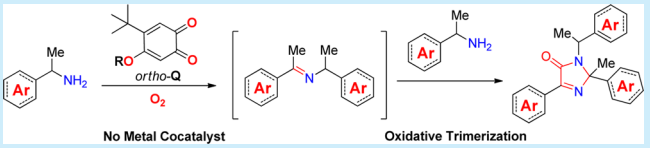
Supporting Information

ABSTRACT: A simple bioinspired *ortho*-quinone catalyst for the aerobic oxidative dehydrogenation of amines to imines is reported. Without any metal cocatalysts, the identified optimal *ortho*-quinone catalyst enables the oxidations of α-branched primary amines and cyclic secondary amines. Mechanistic studies have disclosed the origins of different performances of *ortho*-quinone vs *para*-quinone in biomimetic amine oxidations.



The enormous potential of oxidative C−H functionalization has spurred significant research efforts in search of highly efficient catalytic systems in synthetic chemistry. In nature, a large portion of enzymatic processes involve C−H activation and functionalization as key steps. The high efficiency and exquisite stereocontrol of enzymatic C−H transformations have inspired chemists to develop small molecule analogues for synthetic applications.[1] Quinone-based enzymes are a class of important metalloenzymes containing Cu^{2+} and quinone cofactors, which can promote aerobic oxidation of primary amines coupled with the reduction of O_2.[2] Mechanistic understanding of this transformation developed by Klinman,[2a−e,3a−k] Sayre,[3l−o] and others[3p−r] has disclosed quinone cofactors as real active centers in mediating C−H oxidation of amine,[3j,o] which underlies the pursuit of biomimetic quinone catalysts, particularly, pure organocatalysts, with an aim to achieve sustainable aerobic amine oxidation reactions.

Recently, notable advances have been developed in the explorations of *p*-**Q1**[4a] and *o*-**Q1**[5b] (Figure 1A) in the catalytic oxidative dehydrogenation of linear primary amines to imines. However, these quinone catalysts did not work with α-branched primary and secondary amines, consistent with the known biocatalytic behaviors of quinone cofactors, e.g., TPQ. Breakthroughs to this limitation have been made with *ortho*-quinones in concert with transition metal cocatalysts.[4−7] In this regard, Kobayashi[6] reported a successful example of secondary amine dehydrogenation[3p,8] by using a cooperative catalytic system of Pt/Ir nanocluster and 4-*tert*-butylcatechol (*o*-**Q2**-H). Stahl[4b,c] and co-workers reported that a simple *ortho*-quinone, 1,10-phenanthroline-5,6-dione (*o*-**Q3**), could promote effective secondary amine oxidation by the combination of different metals such as ZnI_2 and [Ru]/[Co].

Thus, to achieve an organocatalytic aerobic oxidation of α-branched primary amine remains elusive despite tremendous efforts in this direction.[9] Previous protocols required metal cocatalysts or were of limited scope with low activity. For

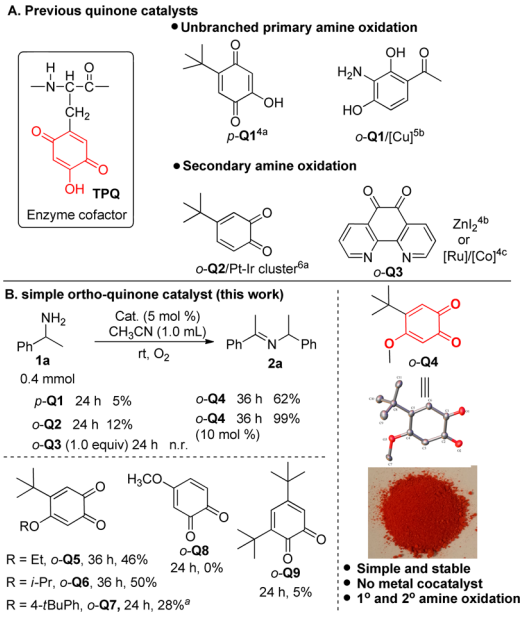


Figure 1. Biomimetic quinone-based catalysts.

quinone catalysts, stoichiometric amount of base[4a] or electrocatalytic system[5c] are needed in the aerobic oxidation of α-branched primary amines. In our studies, we sought to develop quinone-type catalysts focusing on the challenging oxidative dehydrogenation of α-branched amines. A simple *ortho*-quinone, e.g., *o*-**Q4**,[3g,h] was identified as a viable catalyst and this bioinspired quinone catalyst turned out to be quite general promoting aerobic oxidation unprecedentedly of both primary amines and secondary amines without the use of any metal

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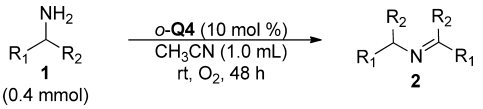
cocatalysts or additives (Figure 1).We chose 1-phenylethanamine as the model substrate and a number of quinone-based catalysts[10] were synthesized and tested (Figure 1B). To our delight, a simple *ortho*-quinone, *o*-**Q4** with a methoxyl group was eventually identified to give a promising result with 62% yield of the desired imine in 36 h. In sharp comparison, the known quinone catalysts such as *p*-**Q1**, *o*-**Q2**, and *o*-**Q3**, which were effective for linear primary or secondary amine oxidation, showed negligible activity with only trace or no products (Figure 1B). Seeing the critical roles of methoxy group (*o*-**Q2** vs *o*-**Q4**), variations on this moiety was probed. Ethoxyl (*o*-**Q5**), *iso*-propoxyl (*o*-**Q6**) and aryloxyl(*o*-**Q7**) were less effective (Figure 1B). By removing *tert*-butyl group (*o*-**Q8**), no imine product was detected and the poor solubility of *o*-**Q8** may be one of the reasons of its low activity under the present conditions (Figure 1B). We also tested Corey's reagent, *ortho*-**Q9**, and only 5% product was observed at ambient temperature (Figure 1B). By increasing the catalyst (*o*-**Q4**) loading to 10 mol %, the yield was further improved with complete transformation. Further optimizations in terms of additives, such as metal cocatalysts and Lewis/Brønsted acids, did not lead to improvement on activity and in many cases inhibitions of the oxidation reactions were observed.

Under the optimized conditions, the scope of the biomimetic quinone-based catalytic system was examined with a range of α-branched primary amines (Table 1). 1-Phenylethanamines substituted with electron-donating and withdrawing groups were well-tolerated undergoing aerobic oxidation to produce secondary imines with high to excellent yields and good *E*/*Z* ratio (**2a**−**k**). In general, electron-deficient substrates (**2b**−**d**, **2h**,**i** and **2k**) were oxidized slowly comparing to electron-rich amines (**2f**,**g**, **2j**). Especially, for **1e**, it needed longer reaction time or higher oxygen pressure to be consumed completely. Bulkier substrate such as diphenylmethanamine also underwent oxidative dimerization to produce an imine product as a white solid (**2l**). The heterocycle amine **1m** proceeded smoothly with good outcome at higher temperature as well (**2m**). Acetylnaphthalene was obtained from deamination of (1-naphthyl)ethylamine with no imine product detected (**2n**). Similar deamination product was also obtained with 1-phenylpropan-1-amine (**2o**). Besides, simple benzylamine has been tested and the reaction went to completion more quickly than branched amines in 12 h (**2p**).

Unexpectedly, we observed further reaction of imine with **1a** to afford an oxidative trimerization adduct, imidazolinone **3a** when the reaction was conducted at a higher temperature (60 °C). *o*-**Q5** was found to be an optimal catalyst for this trimerization process (Figure 2, eq 1). The quinone catalyst seems to be also involved in the late stage oxidation as no desired adduct was observed in the absence of catalyst (Figure 2, eq 2).[11] The use of less loading of catalyst was found to favor the trimerization (Figure 2, eq 1), presumably as a result of balancing the imine formation (e.g., **2a**). The reaction can be applied to a number of 1-phenylethanamines particularly those bearing electron-donating substitutes with moderate yields, providing a distinctive pathway for the synthesis of imidazolinones (Scheme 1).

Table 1. Aerobic Oxidation of Primary Amines[a]



entry	product	entry	product
2a	99% (86%)[b] *E*:*Z* 9:1	**2b**	80% *E*:*Z* 14:1
2c	97% *E*:*Z* 14:1	**2d**[c]	98% *E*:*Z* 14:1
2e[d]	99% *E*:*Z* >19:1	**2f**	75% *E*:*Z* 8:1
2g	95% *E*:*Z* 13:1	**2h**	95% (81%)[c] *E*:*Z* 10:1
2i[c]	95% *E*:*Z* 14:1	**2j**	89% *E*:*Z* >19:1
2k[c]	99% *E*:*Z* > 19:1	**2l**[e]	96% (92%)[c]
2m[e]	83% *E*:*Z* > 19:1	**2n**[e]	53%
2o[e]	25%	**2p**[f]	99%

[a]Yield was determined by ^{1}H NMR analysis. [b]1.0 mmol scale. [c]For 72 h. [d]For 5 atm O_2. [e]60 °C. [f]For 12 h.

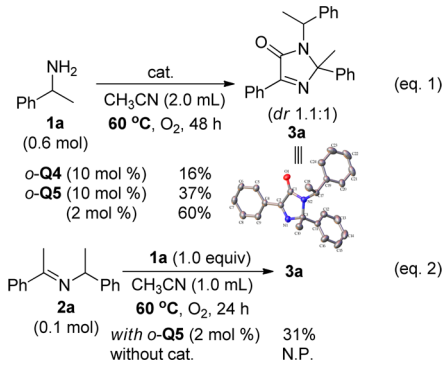
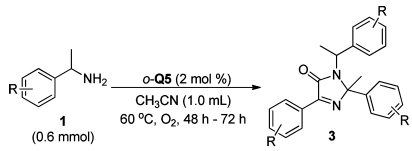


Figure 2. Biomimetic quinone-based catalysts.

Scheme 1. Oxidative Trimerization[a]



3a, R = H, 60% yield, *dr*: 1.1:1
3b, R = 4-Br, 40% yield, *dr*: 1.1:1
3c, R = 4-Me, 65% yield, *dr*: 1:1.2
3d,[b] R = 4-OMe, 51% yield, *dr*: 1:1.1
3e, R = 3-Br, 42% yield, *dr*: 1:1.1
3f, R = 3-OMe, 54% yield, *dr*: 1:1.1

[a]Isolated yield. [b]Unseparated isomers.

Mechanistically, bioinspired oxidation of amines to imines may occur via covalent pathways, either transamination (**I**)[3b,c,e−h,l−n] or addition−elimination (**II**),[3p,8] as previously proposed, or noncovalent direct H-abstraction pathway (**III**) (Figure 3). The possibility of amine oxidation by electron transfer could be ruled out by the observed large KIE = 2.9 in the stoichiometric reactions of *o*-**Q4** with **2a** and α-deuterated **2a**, respectively (Figure 4, eq 1). The significant KIE was supportive of the direct H-transfer pathways (**I**−**III**). Our DFT

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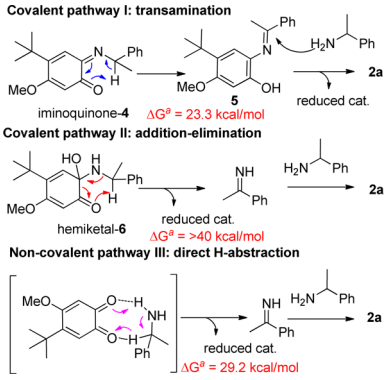


Figure 3. Possible pathways leading to product imine.

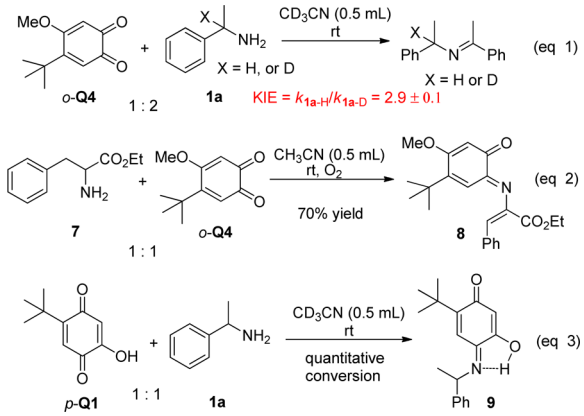


Figure 4. Stoichiometric reactions of α-branched amines with quinone catalysts.

studies on the three possible H-transfer pathways **I**–**III** revealed that the transamination pathway (**I**)[3g,h] is favored over pathways **II** and **III** by >5.0 kcal/mol (Figure 3). The in situ NMR identifications and characterizations of intermediates in reactions of *o*-**Q4** and **2a** has not been very successful; however, we could observe those signals ascribing to iminoquione **4**/**5** as well as the reduced-**Q4** by high resolution ESI-MS (see Supporting Information for details). In addition, the isolation of a stable *aza-ortho*-quinone **8** (Figure 4, eq 2), an oxidized product of the iminoquinone intermediate (e.g., **7**, Figure 3, pathway **I**) in the reactions of aminoester **7**, added further support to the transamination pathway.

Recent theoretical studies by Zhu[12] have revealed that *ortho*-quinone generally has larger hydride affinity than its *para*-quinone derivative. Our calculations based on Zhu's empirical equation (see Supporting Information) gave ΔG_{HA}(*p*-**Q1**) ≈ 61.4 kcal/mol and ΔG_{HA}(*o*-**Q4**) ≈ 73.9 kcal/mol, indicating the *ortho*-quinone **Q4** has stronger ability to abstract H atom, in line with the observed catalytic behaviors. To gain more insight into the origins of different performance of *para*-quinone **Q1** and *ortho*-quinone **Q4**, we have also investigated the stoichiometric experiments with *p*-**Q1** in MeCN-d_3 monitored by ^{1}H NMR (Figure 4, eq 3). 1-Phenylethanamine **1a** was consumed quickly, but no oxidized iminie product was observed, consistent with the known inert nature of *p*-**Q1** in branched amine oxidations. Instead, the reaction was stopped at the initial imine formation stage and the corresponding imine **9** was quantitatively formed and could be isolated and fully characterized by NMR spectroscopy (see Supporting Information). The structural optimization of **9** indicated a strong intramolecular O–H···N hydrogen bond which presets the α-C–H in an unfavored geometry for H-transfers (Figure 5).

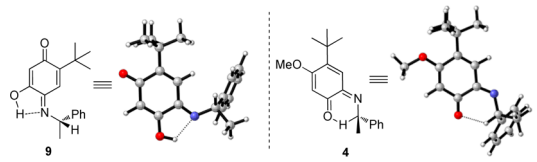
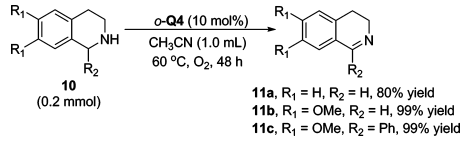


Figure 5. Calculated geometries of iminoquinone **4** and **9**.

Indeed, our DFT calculations on α-H abstraction revealed that both the substrate-assisted intermolecular H-transfer and the intramolecular transfer are disfavored requiring ca. 30–33 kcal/mol (see Supporting Information). Recently, Stahl[4a] reported the oxidation of 1-phenylethanamine by *p*-**Q1** required a stoichiometric amount of base, pinpointing the difficulties of the H-abstractions with *p*-**Q1**. In sharp contrast to the *para*-quinone *p*-**Q1**, the internal O–H···N hydrogen bond is absent in iminoquinone **4**, the key intermediate in the oxidation with *o*-**Q4**. Instead, a weak C–H···O was clearly noted (Figure 5), setting the stage for facile H-transfer. In this case, the intramolecular proton transfer process required only 23.3 kcal/mol (Figure 3, pathway **I**).

We also challenged this *ortho*-quinone catalyst in the oxidation of cyclic secondary amines, for which previous examples normally required metal cocatalysts for effective conversions.[4b,c] To our delight, *o*-**Q4** smoothly promoted the oxidation of tetrahydroisoquinoline **10a** to dihydroisoquinoline under standard condition and slightly above ambient temperature (60 °C) was applied to facilitate complete conversion (Scheme 2, **11a**). The reactions worked well with substituted tetrahydroisoquinolines (**11b** and **11c**).

Scheme 2. Aerobic Oxidation of Cyclic Secondary Amines[a]



[a]Yield was determined by ^{1}H NMR analysis.

In summary, we have developed a simple bioinspired *ortho*-quinone catalyst for the aerobic oxidation of amines. The current organocatalyst enables effective oxidations of α-branched primary amines and cyclic secondary amines without any metal cocatalysts. Mechanistic studies verified that the transamination pathway, plausible only for α-unbranched amines in nature,[2] would also work for the oxidation of more challenging α-branched primary amines with our bioinspired small molecular catalyst, and these efforts disclosed the origins of different performance of *para*-quinone and *ortho*-quinone in biomimetic amine oxidations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, detailed characterization data of substrates, catalysts and products, X-ray crystal structure, computational details and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) See the Supporting Information for a proposed mechanism. The way the quinone catalyst participates in the late aerobic oxidation remains obscure at this moment.

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