Letter

Biomimetic Oxidative Deamination Catalysis via ortho-Naphthoquinone-Catalyzed Aerobic Oxidation Strategy

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Biomimetic Oxidative Deamination Catalysis via *ortho*-Naphthoquinone-Catalyzed Aerobic Oxidation Strategy

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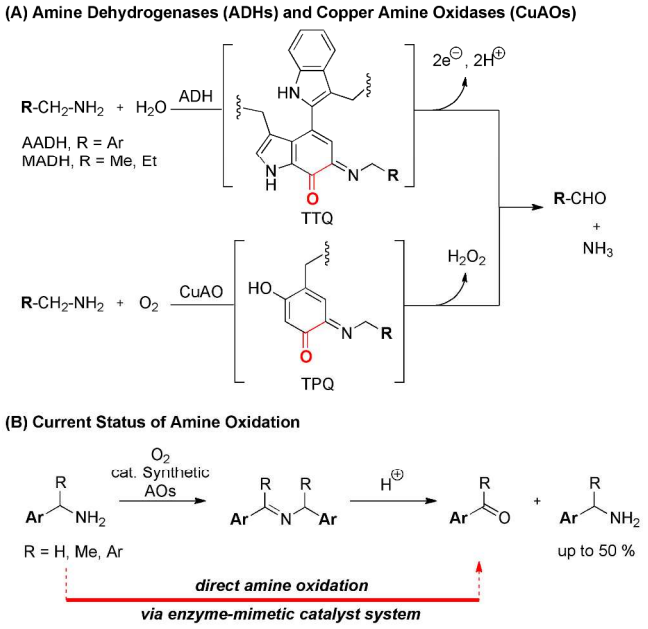
KEYWORDS: aerobic oxidation, deamination, organocatalysis, ortho-naphthoquinone, prototropic rearrangement

ABSTRACT: An *ortho*-naphthoquinone-catalyzed *oxidative* deamination reaction has been developed where the molecular oxygen and water serve as the sole oxidant and nucleophile. The current *aerobic* deamination reaction proceeds via the ketimine formation between *ortho*-naphthoquinones and amines followed by the prototropic rearrangement and hydrolysis by water, representing a biomimetic *oxidative* deamination of amine species in the human body by liver and kidneys. The compatibility of *ortho*-naphthoquinone organocatalysts with molecular oxygen and water opens up a new biomimetic catalyst system that can function as versatile deaminases for a variety of amine-containing molecules such as amino acids and DNA nuclear bases.

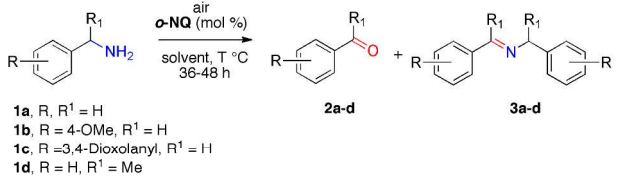
Amine dehydrogenases are periplasmic quinoproteins involving the bacterial growth on primary amines as a source of carbon and nitrogen.[1] Aromatic amine dehydrogenase (AADH) is specific for primary amines while methylamine dehydrogenase (MADH) displays its specificity for smaller amines such as methylamine and ethylamine.[2] These enzymes are tryptophan tryptophyquinone (TTQ)-dependant and catalyze the deamination of primary amines to aldehydes and ammonia (Scheme 1A). Another class of enzymes that perform the oxidation of primary amines to aldehydes is periplasmic as well as human copper amine oxidases (CuAOs) that utilize a redox cofactor, topaquinone (TPQ), and molecular oxygen in a variety of biological processes such as the oxidation of neurotransmitters in animals, thus leading to the formation of ammonia and hydrogen peroxide as byproducts.[3] Recently, tremendous research efforts have been made to the development of CuAOs-like biomimetic catalysts that could bring the significant substrate scope that natural enzymes can not offer (Scheme 1B).[4] Thus, the synthetic *ortho*-quinone catalysts enabled the aerobic oxidation of α-branched primary benzylic amines[5] and secondary amines.[6] However, the current CuAOs-like biomimetic catalyst systems convert primary and secondary amines to imines and ketimines, respectively. A subsequent hydrolysis of imines and ketimines will be required to obtain the *true* enzymatic oxidation products, aldehydes or ketones, and also lead to the recovery of amine starting materials up to 50% yields. This means that the CuAOs-like biomimetic catalysts scavenge the 50% of amine substrates, only leading to the maximum yield of 50% of aldehyde/ketone products. Previously, the Corey group demonstrated the transamination reaction protocol that combined the amines (R_2CHNH_2) and mesitylglyoxals (Ar-CH_2CHO) to form Schiff bases which underwent prototropic rearrangement to isomeric Schiff bases. The subsequent acid hydrolysis of the newly formed Schiff bases led to the desired ketones.[7] Recently, the group of Srogl reported the aerobic oxidation of ascorbic acid to dehydroascorbic acid that condensed with amines to give aldehydes and ketones upon acid hydrolysis.[8] At the present time there exist no practical catalytic systems that perform the direct aerobic oxidation of amines to aldehydes and ketones without using the separate hydrolysis step and the stoichiometric amount of oxidants.[9] As a consequence, the development of one-pot catalytic aerobic oxidation of primary amines to aldehydes and ketones, *the true enzyme-mimetic catalyst system*, remains significant unmet need in aerobic oxidation protocols.[10] Herein, we report the development of an unprecedented promiscuous enzyme-mimetic organocatalyst system that skillfully promotes the ADH-like oxidation of primary amines, the CuAOs-like oxidation of α-branched primary amines, and the deaminase-like reactivity for DNA nuclear bases.

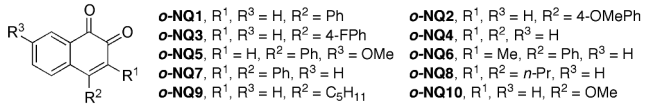
SCHEMES 1. (A) Amine Dehydrogenases and Cupper Amine Oxidases. (B) Proposed Enzyme-mimetic Catalytic System



With an aim of developing an enzyme-mimetic catalyst system that can utilize water (like ADHs) and molecular oxygen (like CuAOs), we envisioned the *ortho*-naphthoquinone-catalyzed direct aerobic oxidation of amines to aldehydes and ketones. Previously, we had shown that the aerobic oxidations of amines were possible via the modular catalyst systems of *ortho*-naphthoquinone with $Cu(OAc)_2$ for homo-coupled imines, with TFA for cross-coupled imines, and with Ag_2CO_3 for the oxidation of secondary amines.[11] Encouraged by the fact that the *ortho*-naphthoquinone catalyst displays robust stability with acidic and basic conditions, we investigated the compatibility of the catalyst system with water (Table 1) as the initial condensation reaction between catalysts and amines produce water molecules during the catalytic cycle. Thus, benzylamine **1a** was treated with a catalytic amount of ***o*-NQ1** (15 mol%) in CH_3CN/H_2O at ambient temperature. The ^1H NMR analysis of the reaction mixture revealed the formation of imine intermediate **3a** in > 90 % yields within 48 h. The imine intermediate was stable under the reaction conditions with intact ***o*-NQ1**. However, upon increasing the reaction temperature to 80 °C, the imine **3a** was hydrolyzed by the residual water in CH_3CN to give benzaldehyde **2a** and benzylamine **1a** where the catalyst ***o*-NQ1** quickly converted benzylamine **1a** to benzaldehyde **2a** (entry 1). While the crude reaction mixture showed the *exclusive* formation of **2a**, the isolated yield was 67 % due to the volatile nature of benzaldehyde **2a**. The use of other benzylamines with higher molecular masses led to the improved isolated yields of aldehydes **2b**-**2c** in 79-84 % yields (entry 2-3). After gaining the valuable reaction profile, we turned our attention to *sec*-primary amine, 1-phenylethylamine, as substrate for the direct oxidation of amines. At ambient temperature, the use of 5 mol % ***o*-NQ1** only led to the formation of ketimine **3d** in 32 % yield alongside 4 % yield of ketone **2d** (entry 4). Increasing the catalyst loading to 10 % mol improved the yields of ketone **2d** and ketimine **3d** to 25 % and 46 %, respectively (entry 5). Screening of other *ortho*-naphthoquinone catalysts (***o*-NQ**) was performed (entry 6-14), but only ***o*-NQ3** possessed the similar catalytic activity as ***o*-NQ1** (entry 7). The solvent screening also confirmed that CH_3CN was the optimal reaction solvent (entry 15-18). To further optimize the catalytic activity of ***o*-NQ1**, the reaction temperature was investigated (entry 19-20), where the optimal reaction temperature of 80 °C provided the ketone **2d** and the ketimine **3d** in 72 % yield and 7 % yield, respectively. The reaction conversion was clearly catalyst loading-dependant, thus the optimal loading of ***o*-NQ1** was set as 15 mol % (entry 21). The control experiments confirmed that the molecular oxygen in air was enough to induce the direct oxidation of amine without an oxygen balloon (entry 22) and the reaction required molecular oxygen to render the catalyst turnover (entry 23). Interestingly, the Stahl's catalyst system,[12] *tert*-butyl-2-yydoxybenzoquinone (TBHBQ), under our optimized conditions provided the ketone **2d** and the ketimine **3d** in 56 % yield and 14 % yield, respectively.

Table 1. Optimization of the Direct Aerobic Oxidation of Amines to Aldehydes/Ketones[a]





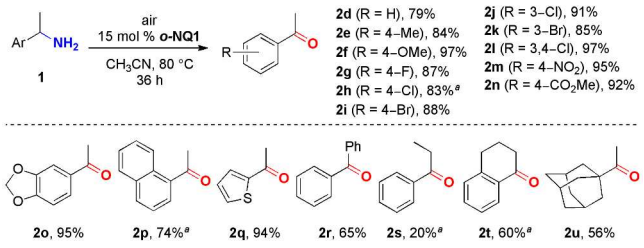
Entry	1	Cat (mol %)	Solvent	T (°C)	Yield 2 (%)[b]	Yield 3 (%)[b]
1	**1a**	***o*-NQ1** (15)	CH_3CN	80	**2a**, 67[c]	**3a**, 0
2	**1b**	***o*-NQ1** (15)	CH_3CN	80	**2b**, 79[c]	**3b**, 0
3	**1c**	***o*-NQ1** (15)	CH_3CN	80	**2c**, 84[c]	**3c**, 0
4	**1d**	***o*-NQ1** (5)	CH_3CN	23	**2d**, 4	**3d**, 32
5	**1d**	***o*-NQ1** (10)	CH_3CN	23	**2d**, 25	**3d**, 46
6	**1d**	***o*-NQ2** (10)	CH_3CN	23	**2d**, 6	**3d**, 36
7	**1d**	***o*-NQ3** (10)	CH_3CN	23	**2d**, 20	**3d**, 44
8	**1d**	***o*-NQ4** (10)	CH_3CN	23	**2d**, 2	**3d**, 11
9	**1d**	***o*-NQ5** (10)	CH_3CN	23	**2d**, 1	**3d**, 40
10	**1d**	***o*-NQ6** (10)	CH_3CN	23	**2d**, 1	**3d**, 21
11	**1d**	***o*-NQ7** (10)	CH_3CN	23	**2d**, 2	**3d**, 8
12	**1d**	***o*-NQ8** (10)	CH_3CN	23	**2d**, 2	**3d**, 17
13	**1d**	***o*-NQ9** (10)	CH_3CN	23	**2d**, 5	**3d**, 37
14	**1d**	***o*-NQ10** (10)	CH_3CN	23	**2d**, 1	**3d**, 21
15	**1d**	***o*-NQ1** (10)	THF	23	**2d**, 6	**3d**, 44
16	**1d**	***o*-NQ1** (10)	$PhCH_3$	23	**2d**, 12	**3d**, 54
17	**1d**	***o*-NQ1** (10)	CH_2Cl_2	23	**2d**, 14	**3d**, 45
18	**1d**	***o*-NQ1** (10)	EtOH	23	**2d**, 5	**3d**, 36
19	**1d**	***o*-NQ1** (10)	CH_3CN	60	**2d**, 52	**3d**, 21
20	**1d**	***o*-NQ1** (10)	CH_3CN	80	**2d**, 72	**3d**, 7
21	**1d**	***o*-NQ1** (15)	CH_3CN	80	**2d**, 100	**3d**, 0
22[d]	**1d**	***o*-NQ1** (15)	CH_3CN	80	**2d**, 98	**3d**, 2
23[e]	**1d**	***o*-NQ1** (15)	CH_3CN	80	**2d**, 18	**3d**, 4
24	**1d**	**TBHBQ** (15)	CH_3CN	80	**2d**, 56	**3d**, 14

[a]Reaction conditions: **1** (0.4 mmol), ***o*-NQ** catalyst (mol %) in solvent (0.4 M) for 36-48 h. [b]Unless stated otherwise, yield was determined by ^1H NMR. [c]Isolated yields using a mixture of $CH_3CN:H_2O$ (3:1). [d]Reaction using oxygen balloon. [e]Reaction under argon. TBHBQ = *tert*-Butyl-2-hydroxybenzoquinone.

With the optimized reaction conditions in place, the substrate scope of the ***o*-NQ1**-catalyzed direct oxidation of amines to ketones was studied using a variety of *sec*-primary amines with different electronic and steric characters (Scheme 2). 1-

Phenylethyl derivatives with different electronic character were all suitable substrates, providing excellent isolated yields of ketones (**2d-2o**) in 79-97 % yield. The sole formation of products was observed, and the analytically pure products were obtained after filtering through a short pad of silica to remove the catalyst ***o*-NQ1**. Upon scaling up the reaction, the recovery of catalyst ***o*-NQ1** was attempted. However, the recovered ***o*-NQ1** remained < 5 % yields due to the formation of several polar by-products including diacid derivatives.[13] Also, the work-up procedure required phase separation, leading to somewhat diminished isolated yields of ketone products. The slight loss of isolated products was mainly due to the volatile nature of ketones. 1-(Naphthalen-1-yl)ethylamine **1p** required 20 mol % catalyst loading to provide the corresponding ketone **2p** in 74 % yield. The use of 1-(thiophen-2-yl)ethylamine **1q** also provide an excellent yield of ketone **2q** in 94 %. Another *sec*-primary amine, diphenylmethanamine **1r**, also underwent the desired oxidation to give ketone **2r** in 65 % yield. The current catalyst system failed to show the catalytic activity for 1-phenylpropan-1-amine **1s**, where the ketone **2s** was isolated in 20 % yield. Interestingly, a cyclic *sec*-primary amine **1t** was directly oxidized under the reaction conditions to give ketone **2t** in 60 % yield. Based on the structural feature of **1s** and **1t**, it could be concluded that the flexible conformation of the ethyl group in **1s** rendered the steric repulsion that prevented the catalyst turn-over activity. The aryl group in *sec*-primary amines turned out to be not required since 1-(adamantan-1-yl)ethylamine **1u** smoothly underwent the oxidation to give the ketone **2u** in 56 % yield.

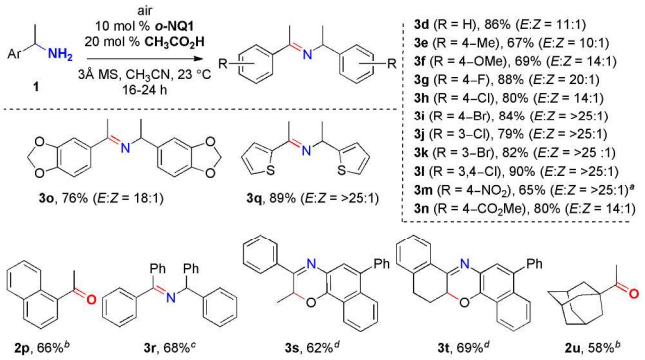
SCHEMES 2. Scope of *sec*-Primary Amines in the *o*-NQ1-Catalyzed Direct Oxidation of Amines to Ketones



[a]20 mol % catalyst.

The fact that the catalyst ***o*-NQ1** enables the direct oxidation of *sec*-primary amines to ketones through the formation of ketimine intermediate led us to re-optimize the reaction conditions to selectively obtain ketimines **3** (see Supporting Information for detail). Scheme 3 lists the scope of ***o*-NQ1**-catalyzed aerobic oxidation of *sec*-primary amines to ketimines. Thus, with the cooperative action of ***o*-NQ1** and acetic acid the oxidation reaction was interrupted at the ketimine stage thanks to the dehydrating effect of 3 Å molecular sieves.[14] The optimized reaction condition was widely applicable to *sec*-primary amines, leading to excellent isolated yields of ketimines (**3d-3r**). However, the corresponding ketimines of 1-(naphthalen-1-yl)ethylamine **1p** and 1-(adamantan-1-yl)ethylamine **1u** could not be identified, where the ketones **2p** and **2u** were the only observed products. This result may signify the steric requirement for the ketimine formation. 1-Phenylpropan-1-amine **1s** and cyclic *sec*-primary amine **1t** were not oxidized, instead the catalyst ***o*-NQ1** was captured by the substrates as benzooxazine derivatives (**3s-3t**).[15] Nevertheless, the results in Scheme 3 represent the practical aerobic oxidation protocol for ketimine synthesis from the *sec*-primary amines.

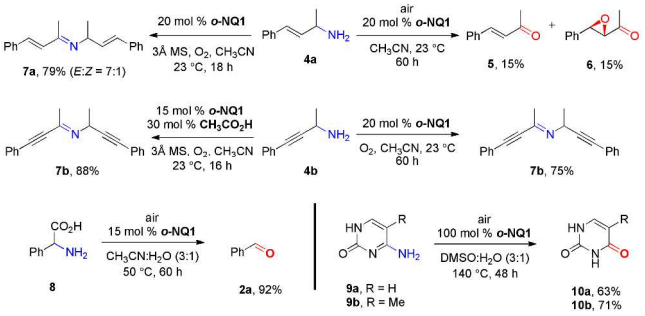
SCHEMES 3. Scope of *o*-NQ1-Catalyzed Aerobic Oxidation of Amines to Ketimines



[a]NMR yield of 96 %. [b]15 mol% catalyst loading at 80 °C. [c]Reaction at 60 °C. [d]100 mol % catalyst loading.

The ***o*-NQ1**-catalyzed direct oxidations of amines to ketones mimic amine dehydrogenases as well as amine oxidases that use water molecule and molecular oxygen, respectively, for their catalytic activities. While the employment of alkenyl and alkynyl amines, **4a** and **4b**, was partially successful in the direct deamination protocol, due to the nucleophilic character of water and by-product, H_2O_2 at elevated reaction temperature the formation of ketimines **7a** and **7b** instead of the corresponding ketone products was observed in 79-88% yields (Scheme 4). Also, the reaction under an oxygen balloon helped the catalyst turn-over at 23 °C, possibly facilitating the redox process between *ortho*-naphthoquinone and 2-aminonaphthalen-1-ol.[16] In addition, the decarboxylative deamination of amino acids revealed the importance of a neighboring aryl group for the catalyst turn-over number, where phenylglycine **8** was converted to benzaldehyde in 92% yield.[17] To explore the possibility of ***o*-NQ1** as deaminase-mimetics[18] that removes amino groups from DNA nuclear bases, we investigated the conversion of cytosines **9** to uracils **10**.[19] After some experimentation, we found that a stoichiometric amount of ***o*-NQ1** could exert the formation of uracils **10** in 63-71% yields.

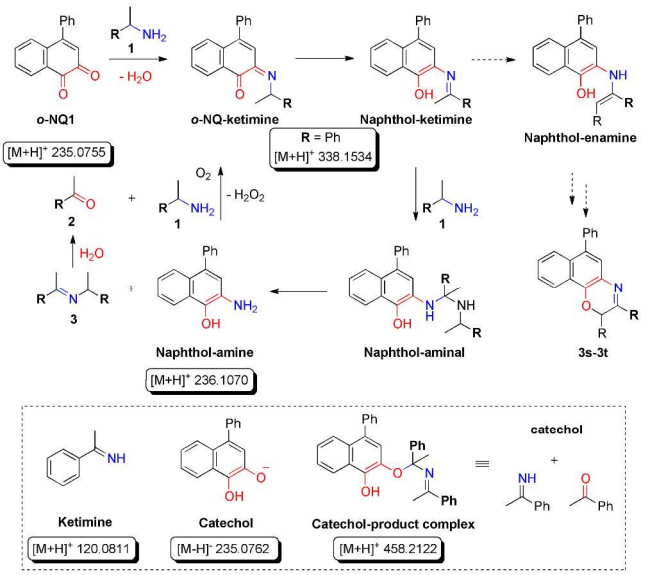
SCHEMES 4. *o*-NQ1-Mediated Direct Deamination of Various Amines (Yields using internal standard)



A proposed reaction mechanism for the direct aerobic deamination is depicted in Scheme 5 based on the HRMS-ESI analysis of the reaction mixture. The *ortho*-naphthoquinone catalyst, ***o*-NQ1**, condenses with amine **1** to give water and ***o*-NQ-ketimine**. While there are two ketone moieties that amine **1**

can condense with, the crystallographic evidence of benzooxazine derivative **3t** clearly demonstrates the site of attack being the 2-carbon position of ***o*-NQ1**. The prototropic rearrangement then occurs to give **Naphthol-ketimine**. Our mass spectra analysis revealed the peak corresponding to either ***o*-NQ-ketimine** or **Naphthol-ketimine** as $[M+H]^+$. **Naphthol-aminal** should be derived from the reaction of the **Naphthol-ketimine** with another molecule of amine **1**. Alternatively, the **Naphthol-ketimine** can isomerize to **Naphthol-enamine** in such cases the catalyst arrest happens to give benzooxazine derivatives such as **3s** and **3t**. The **Naphthol-aminal** undergoes the equilibrium-driven dissociation of ketimine **3** to give **Naphthol-amine** that on exposure to air spontaneously oxidizes to regenerate catalytically active species to re-enter the catalytic cycle.[11] The formations of **Naphthol-amine** as well as the reduced form of ***o*-NQ1**, **Catechol**, were also established from the MS analysis of the reaction mixture. Ketimine **3** is hydrolyzed to give ketone **2**, and amine **1** re-enters the catalytic cycle. From the MS analysis of the reaction mixture we also identified the formation of unsubstituted **Ketimine**, possibly from the reaction between the ketone **2** and NH_3 by-product. Also, we observed the formation of **Catechol-product complex**, representing the resting state of **Catechol** intermediate (see Supporting Information for HRMS-ESI data).

SCHEMES 5. A Proposed Catalytic Cycle for the Aerobic Deamination Based on HRMS-ESI Analysis



In summary, we have developed a novel *aerobic* deamination reaction to directly access to ketones and ketimines from α-branched primary amines. The direct formation of ketones from amines has been, for the first time, achieved in good to excellent yields thanks to the mild organocatalyst, *ortho*-naphthoquinone, with a distinctive amine activation mode. Another key feature of the deamination catalyst is its applicability to a diverse array of amine-containing molecules, where the unprecedented deamination activity for amino acids and DNA nuclear bases has been demonstrated with the specific substrate dependency. Further extension of the aerobic deamination reactions is currently underway, and our results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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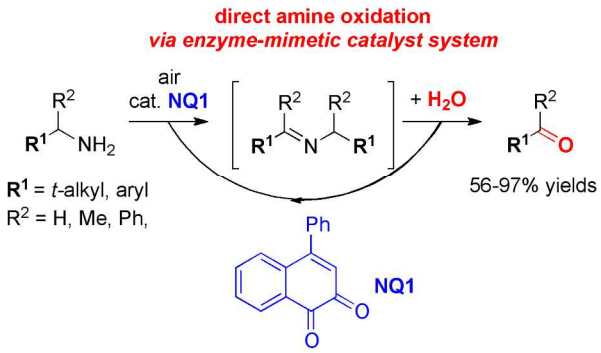
direct amine oxidation
via enzyme-mimetic catalyst system
air
cat. NQ1
+ H2O
R1 = t-alkyl, aryl
R2 = H, Me, Ph,
56-97% yields
Ph
NQ1
O
O