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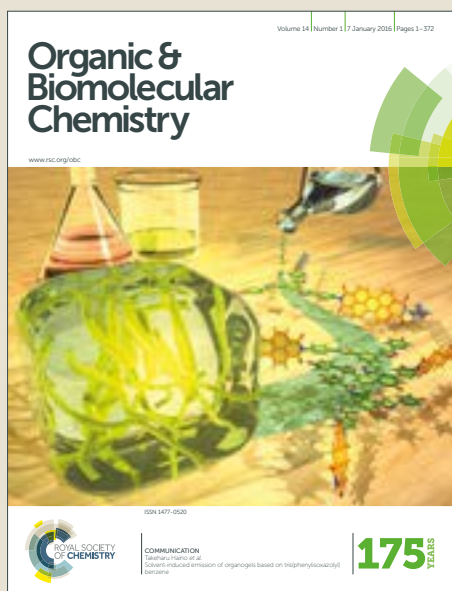
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Aerobic catalytic systems inspired by copper amine oxidases: recent developments and synthetic applications

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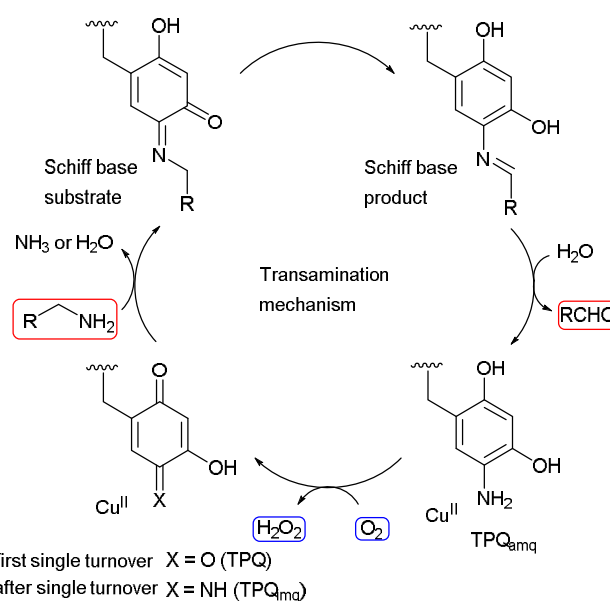
Recent efforts to design synthetic quinone-based catalysts for the efficient aerobic oxidation of amines to imines have been inspired by copper amine oxidases (CuAOs), a family of metalloenzymes which selectively converts primary amines into aldehydes, using molecular oxygen through the cooperation of a quinone-based cofactor, 2,4,5-trihydroxyphenylalanine quinone (TPQ) and a copper ion. Two distinct classes of bioinspired quinone-based catalytic systems have been developed. The first class consists of catalytic systems, which mimic the activity of CuAOs by exhibiting exquisite selectivity for primary amines. The second class is constituted by catalytic systems, which allow the expansion of the substrate scope to the oxidation of α -branched primary amines and secondary amines including nitrogen heterocycles, two reaction types that natural CuAOs are not able to accomplish. These catalytic oxidative green processes can be applied to the C-H functionalization of primary amines and to the synthesis of several nitrogen-containing heterocycles.

Introduction

Copper amine oxidases (CuAOs) are ubiquitous enzymes isolated from mammals, many higher-order plants, fungi, yeasts and bacteria, which play a vital role in the physiology and pathology of mammals in controlling the metabolism of various primary monoamines, diamines and polyamines of endogenous or xenobiotic origin.¹ Interest in CuAOs has greatly increased in recent years, especially since the discovery that human vascular adhesion protein-1 (VAP-1), which regulates leucocyte trafficking and glucose transport, is a CuAO enzyme. VAP-1 has been shown to be upregulated at sites of inflammation and has been implicated in human diseases such as diabetes mellitus, congestive heart failure and liver disease.² So the rational design of selective inhibitors of CuAOs as potential therapeutic agents is of current interest.³

CuAOs catalyze the selective aerobic oxidation of primary amines to aldehydes through the synergistic action of a quinone-based cofactor, 2,4,5-trihydroxyphenylalanine quinone (TPQ), and a copper ion (Scheme 1).^{4,5} TPQ is derived from a conserved tyrosine in a self-processing, post-translational event that requires only copper and molecular oxygen.^{3,6} Through the utilization of synthetic models of TPQ cofactors,⁷ and using benzylamine as the model substrate, it

has been established that TPQ promotes the conversion of a primary amine into an aldehyde through a transamination process which proceeds via two half reactions (Scheme 1):⁸ a reductive half reaction in which the amine substrate RCH_2NH_2 is oxidized to the aldehyde $RCHO$, leaving TPQ as a reduced aminoquinol form TPQ_{amq} , followed by an oxidative half-reaction which corresponds to the reduction of molecular oxygen to hydrogen peroxide, with concomitant formation of TPQ_{imq} .



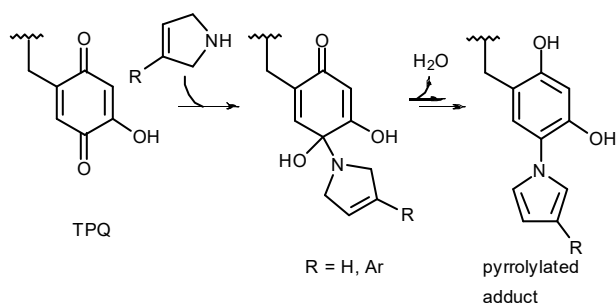
Scheme 1 Transamination mechanism followed by copper amine oxidases *in vivo*.

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Although the oxidation of the primary amine substrate is mediated by the quinone cofactor without direct involvement of the copper ion, this might play a role in orienting the TPQ ring correctly in the active site and in facilitating the reduction of O_2 to H_2O_2 .⁹ Very likely, the final step under single turnover conditions is a transamination reaction to form the Schiff base substrate without the need to regenerate TPQ.^{3,8a}

Whereas TPQ oxidizes a wide range of primary amines, short to long-chain aliphatic mono- and diamines including arylalkylamines,³ it fails to oxidize secondary and tertiary amines. Accordingly, 3-pyrroline derivatives have been shown to be transamination-specific mechanism-based inactivators through the formation of a stable pyrrolylated cofactor that cannot be reoxidized to the starting quinone (Scheme 2).¹⁰



Scheme 2 Proposed pathway of CuAOs inactivation by 3-pyrroline derivatives.¹⁰

An important benefit of knowing the CuAOs mechanism is its potential application in the design of synthetic biologically inspired catalysts. The discovery of small-molecules catalysts capable of performing controlled aerobic oxidations under very mild conditions in a way reminiscent of enzyme catalysis is in constant demand by the pharmaceutical and chemical industries.¹¹

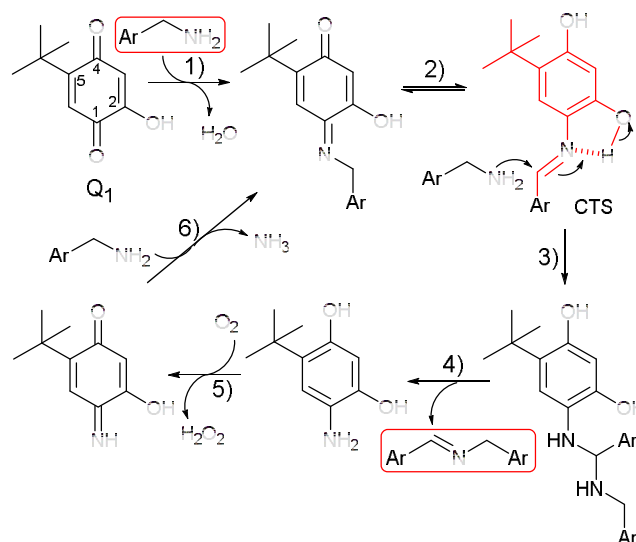
As a consequence, the general interest in amine oxidation chemistry¹² has stimulated efforts to discover effective quinone-based catalysts inspired by CuAOs for the aerobic oxidation of amines to imines.^{13,14} Imines are a very important class of compounds in chemistry that have widely been utilized as pivotal intermediates in the synthesis of fine chemicals and numerous biologically active compounds.¹⁵ Although the enzymatic transamination mechanism is not in itself a suitable path to mimic the generation of imines, in the absence of water, the Schiff base product can undergo a direct addition of the amine substrate RCH_2NH_2 leading to a dimeric imine condensation product $RCH=NCH_2R$ instead of the aldehyde (Scheme 3).⁷ Recently, organic chemists have developed bioinspired quinone-based catalytic systems that utilize dioxygen or, more preferably, ambient air as the sole oxidant, with two objectives: a) to achieve sustainable aerobic amine oxidation reactions; b) to expand the scope of possible substrates. This paper aims to provide an overview on this area which developed rapidly during the last five years. It is organized around two classes of bioinspired quinone-based catalytic systems. The first class consists of catalytic systems, which mimic the activity of CuAOs by exhibiting exquisite

selectivity for primary amines. The second class is constituted by catalytic systems, which allow the expansion of the substrate scope to the oxidation of α -branched primary amines and secondary amines, two reaction types that natural CuAOs are not able to accomplish. The application of these green processes to the C-H functionalization of primary amines and to the synthesis of several nitrogen-containing heterocycles is also presented.

Bioinspired catalysts which exhibit the selectivity of CuAOs for primary amines

Organocatalysts

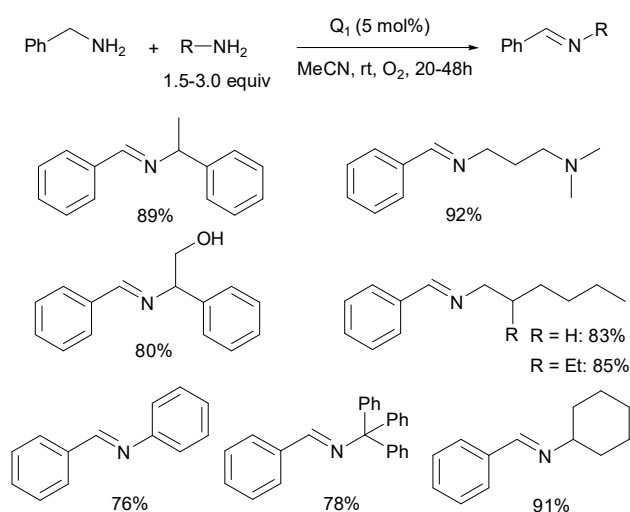
Inspired by biochemical model studies,^{7b,c} Wendlandt and Stahl have developed a highly chemoselective method for the aerobic oxidative coupling of primary benzylic amines to yield homocoupled imines using the synthetic TPQ analog, 5-*tert*-butyl-2-hydroxy-1,4-benzoquinone Q_1 (Scheme 3).¹⁶ High yields of imines up to 93% were obtained, in acetonitrile, at room temperature, under 1 atm of molecular oxygen, from variously substituted benzylic amines including the heterocyclic furfurylamine. As for CuAOs, secondary amines and tertiary amines were not oxidized under the same experimental conditions. The chemoselectivity for primary amines could be easily explained by a transamination process close to that reported for natural CuAOs (Scheme 3).⁸



Scheme 3 Proposed ionic transamination mechanism for the aerobic oxidation of primary amines to imines catalyzed by Q_1 and other quinone-based models cofactors.⁷

As shown for TPQ, the presence of the hydroxyl group at the 2-position plays a crucial role in protecting the quinone ring from ring amination and in directing nucleophilic addition of amine exclusively to the C-1 position (Scheme 3, step 1).^{7a} Also, the activation of the imine function for further nucleophilic attack by the amine (Scheme 3, step 3), leading to the extrusion of homocoupled imine (Scheme 3, step 4), is very

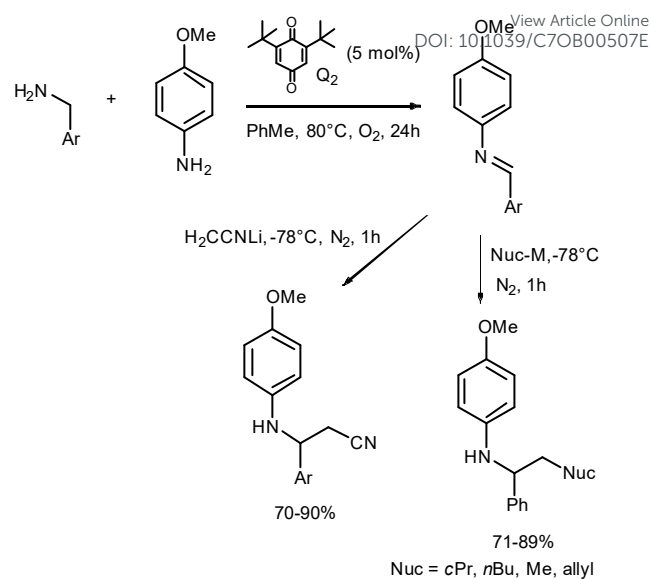
likely provided by an intramolecular hydrogen bond between the 2-hydroxy group and the imine nitrogen, generating a highly reactive cyclic transition state (CTS).¹⁷ This activated nucleophilic attack of amine, which give an aminal intermediate (Scheme 3, step 3) would constitute a driving force for the overall transamination process thereby preventing any competitive Michael addition reaction. Aerobic oxidation of the generated aminophenol form (Scheme 3, step 4) generates the iminoquinone organocatalyst (Scheme 3, step 5), which can undergo transimination with the amine substrate (Scheme 3, step 6) and close the catalytic cycle by passing Q_1 . Interestingly, selective cross-coupling products could also be obtained by running the reaction in the presence of a second nonreactive primary amine. As shown in Scheme 4, primary amines bearing alcohol or amine functionalities underwent effective cross-coupling with benzylamine, without oxidation of the alcohol or amine fragment.



Scheme 4 Q_1 -mediated aerobic cross-coupling of benzylamine with activated and non-activated primary amines.

The discovery of quinone-based catalysts has also allowed the *in situ* trapping of secondary imines for further reactions. Accordingly, Clift and co-workers have recently utilized the commercially available 2,6-di-*tert*-butyl-1,4-benzoquinone Q_2 as an organocatalyst for the preparation of α -branched amines through a sequential quinone-promoted primary amine oxidation/nucleophilic addition process (Scheme 5).¹⁸ Like Q_1 , Q_2 meets some criteria essential for acting as an efficient catalyst for amine oxidation. Especially, it is sterically encumbered to prevent conjugate addition of the amine while leaving the C-4 position accessible enough to allow condensation of the amine substrate.

As in the case of TPQ cofactor and Q_1 , α -branched amines and secondary amines were not oxidized under the same experimental conditions. However, this oxidative C-H functionalization protocol could be extended to allylic amines provided higher amounts of Q_2 catalyst (20 mol%) were used.

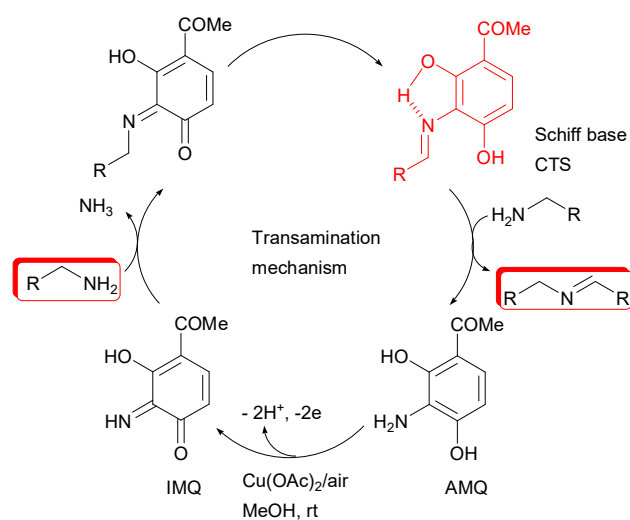


Scheme 5 Sequential Q_2 -mediated α -functionalization of primary amines.

Finally, using simple organocatalysts, the amine substrate scope is limited to benzylic-type and allylic amines.^{7,16,18} The oxidation of non-activated primary alkylamines, which are natural substrates for CuAOs,¹⁹ is inherently more challenging and requires the development of cooperative catalytic systems.

Cooperative catalytic systems

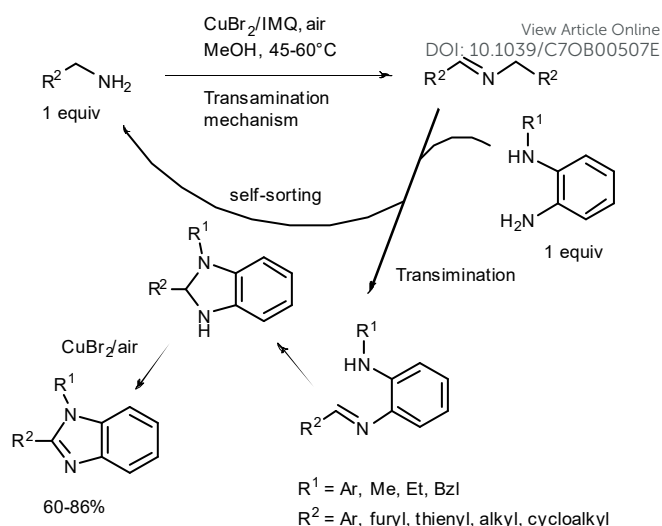
Our group has described a CuAO-like homogeneous co-catalytic system for the chemoselective oxidation of primary amines to imines at room temperature under ambient air.²⁰ The catalytic process combines two redox couples in a way reminiscent of other biomimetic catalytic systems:²¹ the *o*-iminoquinone organocatalyst IMQ, first discovered from electrochemical studies,²² is the substrate-selective catalyst whereas the copper (II) salt serves as an electron-transfer mediator. The highly reactive *o*-iminoquinone organocatalyst IMQ is generated *in situ* from the corresponding *o*-aminoquinol AMQ which can be easily synthesized in two steps from 2-nitroresorcinol.²³ The oxidation process starts with atmospheric oxygen and continues in a cascade-like manner by passing the oxidation potential of dioxygen through the copper salt (0.2 mol%) to IMQ (2mol%), which finally oxidizes the amine substrate through a transamination mechanism analogue to that reported for natural CuAOs (Scheme 6).⁸ The reaction is enhanced through the participation of 1-acetyl and 2-hydroxy substituents, as they prevent the competing formation of Michael adducts. Analogous to the hydroxy groups of TPQ and Q_1 , the presence of the active 2-hydroxy substituent, which is engaged in an intramolecular hydrogen bond with the imine nitrogen to form a highly reactive Schiff base CTS, is required for the successful operation of the catalytic process. Accordingly, the analogue of AMQ, which lacks the 2-hydroxy substituent, generated an *o*-iminoquinone species which was devoid of catalytic efficiency.^{22c}



Scheme 6 Proposed ionic transamination mechanism for the Cu^{II} /IMQ-mediated aerobic oxidation of primary amines to imines.

In the presence of a second primary aliphatic amine, functionalized cross-coupled imines could be prepared in high yields through the transamination mechanism that leads to the homocoupled imine intermediate followed by dynamic transimination (Scheme 7). As a consequence, just one equivalent of each primary amine was sufficient to achieve exclusive formation of the cross-coupled imine product.²⁴ This oxidative strategy related to dynamic self-sorting chemistry has previously been used to obtain thermodynamically disfavoured products.^{16,25}

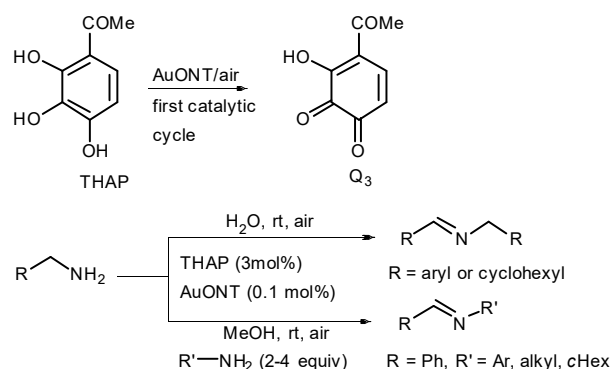
Unlike simple quinone-based organocatalysts,^{7,16,18} IMQ was also able to oxidize non-activated primary aliphatic amines that are substrates for CuAOs enzymes.^{20,22,24} Note, when compared with the direct electrochemical oxidation of non-activated primary aliphatic amines, which occurs at high anodic potential ($E > +1.5$ V vs SCE), 1.0 V was gained using IMQ as the electrocatalyst.^{22d} This result corroborated that, in the aerobic cooperative catalytic system Cu^{II} /IMQ, the copper salt facilitates the aerobic oxidation of AMQ to IMQ. Although the aliphatic imines could be observed through monitoring the ^1H NMR spectrum, their instability and isomerisation into the enamine tautomer did not permit their isolation.²⁶ Nevertheless, the mild reaction conditions proved to be useful for trapping the scarcely stable aliphatic imines *in situ* for further reactions. Through acid-free tandem oxidative Diels-Alder reaction, aliphatic imines could react at room temperature as dienophile with Danishefsky's diene to form dihydro-4-pyridones²⁴ whereas, in the presence of *o*-aminoanilines, they were engaged in cyclocondensation reaction to furnish 1,2-disubstituted benzimidazoles, provided slightly elevated temperatures of 45–60°C are applied (Scheme 7).²⁷



Scheme 7 Bioinspired CuBr_2 /IMQ-mediated cascade reaction sequence leading to 1,2-disubstituted benzimidazole derivatives.

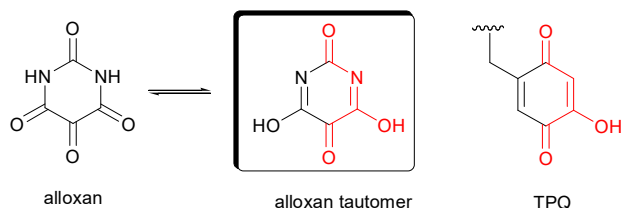
Although this cooperative catalytic system was able to work under ambient air with high atom economy and was compatible with both benzylic and non-activated primary amines, the use of a commercially available quinone-based organocatalyst would offer enhanced practicality.

Accordingly, Doris and co-workers have developed an effective heterogeneous co-catalytic system which uses commercially available 2,3,4-trihydroxyacetophenone (THAP) as a precursor of IMQ, in combination with a nanohybrid system (AuONT) made of gold nanoparticles assembled on polymerized polydiacetylene nanotubes.²⁸ Not surprisingly, this heterogeneous cooperative catalytic system behaved like the Cu^{II} /IMQ homogeneous co-catalytic system and followed the same transamination mechanism (Scheme 6) at the exception of the first catalytic cycle which engaged the *o*-quinone species Q_3 generated from THAP (Scheme 8). Interestingly, AuONT co-catalyst could be recovered by centrifugation and reused five times without any loss of activity.



Scheme 8 Selective aerobic oxidation of primary amines mediated by the cooperative heterogeneous system AuONT/THAP.

Recently, Carbery and co-workers have been drawn to the structure of commercially available alloxan due to the structural analogy of its tautomer with TPQ cofactor (Scheme 9). The authors demonstrated that the combination of alloxan (2.5 mol%) and CuCl (1 mol%) constituted an effective homogeneous co-catalytic system for the aerobic oxidation of primary benzylic-type amines to imines under ambient air. Provided that 5 mol% of both alloxan and CuCl were used, selective oxidative cross-coupling of benzylamine with variously substituted anilines could be realized, while aliphatic amines were found to be poor coupling partners for similar reactions.²⁹



Scheme 9 Similarity between alloxan tautomer and covalently bound quinone cofactor TPQ

Although the co-catalytic system share common features with CuAOs such as the utilization of a quinone mimetic organocatalyst together with a copper salt, mechanistic investigations revealed divergence in the reaction mechanism which adopted a radical character and does not proceed through a quinone-imine step. As a consequence, the CuCl/alloxan system better resembled the flavin/alloxan-mediated oxidation of amines.³⁰

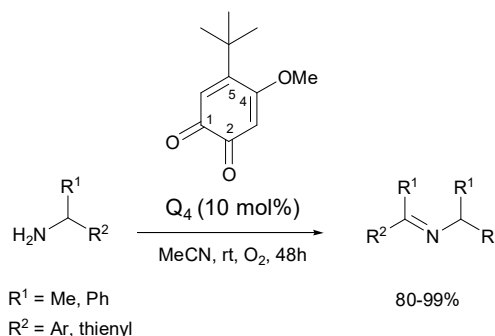
The catalytic systems reported as yet for the oxidation of amines to imines have been designed to reproduce exquisite enzymatic reactivity and selectivity for primary amines. They function essentially under ambient air, which is the ideal oxidant in terms of safety and sustainability. In the meanwhile, the organic chemists have also sought to surpass the activity of CuAO enzymes by increasing the scope of amine substrates to sec-primary amines and secondary amines.

Bioinspired catalysts able to expand the amine substrate scope

Organocatalysts

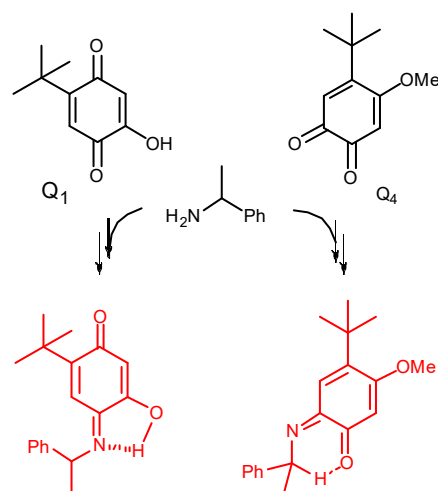
Luo and co-workers have demonstrated that the 4-methoxy-5-*tert*-butyl-*o*-quinone organocatalyst Q_4 enables efficient aerobic oxidation, at room temperature under an O_2 atmosphere, of α -branched primary benzylic amines considered as poor substrates for CuAOs cofactors (Scheme 10).³¹ Through DFT studies, they pointed out that the transamination pathway, plausible only for linear primary amines in nature, could also work for the oxidation of α -branched primary benzylic amines by Q_4 . They examined the aerobic oxidation of *sec*-benzylamine mediated by Q_1 and Q_4 .

In the presence of Q_1 , the reaction was stopped at the Schiff base substrate stage (Scheme 11) which was isolated and characterized by NMR analysis.



Scheme 10 Q_4 -mediated aerobic oxidation of α -branched primary benzylic amines.

A strong intramolecular hydrogen bond between the imine nitrogen and the hydroxy substituent was evidenced by X-ray crystallography showing the difficulty of H-abstraction with Q_1 . In contrast, no similar hydrogen bond was observed in the Schiff base substrate stage of Q_4 , while a weak hydrogen bond was noted between C-H and the *o*-iminoquinone oxygen facilitating H-transfer.³¹ These results may account for the different performance of *p*-quinone versus *o*-quinone in the aerobic oxidation of α -branched primary amines.



Scheme 11 Intramolecular hydrogen bond characterized by X-ray crystallography at the Schiff base substrate stage of Q_1 and Q_4 .

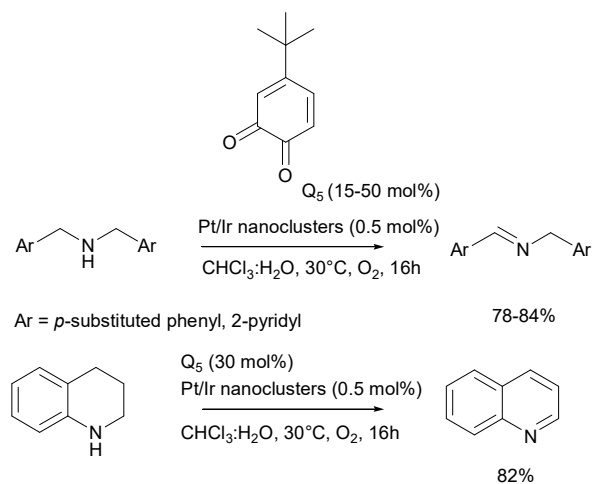
Cooperative catalytic systems

More challenging, the possibility of expanding the scope to the oxidation of secondary amines, a reaction type that CuAOs are not able to accomplish, was extensively explored. This reaction required the development of cooperative catalytic systems including a quinone-based organocatalyst.

The group of Kobayashi was the first to report a heterogeneous nanocluster catalyst acting cooperatively with

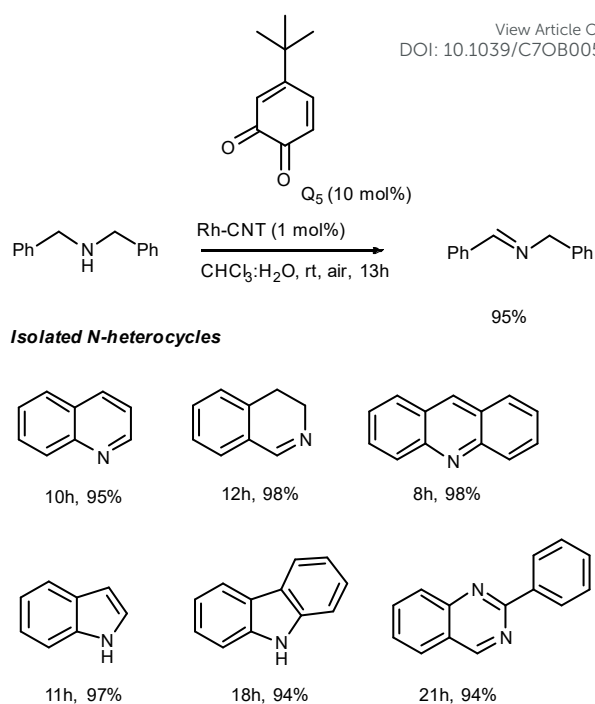
a quinone organocatalyst cofactor for the oxidation of secondary amines to imines under mild conditions.³² Although metal nanoclusters have been recognized as highly active catalysts for various aerobic oxidations, they had limited utility in converting amines to imines because of high temperatures required.³³ The bioinspired cooperative system consists of a heterogeneous Pt/Ir bimetallic nanocluster catalyst (0.5 mol%) immobilized on a styrene based copolymer support, and 4-*tert*-butyl-*o*-quinone Q₅ (15-60 mol%) as the substrate selective organocatalyst (Scheme 12). Various *p*-substituted dibenzylamines were converted, at 30°C under 1 atmosphere of O₂, into the corresponding imines in high yields. In the case of 1,2,3,4-tetrahydroquinoline, a second dehydrogenation reaction occurred to produce quinoline. Note primary benzylic amines could also be oxidized to imines at the exclusion of amines bearing electron-withdrawing substituents.

Whereas the chemoselectivity of CuAOs and that of quinone-based organocatalysts Q₁-Q₄ and IMQ for primary amines has been readily explained through the transamination process, mechanistic investigations revealed divergence in the reaction pathways because secondary amines have been shown to be inhibitors of quinones such as Q₁ through the formation of irreversible covalent adducts.^{10,34} An alternative mechanism was proposed in which a quinone hemiaminal intermediate is complexed to the metal nanocluster surface and undergoes a hydride transfer process leading to the desired imine.

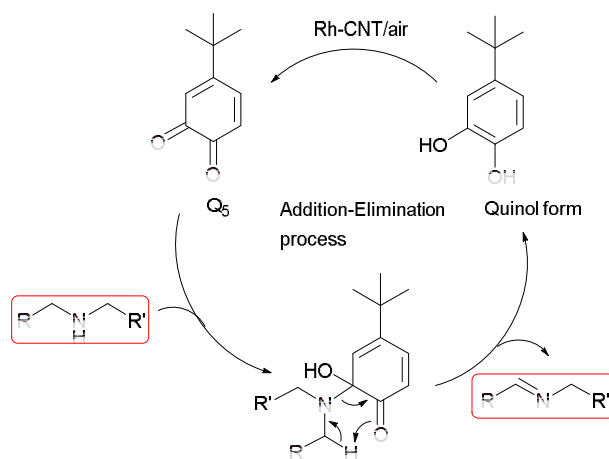


Scheme 12 Aerobic oxidation of secondary amines catalyzed by the Pt/Ir-Q₅ cooperative catalytic system.

Doris and co-workers have reported a similar cooperative action of Rh nanoparticles, supported on carbon nanotubes (Rh-CNT) as co-catalyst with Q₅ for the aerobic dehydrogenation, at room temperature under ambient atmosphere, of *N*-heterocycles and dibenzylamine (Scheme 13).³⁵ The reaction likely proceeds through an addition-elimination pathway (Scheme 14).

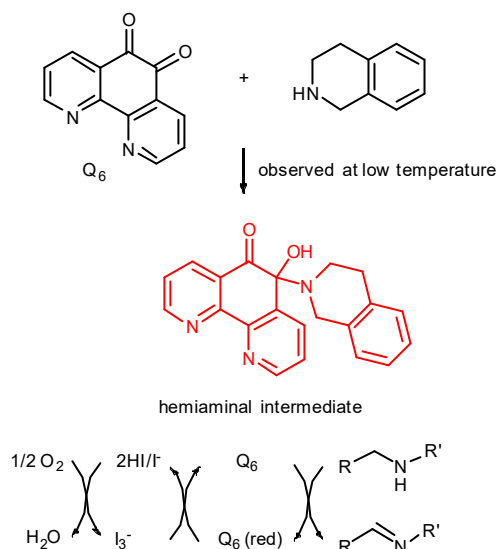


Scheme 13 Aerobic dehydrogenation of secondary amines catalyzed by the Rh-CNT/Q₅ cooperative catalytic system.



Scheme 14 Suggested addition-elimination pathway for the Rh-CNT/Q₅-mediated aerobic dehydrogenation of secondary amines.

Wendlandt and Stahl have provided the first direct evidence for the non-biomimetic addition-elimination pathway, including observation of the hemiaminal intermediate by ¹H NMR spectroscopy at low temperature (Scheme 15).



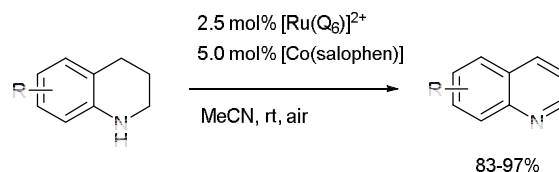
Scheme 15 Proposed addition-elimination mechanism for the ZnI_2/Q_6 -mediated aerobic dehydrogenation of secondary amines and *N*-heterocycles; observation of the hemiaminal intermediate by NMR spectroscopy.³⁶

They have demonstrated that the synergistic combination of 1,10-phenanthroline-5,6-dione Q_6 , with ZnI_2 as the co-catalyst, promotes, under atmospheric oxygen at room temperature, dehydrogenation of secondary amines and *N*-heterocycles.³⁶ Q_6 exhibits a bifunctional character resulting from the *o*-quinone moiety and the distal nitrogen atoms prone to coordination with metals.³⁷ The ZnI_2 co-catalyst not only enhances the amine oxidation activity, but also provides a source of iodide, which plays a critical redox role in mediating aerobic reoxidation of the reduced catalyst as shown in Scheme 15. However, the ZnI_2/Q_6 catalytic system had some limitations as the reactions often required up to 48h to reach completion and certain product classes were not easily accessible. For example, tetrahydroquinoline underwent dehydrogenation to quinoline in only 18%.

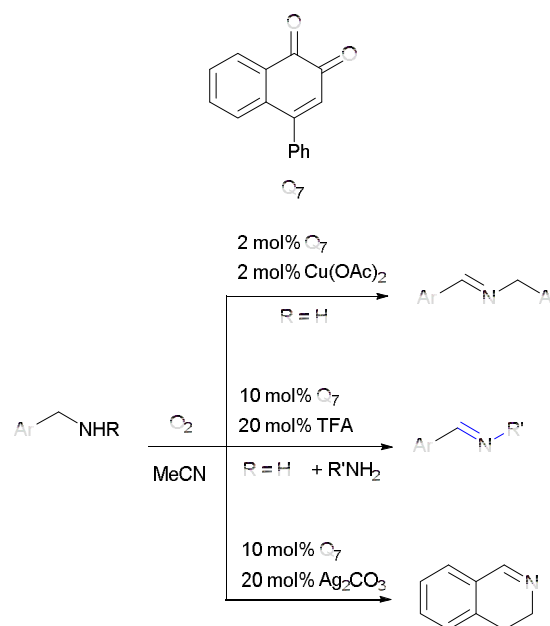
Thus, improved Q_6 -based catalytic systems were further elaborated to expand the amine substrate scope to tetrahydroquinolines, at room temperature with ambient air, as the terminal oxidant. Using an octahedral $[\text{Ru}(\text{Q}_6)_3]^{2+}$ catalyst, in combination with $[\text{Co}(\text{salophen})]$ as a co-catalyst, resulted in a marked improvement of the reaction rate and led to variously substituted quinolines in high yields (Scheme 16).³⁸

Finally, Oh and co-workers have described a cooperative catalytic system which utilizes the synthesized 4-phenyl-*o*-naphthoquinone Q_7 whose efficiency can be modulated through the nature of the co-catalyst (Scheme 17).³⁹ Using $\text{Cu}(\text{OAc})_2$ as the co-catalyst, the resulting system resembles the $\text{Cu}(\text{OAc})_2/\text{IMQ}$ system and allows the selective aerobic oxidation of primary benzylic amines to imines. However, in contrast to the $\text{Cu}(\text{OAc})_2/\text{IMQ}$ system, it failed to oxidize non-activated primary amines. Replacing $\text{Cu}(\text{OAc})_2$ by 20 mol% TFA

facilitated the formation of cross-coupled imines in high yields. The mild aerobic oxidation protocol could be further applied to the dehydrogenation of *N*-heterocycles by changing $\text{Cu}(\text{OAc})_2$ to Ag_2CO_3 .



Scheme 16 Dehydrogenation of tetrahydroquinolines to quinolines with the $[\text{Ru}(\text{Q}_6)_3]^{2+}/[\text{Co}(\text{salophen})]$ cooperative catalytic system under ambient air.



Scheme 17 Scope of Q_7 -catalyzed aerobic oxidation of amines modulated by the nature of the co-catalyst.

Conclusions

The development of biomimetic methods that utilize environmentally benign oxidants such as molecular oxygen or, much better, ambient air at room temperature, and avoid deleterious side reactions, is one of the most promising goals in oxidation chemistry today.

Natural CuAO enzymes have revealed their efficiency as catalysts to perform controlled aerobic oxidation of amines under mild conditions. These enzymes couple the oxidation of primary amines to aldehydes with the reduction of O_2 to H_2O_2 , through the synergistic action of a quinone-based cofactor TPQ and a copper ion.

Recently, there has been a boost in the development of various catalytic methods for the aerobic oxidation of amines to imines given the widespread importance of imines as

pivotal synthetic intermediates in a plethora of reactions such as reductions, additions, condensations and cycloadditions. Imines also serve as essential pharmacophores in numerous biologically active compounds.

During the last five years, researchers have begun to realize that CuAOs could constitute a rich source of inspiration for the rational design of small-molecules catalysts for the oxidation of amines to imines. Two approaches have been then envisaged.

The first approach consists of the design of biomimetic quinone-based catalytic processes, allowing to reproduce the enzymatic reactivity and selectivity for primary amines. These systems generally function under ambient air, at room temperature and follow a transamination mechanism reminiscent of that reported for natural CuAOs. However, organocatalysts are exclusively active on benzylic amines and the discovery of more reactive quinone species able to oxidize non-activated primary aliphatic amines, which are substrates for CuAOs, remains a challenge. Through the cooperative action of a metal ion as a redox mediator, the sole Cu^{II}/IMQ system was sufficiently reactive to oxidize non-activated primary amines because it closely resembles the enzymatic system.

In a second approach organic chemists have sought to surpass the activity of CuAO enzymes by increasing the scope of amine substrates. They have designed organocatalysts and cooperative catalytic systems for the oxidation of α -branched-primary amines and secondary amines, two reaction types that natural CuAOs are not able to accomplish. In the case of the oxidation of secondary amines, a shift from the transamination path to the addition-elimination mechanism was clearly demonstrated through the characterization of an hemiaminal intermediate. Finally, the utilization of biocompatible rather than rare and precious metals as co-catalyst should allow the development of new improved sustainable catalytic systems.

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