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Symbiotic Transition-Metal and Organocatalysis for Catalytic Ambient Amine Oxidation and Alkene Reduction Reactions

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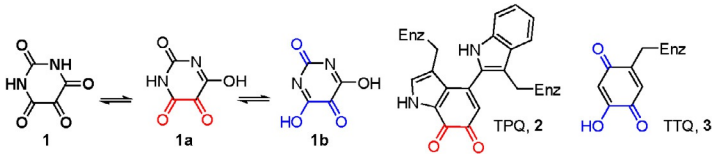
A new oxidation reaction based on two simple catalysts, namely, alloxan and a Cu^{I} salt, is highly effective for the aerobic oxidation and oxidative cross-coupling of amines. The reaction is operationally simple, reaction atmospheres enriched in dioxygen are obviated, and neither catalyst component requires prior synthesis. Mechanistic investigations have been performed and point towards a complex reaction manifold with evidence that supports a catalytic cycle that does not proceed through a quinone-imine step. Additionally, this dual catalyst system is efficient to effect diimide-mediated hydrogenation reactions of alkenes and alkynes, a transformation that has not been reported previously in the context of quinone catalyst systems.

Monoamines such as phenethylamine and serotonin are important biochemical substrates that have a wide range of roles.[1] Nature dehydrogenates monoamines by two key enzymatic pathways, namely, the flavin-dependent[2] and copper-dependent oxidase pathways.[3] In the case of the flavin-dependent monoamine oxidase, no consensus has been reached with respect to the mechanism of operation. In contrast, the consensus for the copper-dependent oxidases is that the mechanism proceeds through a pyridoxal-like transamination mode.[4]

Recently, we presented a model system that mimics the reactivity of monoamine oxidase B (MAO B) and operates with a synthetic flavin to convert amine substrates, which are processed readily by MAO B, that is, benzylamines, to imines under ambient conditions.[5] In this transformation, an additional redox mediator, alloxan (**1**; Scheme 1), is used, which was proposed to act as a single-electron acceptor. Alloxan has the capacity to undergo two tautomerisation events (Scheme 1; **1**↔**1a**↔**1b**), which thus offers a structural homology to *ortho*- and *para*-quinone structures. We were struck, however, by the structural similarities between alloxan and the quinone co-factors tryptophan tryptophylquinone (TTQ; **2**) and 2,4,5-trihydroxyphenylalanine quinone (TPQ; **3**) present in copper-dependent amine oxidases (Scheme 1).[6]

These quinoproteins are an important family of redox-active enzymes, which function in part through the efficient harnessing of ambient oxygen as the terminal oxidant.[7] As an oxidant, ambient oxygen is arguably the ideal oxidant with respect to safety and sustainability. In this regard, synthetic chemists have often sought to find a balance to reproduce exquisite enzymatic reactivity and selectivity with synthetic generality and pragmatism. As the synthesis of imines is a valuable transformation,[8] there is a need for simple air-driven amine oxidation reactions. In this respect, there has been a recent growth in interest in the development of quinoprotein-like amine dehydrogenation reactions, as well as transition-metal catalysed oxidations under ambient conditions.[9] However, the development of efficient methodologies based upon readily available catalysts and effective at room temperature under ambient air is a pertinent synthetic challenge.

The translation of quinoprotein-like amine oxidations into effective synthetic reactions has led to two key problems. Firstly, the development of readily available catalyst systems is crucial to realise the synthetic power of biomimetic chemistry. Secondly, chemistry that proceeds under ambient conditions is a key goal. Thus far, there have been examples of the use of biomimetic quinone molecules in catalytic amine redox transformations as electrochemical oxidants,[9a] as a single catalyst[9c] and with a Cu co-catalyst,[9b] all of which require multi-step synthesis of the quinone mediator and, in some cases, with sensitive synthetic intermediates that require attention en route.



Scheme 1. Alloxan tautomerisation and structural parallels to the covalently bound quinone co-factors TPQ and TTQ.

The possibility that alloxan may act as a quinone co-factor mimetic was suggested by two considerations. The readily ac-

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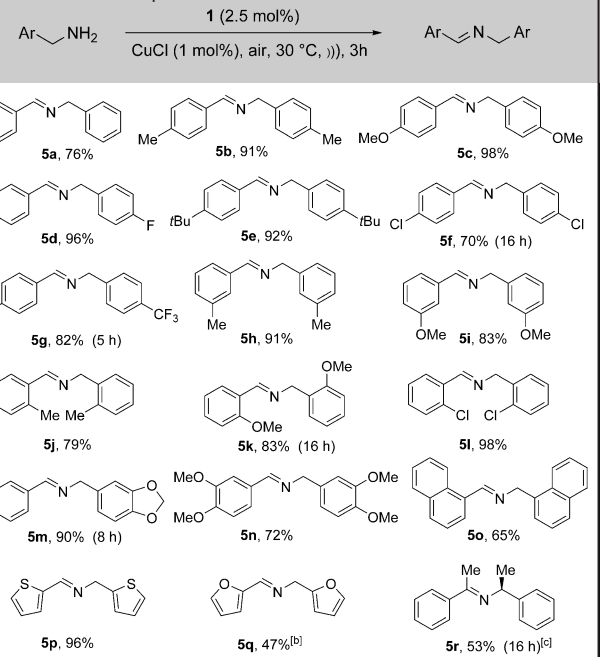
cessible tautomers (**1a–b**) would offer a structural overlap with the quinone co-factors **2** and **3**, that is, the *ortho*- and *para*-quinone fragments. Additionally, as a commercially available product, alloxan would offer enhanced practicality, as mentioned above. Accordingly, the feasibility of amine dehydrogenation using alloxan and Cu catalysis was examined, and the initial results are presented in Table 1.

Table 1. Substrate scope.[a]



[a] Changes to standard reaction time shown in parentheses if applicable. [b] Copper(I) 3-methylsalicylate used. [c] Reaction also completed independently using the enantiomeric substrate (*R*)-α-methylbenzylamine (50% yield).

Acetonitrile is the best choice of solvent of those examined. Ultimately, a loading of 1 mol% CuCl and 2.5 mol% alloxan monohydrate was reached, which offers a low catalytic loading. Pleasingly, both from an atom economy and price perspective, the reaction was possible with such a simple Cu salt, without recourse to any other ligands. Sonication in a low-power cleaning bath improves the reproducibility and performance of this amine dehydrogenation reaction. This sonication may result in both homogenisation of the reaction and also, potentially, the enhancement of the transfer of atmospheric oxygen to the bulk reaction.[10]

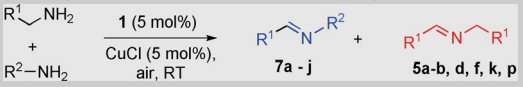
After we had optimised this oxidative dimerisation of benzylamine, a range of arylmethylamine substrates was investigated. Generally, this transformation works well over a relatively short time with a low loading of the dual commercial catalysts under an air atmosphere.

An examination of the substrates listed in Table 1 suggests that the reaction is efficient for both electron-rich and electron-deficient substrates, for example, in the formation of **5c** and **5g**. Previous reports on quinoprotein mimicry have shown a substantial dependence on electronics, and electron-rich aryl rings are better substrates.[9c] The only exception to the excellent reactivity of benzylamines was 2-furylamine (**4q**).[9c,f] This was partially obviated by the use of copper(3-methylsalicylate), a less labile Cu ligand (the yield was $<20\%$ if CuCl was used). This effect was also observed in the oxidation of 2-methoxybenzylamine, which required 16 h reaction time, whereas the oxidation of 4-methoxybenzylamine was complete in 3 h.

The more hindered substrate *S*-α-methylbenzylamine (**4r**) was a reasonable substrate for this reaction, although it is a less common substrate for such oxidations.[11] Additionally, the coupling of aliphatic amines was attempted, and only trace amounts of oxidised product were observed.

Inspired by recent work on the oxidative cross-coupling of benzylic amines with less oxidisable amines[9b,c,f,12] and the potential applications that relate to dynamic self-sorting chemistry,[8,13] the developed Cu^{I}/alloxan dual catalyst system was applied to the reaction of a benzylamine with an aniline (Table 2).

Table 2. Catalytic ambient oxidative cross-coupling reactions.



Entry	R^1	R^2	Yield [%][a]	Selectivity[b]
1	4-Me-C_6H_4	4-Me-C_6H_4	96	25:1
2	4-Me-C_6H_4	4-OMe-C_6H_4	90	>25:1
3	Ph	4-OMe-C_6H_4	64	>25:1
4	4-Me-C_6H_4	4-F-C_6H_4	84	16:1
5	4-F-C_6H_4	4-OMe-C_6H_4	72	>25:1
6	4-Cl-C_6H_4	4-OMe-C_6H_4	55	>25:1
7	2-thiophenyl	Ph	55	1:1.6
8	2-OMe-C_6H_4	Ph	87	11.5:1
9	4-Me-C_6H_4	4-pyridyl	68[c]	<1:25
10	Ph	*n*-oct	11 (24)[d]	2.2:1
11	4-Me-C_6H_4	$(CH_2)_2$Ph	19 (29)[d]	2:1

[a] Isolated yield if we assumed 100% cross-coupled product. [b] Assessed by ^{1}H NMR spectroscopy. [c] Yield of homo-coupled product. [d] Assessed by comparison to an internal standard of 1,3,5-trimethoxybenzene; yield of cross-coupled product only (total imines in parentheses).

Initial exploration demonstrated promising reactivity and selectivity for the reaction of *p*-toluidine and 4-methylbenzylamine (Table 1, entry 1). Good chemoselectivity was generally observed with $\geq$25:1 selectivity in favour of the hetero-coupled imine **7** observed if anilines with electron-donating groups were used (entries 1–3, 5 and 6). The oxidative cross-coupling with the hetero-aromatic aniline 4-aminopyridine was also attempted, and only homo-coupled product **5b** was isolated from the reaction mixture (entry 9). Aliphatic amines were found to be poor partners in this reaction (entries 10 and 11), perhaps because of catalyst deactivation effects.

An attempt to study the kinetic profile has revealed that this catalytic reaction is complex (Supporting Information). Over the range of $BnNH_2$ concentrations studied, the reaction was best fitted to a linear, zero-order plot but had a fractional and non-linear reaction order by way of a $\ln[BnNH_2]$ versus $\ln(k_{obs})$ plot, which suggests a degree of rate dependence upon amine

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concentration. The rate for alloxan displayed first-order kinetics at relatively low concentrations but deviation at higher alloxan concentrations.

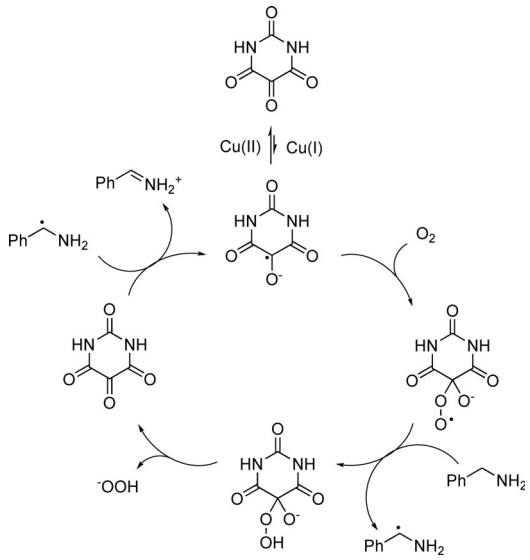
This observation is consistent with that of Eckert and Bruice who observed amine oxidations mediated by phenanthroline-quinones to proceed by pseudo-first-order kinetics with respect to quinone at high amine concentrations, which deviated at low amine concentrations because of the formation of semiquinone species, that is, the reaction mechanism adopts a radical character.[14]

Additionally, the reaction also showed a dependence on [CuCl] that approximates to first order, which suggests that over most concentrations a possible rate-determining step might be the Cu^{II}-mediated oxidation of a reduced alloxan species. Finally, if the reaction was conducted under an atmosphere of O_2, a faster reaction was observed for the first 15 min, after which no further amine oxidation was monitored.[15]

X-band EPR spectroscopy of MeCN solutions, at room temperature and 120 K, was used to probe both the oxidation state of Cu and the presence of any organic radical species during the reaction turnover. A strong EPR signal that displayed a four-line hyperfine structure was observed, commensurate with the presence of a Cu^{2+} ($3d^9$) ion, *only* after the addition of benzylamine. No organic radical species were detected during these experiments. Simulation of the frozen-solution EPR spectra provides g_{zz} values much larger than the values of g_{xx}, and g_{yy}, which suggests a symmetry close to axial (square planar or axially elongated), and with the unpaired electron located in the $d_{x^2-y^2}$ orbital. The spectrum of the reaction mixture after 2 h shows three components (at fields $B_{x(1)}$, $B_{y(2)}$ and $B_{z(3)}$), which reveals a distortion toward a rhombic coordination sphere and corresponds to the three different coordination axes, *x*, *y* and *z*, of the magnetic tensor. This may be explained by differences in Cu–ligand binding along the *x*, *y* and *z* axes or differences in the nature of the ligands coordinated along these axes, which could be caused by the consumption of benzylamine that may act as a ligand for Cu^{II} (Figure 1).

The involvement of a Cu-containing species in the rate-determining step but a lack of appreciable build up of Cu^{II} before the addition of amine seemed inconsistent with the quinoidal mechanism proposed for Cu-containing amine oxidases, in which Cu^{II} would need to be present before the first turnover to mediate O_2 re-oxidation of alloxan from dialuric acid. Additionally, we saw no evidence of the formation of murexide in this reaction, which would be expected to form if a dialuric acid intermediate was involved and would also be expected to be a catalyst deactivation pathway.[16]

We propose, based on the data discussed, that we see a rapid pre-equilibrium between alloxan and its one-electron-reduced form, nevertheless far enough towards the starting alloxan/Cu^{I} pair that we do not observe formation of the Cu^{II} by EPR spectroscopy at this stage. A further reaction of O_2 could add into an alloxan radical to form a peroxy radical (Scheme 2).



Scheme 2. Plausible reaction mechanism.

Upon amine addition, the small amount of formed peroxyl abstracts a hydrogen atom to form a hydroperoxide and extrude H_2O_2 to regenerate alloxan. Alloxan, like similar tricarbonyls, would be expected to accept an electron rapidly from an α-amino radical to form a semi-reduced alloxan, which is re-oxidised.[17]

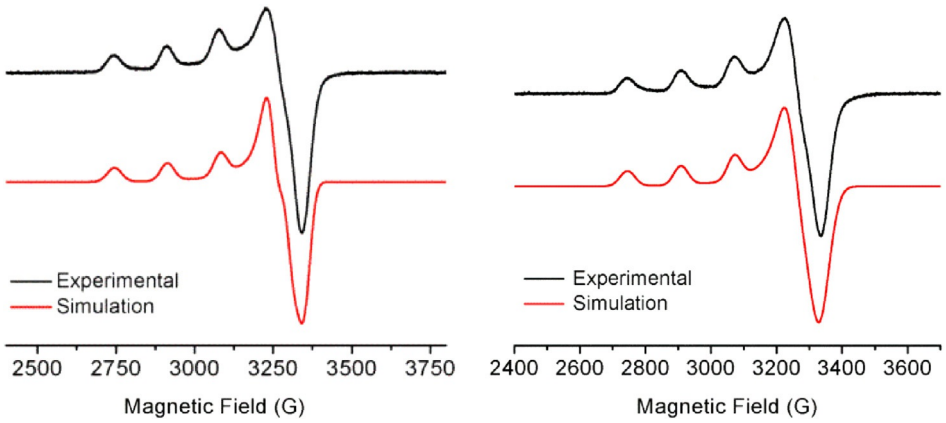


Figure 1. EPR spectrum that displays Cu^{II}-centred paramagnetic species upon amine addition (left) and after 2.5 h (right) at 120 K.

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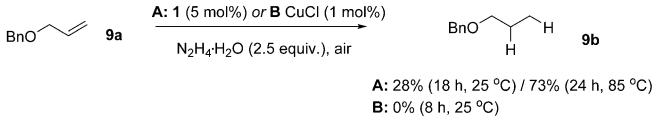
A rate-determining step that involves [Cu] does not fit if the Cu single-electron transfers are in rapid equilibrium; however, an alternative rationalisation is that CuCl may be activated by the presence of amine (given that we would expect Cu amine complexes to be formed).

This study details the oxidation of amines to imines using the Cu^{I}/alloxan system and parallels our recent flavin/alloxan oxidation of amines.[5] With this apparent reaction homology, further synthetic reactions that are catalysed by flavin and concern N-nucleophiles were sought to expand the scope of this protocol. Accordingly, the generation of diimide from hydrazine[18] to enable the pseudo-hydrogenation of alkenes and alkynes was assessed.

We worked initially with benzylallyl ether as the substrate, and a clean olefin pseudo-hydrogenation is attainable using CuCl (1 mol%) and alloxan (5 mol%) under ambient conditions with moderate heating (Table 3, entry 1). Reliable alkene reduction was possible with this protocol, unsaturated sulfides were also suitable and no sulfoxide was observed (entries 2 and 4) as has been reported with a flavin catalyst.[18a] This study has also demonstrated that internal alkenes require more forcing conditions and regio-selectivity is achievable in cases in which more than one alkene is present (entries 7 and 8). Finally, terminal alkynes such as the monoamine oxidase inhibitor pargyline (**8e**) were also reduced in good yields to the corresponding alkane **9e** (entry 9). No N-oxide was observed from this ambient reaction. Internal alkynes, such as **8f**, can also be reduced fully if extended reaction times are employed (entry 10). We have also noted that there was no erosion of enantiomeric purity with this substrate. The reaction tolerated basic amine functionalities such as that in entries 6 and 9.

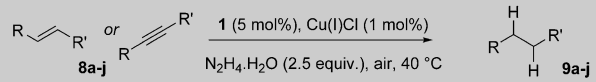
Although the oxidative Cu^{II}-mediated generation of a diimide to effect alkene reduction is known,[19] to the best of our knowledge, a Cu^{I}-catalysed aerobic hydrazine oxidation has not been reported. Notably, this reduction reaction with alloxan as the sole catalytic species was possible without any Cu additives. Conversely, $Cu^{I}Cl$ alone did not promote the reaction (Scheme 3).

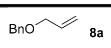
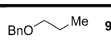
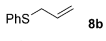
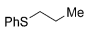
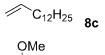
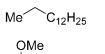
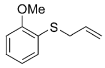
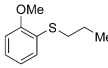
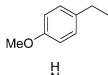
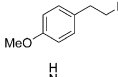
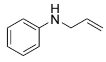
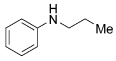
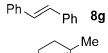
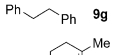
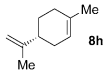
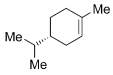
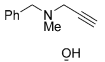
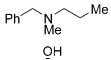
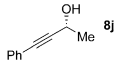
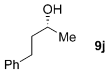


Scheme 3. Control reactions that show reduction mediated by **1** but not CuCl, assayed by ^{1}H NMR spectroscopy.

In conclusion, the combination of alloxan and $Cu^{I}Cl$ has been developed as an efficient system for the aerobic oxidation of amines to imines. This protocol is also adaptable to an oxidative hetero-imination reaction if used for electronically different amines. This catalyst system is able to perform diimide-type aerobic alkene and alkyne reductions with hydrazine. Initial mechanistic studies suggest that the rate-determining step involves both Cu species and alloxan but not the substrate amine.

Table 3. Catalytic ambient reduction of alkene and alkyne substrates.



Entry	Substrate	Product	*t* [h]	Yield [%]
1	 8a	 9a	18	93
2[a]	 8b	 9b	18	91
3	 8c	 9c	18	93[c]
4[a]	 8d	 9d	18	95
5	 8e	 9e	18	98
6	 8f	 9f	18	90
7[a,b]	 8g	 9g	24	77[c]
8[a]	 8h	 9h	3	71[d]
9[a]	 8i	 9i	18	69
10[b]	 8j	 9j	72	87

[a] $N_2H_4{\cdot}H_2O$ (5 equiv.). [b] Conducted at 85 °C. [c] Conversion assessed by ^{1}H NMR spectroscopy. [d] GC yield.

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Keywords: amines · copper · cross-coupling · homogeneous catalysis · oxidation

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