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Review
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Developments in the Aerobic Oxidation of Amines

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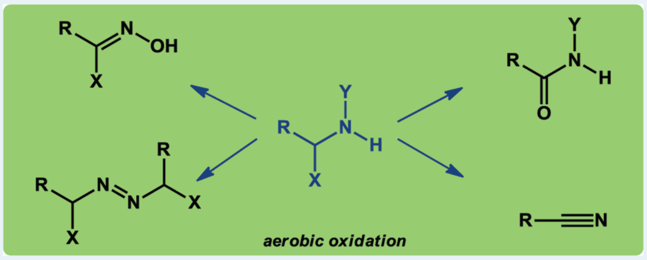
ABSTRACT: The oxidative upgrading of amines offers great opportunities for the sustainable production of key N-containing building-blocks for the modern chemical industry. Compared to other oxyfunctionalizations, and despite their potential, amine oxidation reactions are barely explored in the literature. This review aims at drawing attention to this important area and highlights both the major achievements and the challenges that still remain.

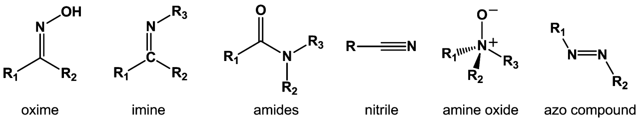


KEYWORDS: *gold catalysis, sustainable chemistry, oxidative dehydrogenation, oximes, imines*

INTRODUCTION

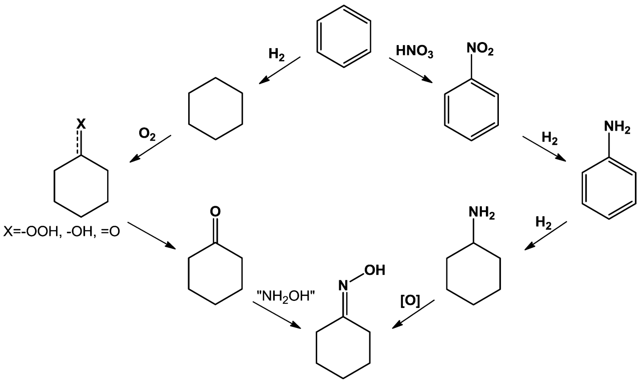
Scheme 1 gives an overview of important nitrogen-containing compounds (e.g., oximes, imines, amides, nitriles, amine oxides, and azo compounds), which could in principle be obtained from a controlled oxidation of an appropriate amine precursor. Some of those compounds represent important industrial building blocks, and deriving alternative synthesis pathways is of high industrial relevance. There is indeed a clear incentive to develop more sustainable production technologies which require less downstream processing.

Scheme 1. Important N-Containing Compounds or Intermediates



Cyclohexanone oxime, for example, is the monomer building block of the polyester Nylon-6 (4 Mt a^{-1}).[1] Conventionally, cyclohexanone oxime is obtained via the ammoximation of cyclohexanone by hydroxylamine (NH_2OH, Scheme 2). Although this process runs at high yield and selectivity, significant quantities of ammonium sulfate (up to 2.2 tonne/tonne oxime) are coproduced.[2] Although not always appreciated, this ammonium sulfate should not be considered as waste as it can be upgraded and used as a fertilizer. Nevertheless, coupling the production of two products (viz., a nylon intermediate and a fertilizer) in the same process has several strategic disadvantages. Therefore, Eni developed a process whereby the ammoximation is performed with in situ generated hydroxylamine, obtained from the H_2O_2-oxidation of ammonia over a microporous titanium silicalite-1 catalyst.[2] As cychexanone and the oxime cannot enter the micropores of the solid catalyst, parallel and consecutive side-reactions are largely prevented. Nevertheless, the bottleneck in this value-chain is the production of cyclohexanone via the autoxidation of cyclohexane.[3−6] The oxidation of cyclohexane runs at a conversion below 5% to avoid overoxidation of the desired oxygenates. The oxidation of cyclohexylamine (obtained from aniline) could—when performed with an appreciable space-time-yield and selectivity—be an attractive alternative route (Scheme 2). This is just one example of how selective amine oxidation could offer interesting and attractive new opportunities.

Scheme 2. Synthesis of Cyclohexanone Oxime: Comparison of the Conventional Route over Cyclohexanone (Left-Hand-Side) and an Alternative Route over Cyclohexyl Amine (Right-Hand-Side)



Although oxyfunctionalizations are important throughout the chemical value-chain, they remain problematic transformations, both with respect to selectivity and the nature of the oxidizing species. Stoichiometric oxidizing reagents such as salts of Cr^{VI} or Mn^{VII} are toxic and produce large amounts of waste.[7,8] Organic metal-free oxidants, such as Dess-Martin periodinane, the Swern oxidant, and various hydroperoxides, such as *tert*-butyl or cumyl hydroperoxide, afford an attractive alternative;

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however, their use is accompanied by the coproduction of an equivalent amount of organic and/or toxic waste (viz., low atom-efficiency). Given its high active oxygen content and environmentally benign byproduct (H_2O), hydrogen peroxide is an oxidant with high potential in the area of green chemistry. Nevertheless, its cost is still prohibitive for less value-added cases.[7,8] Therefore, although a number of approaches for the partial oxidation of amines exist with such traditional oxidants, aerobic oxidation (i.e., oxidation with molecular oxygen) is by far the most attractive and sustainable option. However, in spite of the recent developments made in the aerobic oxidation of alcohols,[9] the oxidation of (isoelectronic) amines is not widely studied. This likely emanates from the increased reactivity of the nitrogen center with respect to oxygen, which typically results in a decreased selectivity toward the desired product. This sensitivity is exemplified in the case of amine scrubbers for Carbon-Capture and Storage (CCS);[10,11] traces of oxygen in the effluent gas result in the oxidative degradation of the active amine, and thus lead to a decreased performance.[12−14]

The aim of this mini-review is to exemplify the oxidative methods by which amines may be used as platform chemicals, and to highlight the historic developments made toward the aerobic oxidative utilization of such amines. The present limitations and pertaining challenges within the field are later highlighted.

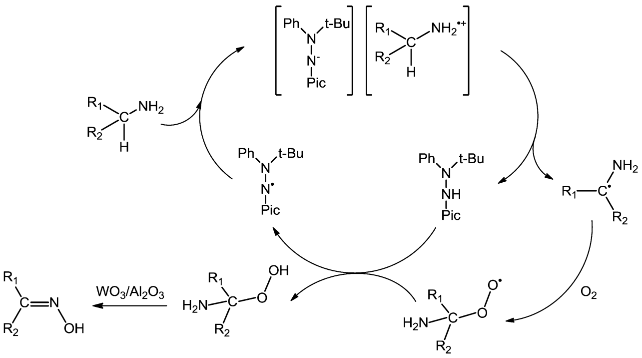
■ OXIMES

The oxidation of cyclohexyl amine to cyclohexanone oxime is, given its industrial importance, well investigated in the academic and patent literature.[15−20] Although this transformation has been widely reported with nonaerobic oxidants, it was not until 1983 that this transformation was reported with molecular oxygen as the terminal oxidant. In their report, Armour et al. demonstrated that a number of SiO_2- and Al_2O_3-supported metal oxides were active for the vapor phase oximation of cyclohexylamine at 150−230 °C.[21] Optimum activity was reached for a catalyst composed of 10 wt % WO_3 supported on Al_2O_3, yielding a selectivity of 64% toward cyclohexanone oxime at 33% conversion. Similar levels of activity and selectivity were also reported for this catalytic system by Kaszonyi et al., who also demonstrated that a Keggin type polyoxometalate (silicotungstic heteropolyacid) was an efficient dopant for Al_2O_3.[22,23] Interestingly, in each of these reports, it was found that both SiO_2 and Al_2O_3 alone were also able to convert cyclohexyl amine to cyclohexanone oxime with O_2, suggesting that a typical redox-based mechanism was not operating under these conditions.

However, though moderate levels of activity and selectivity were achieved in these vapor-phase approaches, some significant disadvantages have to be mentioned. *N*-(cyclohexylidene)-cyclohexylamine and the corresponding ketone were detected as major byproduct; in addition, nitrocycloalkanes, bis-cycloalkyl-amines, and cycloalkenes were observed as trace contaminants of the product stream. The catalyst also deactivated after 3−4 h because of the deposition of high molecular weight tar products.

An alternative approach toward the one-step aerobic oximation of amines was recently considered by Suzuki et al., who investigated the oximation of cyclohexylamine (among other amines) in the liquid-phase.[24] In this case, heterogeneous tungsten on alumina (WO_3/Al_2O_3) was again used, though in combination with an organo-catalyst (1,1-diphenyl-2-picrylhydrazyl, DPPH), to produce cyclohexanone oxime at yields of up to 90% under mild reaction conditions (80 °C, 4 h). Moreover, this system also appears to be applicable to other amine substrates, with cyclic amines (C_5-C_{10}) and even aliphatic amines yielding oximes at high yields (>70%) and selectivity. An important aspect of this catalytic system is its high selectivity toward the amine functional group; in systems comprising two oxidizable groups (e.g., 4-hydroxycyclohexyl amine), chemoselective oxidation yielded the corresponding oxime at over 80% selectivity. A highly selective radical-mediated homogeneous mechanism, producing first the α-aminocyclohexyl peroxyl radical and later α-aminocyclohexyl hydroperoxide, was proposed, with a subsequent heterogeneous transformation of this hydroperoxide yielding the oxime at high selectivity (see Scheme 3).

Scheme 3. One-Electron Transfer Mechanism Proposed for the Oximation of Cyclohexylamine by WO_3/Al_2O_3/DPPH; Adapted from Reference 24



However, this mechanism remains very speculative, especially as very little is known about α-amino-peroxyl radicals in general. Indeed, a recent study combining theoretical modeling and experimental investigations has suggested that the most likely product arising from the aminoperoxyl radical is not α-aminocyclohexyl hydroperoxide, but cyclohexylimine, formed via $HO_2^{\bullet}$ radical elimination.[25] Within this alternative mechanism, the role of the catalyst would be to act as a Lewis acid, thereby facilitating the epoxidation of the intermediate imine with H_2O_2, formed in situ via the elimination of $HO_2^{\bullet}$ and subsequent H-abstraction. The oxazirane would subsequently rearrange to the oxime. In the absence of the WO_3/Al_2O_3 catalyst, cyclohexanone was obtained in 90% yield, thereby demonstrating the crucial role of the solid catalyst in steering the selectivity.

A low temperature liquid-phase oxidation was also investigated by Klitgaard et al.,[26] demonstrating that TiO_2 alone could also catalyze the oximation of cyclohexylamine. However, although oxime selectivities up to 70% were reported at a cyclohexyl amine conversion reaching 16%, the reaction rate was very low and the reaction did not reach completion for 10 days. In view of this poor reactivity, the authors instead proposed an alternative one-step route toward ε-caprolactam via the oxidation of 1,6-hexanediamine by TiO_2-supported gold nanoparticles. However, under optimum reaction conditions (i.e., 90 °C, 2 bar O_2), the ε-caprolactam yield was still very low (≤10%). Later, this alternative route was also explored in the vapor-phase by Rakottyay et al.[27] Though more selective than the liquid phase equivalent, little significant improvement was found for this system when performing reactions in the vapor phase.[27] Trace amounts of butyrolactam, valerolactam, 4-, 5-, and 6-membered Schiff bases, pentanedinitrile, pyridine, tetrahydropyridine, and methyl-5-cyanopentanoate were also observed in the effluent.

■ NITRILES AND IMINES

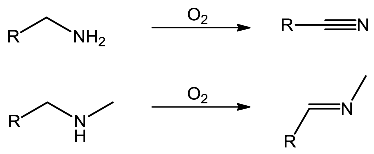
Nitriles are an important class of intermediates that are industrially used for the production of polymers. On a commercial scale, nitriles are typically produced either by the ammoxidation (1) or cyanation (2) of an olefin such as propene or 1,3-butadiene.[28]

$$H_3C{-}CH{=}CH_2 + \frac{3}{2}O_2 + NH_3 \rightarrow NC{-}CH{=}CH_2 \tag{1}$$

$$H_2C{=}CH{-}CH{=}CH_2 + 2HCN \rightarrow NC(CH_2)_4CN \tag{2}$$

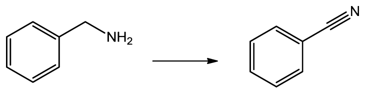
The oxidative dehydrogenation (ODH) of amines (Scheme 4) could offer an alternative route toward these valuable intermediates which avoids dangerous reagents such as HCN. Although it may be expected that secondary amines will dehydrogenate to yield imines, with primary amines being further dehydrogenated to the corresponding nitriles (Scheme 4), the nature of the catalytic system can significantly alter the expected selectivity. Thus, the following section largely focuses on the nature of the catalytic element, as opposed to the particular substrate under investigation, as this determines the observed chemistry to a much greater extent.

Scheme 4. Oxidative Dehydrogenation Routes for Primary and Secondary Amines



Ruthenium Based Catalysts. The dehydrogenation of amine ligands coordinated to transition metal centers is well documented.[29−34] Early reports concerning the oxidative conversion of amines to nitrile species were indeed focusing on the (undesired) oxidative degradation of various transition metal-coordinated amine ligands, such as EDTA. It was at this early stage that the ability of ruthenium to aerobically oxidize amines to the corresponding nitrile species was first reported by McWhinnie et al., describing that upon exposure of a ruthenium(II) hexakismethylamine complex to dioxygen, some of the coordinated amine ligands were irreversibly oxidized under ambient conditions to coordinated nitrile species.[29] The authors concluded that the coordinated amine ligands displayed enhanced reactivity compared to the noncoordinated analogues, thus suggesting that ruthenium-based materials may be suitable catalysts for the oxidation of amines with molecular oxygen. Nevertheless, it was not until the pioneering studies of Tang et al. that a catalytic reaction for the ODH of amines was reported.[35] This group discovered that hydrated ruthenium chloride is an active catalyst for the aerobic oxidation of amines under mild conditions (100 °C, 2−3 atm O_2). Among a number of primary and secondary amines, the best activity was obtained for activated aromatic amines (e.g., benzyl amine, see Table 1), which was fully converted to a mixture of benzonitrile (53% selectivity) and benzamide (30% selectivity), among other byproducts. Unfortunately, the catalyst was found to be poorly selective toward aliphatic nitriles, which were obtained at less than 25% selectivity. In addition, the turnover frequency (TOF; 0.3 h^{-1}) should be improved significantly.

Table 1. Catalytic Activity of Various Ru-Based Catalysts for the Oxidation of Benzylamine

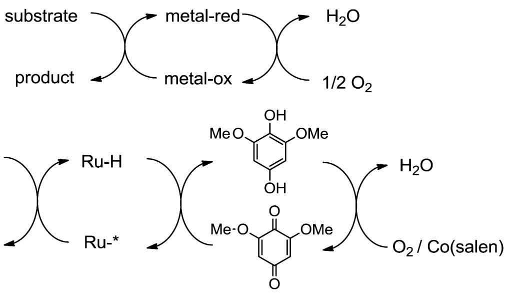


entry	catalyst	metal (mol. %)	TOF[a] (h^{-1})	ref.
1	$RuCl_3$	1.0	0.3	34
2	Ru/HAP	16.9	0.4	45
3	Ru/Al_2O_3	2.8	29	46
4	Ru/Fe_3O_4	3.8	3.0	50
5	Ru/Co_3O_4	1.7	36	51
6	Ru/TiO_2	5.0	1.9	52
7	$[Ph_4(\eta 5\text{-}C_4CO)Ru(CO)_2]_2$	2.0	7.0	42

[a] TOF calculated as "moles of benzonitrile produced per mole of metal per hour".

Following these early studies, a number of homogeneous ruthenium complexes have been reported for the aerobic oxidation of amines.[36−41] Bailey et al. prepared for instance a ruthenium-porphryin complex (*trans*-[Ru(tmp)(O)$_2$]) which converts both aromatic and aliphatic amines to the corresponding nitriles at 100% selectivity at only 50 °C. One of the most elegant homogeneous systems was developed by Bäckvall and co-workers.[42,43] This group utilized a multicomponent coupled system, involving a ruthenium transfer hydrogenation catalyst (the Shvo catalyst),[44] an electron-rich quninone (2,6-dimethoxy-1,4-benzoquinone), a Co(salen) cocatalyst, and molecular oxygen. The authors proposed that this coupled system could overcome the high energy barriers traditionally encountered in oxidation processes by allowing reoxidation of the reduced metal to take place in a series of redox steps (Scheme 5). In this system, the quinone acted as an H-acceptor to the reduced form of the metal, thereby reoxidizing the metal center for a consecutive catalytic cycle. The reduced quinone was subsequently reoxidized by molecular oxygen in the presence of the cobalt(salen) catalyst. However, although the transfer dehydrogenation step with 1.5 equiv of quinone efficiently oxidized *N*-phenyl-1-phenylethylamine to the corresponding imine at a yield of 97% (TOF of 24 h^{-1}), it must be noted that the coupled system (which included reoxidation of only 20 mol. % of quinone) was significantly less active, achieving a TOF of only 7 h^{-1} (88% selectivity).

Scheme 5. Coupled Biomimetic System Employed by Samec et al.; Adapted from Reference 42



However, for large scale, continuous production, heterogeneous catalysts are often preferred. The work of Mori et al., who prepared an active and selective *heterogeneous* ruthenium catalyst for the ODH of amines, may therefore be considered as a major progression in the field.[45] The reported catalyst, a hydroxyapatite-bound Ru^{3+} system (Ru/HAP), was found to be active and selective for the oxidation of a number of primary amine substrates. Although low TOFs were observed, the catalyst was found to be truly heterogeneous (i.e., no leaching of active species into solution could be observed), reusable, and selective to the amine functional group. Indeed, in a competitive oxidation study of *n*-octylamine and octan-1-ol, *n*-octanitrile was exclusively obtained in 91% yield.

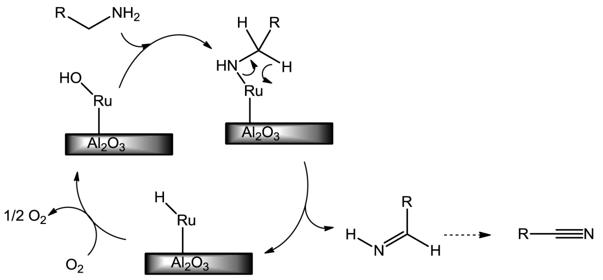
In a seminal series of publications, the group of Mizuno later described supported ruthenium catalysts that were significantly more active for the oxidative dehydrogenation of amines than Ru/HAP.[46−50] Their work initially focused on alumina-supported ruthenium hydroxide ($Ru(OH)_3/Al_2O_3$), which had previously been reported to be both highly active and selective for the oxidation of alcohols.[46] This catalyst managed to oxidize both aromatic and aliphatic amines at TOFs which are more than 60 times higher than Ru/HAP. Although a slightly decreased nitrile selectivity was observed during benzyl amine oxidation (82%), the catalyst also benefitted from significantly decreased metal loadings with respect to Ru/HAP, with only 1.4 wt % ruthenium being sufficient for catalytic activity. By comparison, Ru/HAP was prepared with a metal loading of 17 wt %.[45]

Given the efficacy of the alumina-supported ruthenium catalysts for this reaction, much work has since been performed to determine the most suitable metal oxide support material.[50−52] Although the TOFs decreased by a factor of 10 with respect to the Al_2O_3-analogues (entry 4 in Table 1), supporting ruthenium hydroxide on to a magnetically separable magnetite (Fe_3O_4) support afforded a heterogeneous catalyst that can easily be removed from a batch reactor.[50] Interestingly, this catalyst was also found to be active for the Meerwein−Ponndorf−Verley reduction of carbonyl compounds with a secondary alcohol. This reaction, which can also be considered as an oxidation of the corresponding alcohol, belongs to a category of oxidations known as transfer dehydrogenations, whereby the active oxidant is a stoichiometric quantity of an unsaturated hydrocarbon (typically a carbonyl compound or an alkene). In fact, transfer dehydrogenations have been widely studied for the oxidation of amines, with the iridium-catalyzed oxidation of primary amines by *tert*-butylethylene being a major example.[53,54]

Further work has since revealed that Co_3O_4 is the most efficient support material for ruthenium-catalyzed amine oxidation (entry 5 in Table 1).[51] Under the influence of this catalyst, the oxidation of benzylamine proceeded to benzonitrile in almost quantitative yield (>99% selectivity at 95% conversion) in only 1 h, corresponding to a TOF of 22 h^{-1}. Optimization of the catalyst later increased this value to 36 h^{-1}, establishing a benchmark for benzonitrile synthesis. By varying the catalyst preparation procedure, the authors concluded that hydrated ruthenium oxide ($RuO_2{\cdot}xH_2O$) was the active species, although the interaction between ruthenium and the Co_3O_4 particles was also found to be important. The role of the cobalt was proposed to emanate from its ability to facilitate the regeneration of the active ruthenium species during the catalytic cycle.

Mechanistic Aspects of Ru-Catalyzed ODH. The ability of ruthenium to exclusively oxidatively dehydrogenate primary amines to the corresponding nitriles at high selectivity appears to be almost unique in the literature, and consequently the mechanism has been widely investigated. A nonradical reaction mechanism, involving a series of β-hydride eliminations between the coordinated amine and the ruthenium center has been proposed (Scheme 6). In the case of primary amines, nitriles are thus formed in a two-step process via an intermediate imine species. Secondary amines on the other hand cannot dehydrogenate further because of the finite number of β-hydrogens, and thus the imine is yielded at high selectivity.

Scheme 6. Catalytic Cycle Proposed by Yamaguchi et al.; Adapted from Reference 42

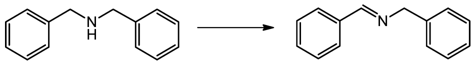


Such a mechanism would also account for the inability of these ruthenium-based systems to directly oxidize tertiary amines; the role of O_2 is to serve as an oxidant to the reduced metal-hydride species, thereby regenerating the catalyst and closing the catalytic cycle. Oxygen is not transferred to the amine, as would be required for the *N*-oxidation of tertiary amines. In fact, the only method of oxidatively converting a tertiary amine under the influence of a ruthenium catalyst involves the preparation of nitriles via oxidative cyanation. Though not a formal oxidation of the nitrogen center, such an approach, first exemplified by Murahashi et al.,[55] is proposed to involve a similar β-hydride elimination mechanism to those proposed for amine ODH. However, it should be noted that given the nature of the substrate (tertiary amine), a free-imine cannot be produced in such a system; instead, the transient imine species formed in situ is nucleophilically attacked by a ^{-}CN anion, to yield an α-amino nitrile species.

Gold Based Catalysts. Following the seminal studies of Haruta et al., the interest in the catalytic activity of gold for selective oxidations has increased exponentially.[56,57] Numerous publications have not only demonstrated that gold is catalytically active for a number of reactions, but also that it is endowed with significant intrinsic activity when it is prepared in such a manner that gold nanoparticles predominate. In particular, the low temperature oxidation of CO,[56] and the oxidation of alcohols,[58] as well as olefins,[59] are topics that have been increasingly reported. Given their high activity and selectivity for various alcohol oxidations, Au-based catalysts have also been explored for the aerobic oxidation of amines.

Imines are highly versatile synthetic intermediates for C-C bond forming reactions and are typically prepared through condensation of an amine with a suitable carbonyl compound.[60] The ability of gold to catalyze the formation of imines via amine ODH was first reported by Zhu et al.[61] It was demonstrated that under relatively mild conditions (100 °C, 24 h, 1 atm O_2), moderate to excellent imine yields could be obtained from various amines over gold powder (entry 1, Table 2). An unusual feature of this process is that contrary to the majority of reports concerning catalysis by gold, bulk gold particles (ca. 10^3 nm in size) were the active species. However, it must be noted that the TOFs for these transformations were incredibly low at only 0.001 h^{-1}, and a substrate/metal molar ratio of 0.04 was required to obtain 64% yield in 24 h. Interestingly, the same bulk-gold system was also active for the oxidative transformations of primary amines to ureas or carbodiimides, with carbon monoxide or isocyanides, respectively.[62] In line with established knowledge, it was later found that supported gold nanoparticles (20−150 nm) were significantly more active than the bulk gold powder (entry 2, Table 2).[63] A key difference between the gold-based systems and those involving ruthenium was exemplified by the observation that primary amines yielded coupled imine products, as opposed to the corresponding nitriles (Scheme 7). To the best of our knowledge, no reports yet describe the full ODH of primary amines to the corresponding nitriles with gold catalysts.

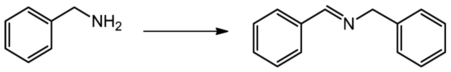
Table 2. Catalytic Activity of Various Au-Based Catalysts for the Oxidation of Dibenzylamine



entry	catalyst	metal (mol. %)	TOF[a] (h^{-1})	ref.
1	Au powder	2540	0.001	61
2	Au/Al_2O_3	12.7	0.3	63
3	$Au(OAc)_3/CeO_2$	1.7	7.2	65
4	$Au(OAc)_3/CeO_2/Fe_3O_4$	1.7	2.2	66
5	$HAuCl_4{\cdot}3H_2O/CeO_2$	1.0	82	67
6	Au/C (activated)	1.0	99	68
7	Au/TiO_2	1.0	3.1	68
8	Au/C (graphite)	5.0	1.1	60

[a] TOF calculated as "moles of dibenzylimine produced per mole of metal per hour".

Scheme 7. Formation of Bimolecular Imines via the ODH of Primary Amines



The use of gold nanoparticles for the aerobic oxidation of secondary amines was concurrently investigated by Baiker and co-workers.[64−67] In this case, both unsupported $Au(OAc)_3$ and supported $Au(OAc)_3/CeO_2$ gold catalysts were used under analogous conditions to those of Zhu et al. A comparison of TOFs reveals however that the acetate-based catalysts were a factor 2-to-3 more active than the alumina-supported Au particles previously reported, and over 7000 times more active than bulk gold.

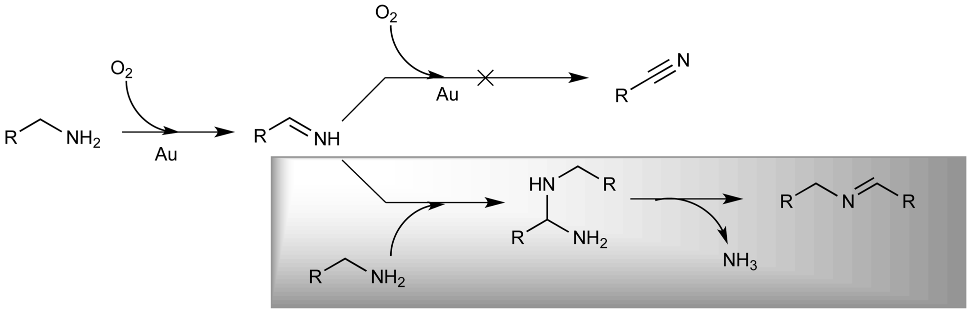
Although gold catalysts are typically formed in dedicated synthesis procedures, the Baiker group subsequently demonstrated that a highly active gold catalyst for the oxidation of secondary amines could in fact be formed without any dedicated synthesis step prior to the reaction.[65] Simply adding the gold precursor ($Au(OAc)_3$) and the support material (CeO_2) to the reaction mixture afforded a highly active heterogeneous catalysis containing gold nanoparticles. The in situ formation of the catalyst afforded a material with superior activity to the analogous preformed materials (entry 3, Table 2). Although straightforward in appearance, a combination of transmission electron microscopy (TEM) and X-ray absorption near edge structure (XANES) spectroscopy revealed that a rather complex catalytic system was in effect during this reaction. Indeed, upon coordination of the amine, gold species were found to leach into the reaction solution, whereupon they were quickly reduced to metallic gold. The nanoparticle gold species were subsequently readsorbed on to the support material, thus yielding the active catalyst in situ. It was therefore concluded that the active species of the reaction was metallic gold species (Au^0), formed in situ via interaction with the amine substrate. The heterogeneous nature of the catalyst was confirmed by hot-filtration studies, and its application to the oxidation of benzylamine, dibenzylamine, and indole clearly demonstrated the broad applicability of the catalyst.

This technique was further explored by the same authors for the synthesis of a highly active and magnetically separable gold catalyst.[66] In this case, the gold nanoparticles formed in situ were deposited onto ceria embedded with superparamagnetic iron oxide (entry 4, Table 2). Although removal of the magnetic catalyst terminated the reaction (thereby confirming the heterogeneous nature of the catalyst), a decrease in conversion of around 5% was observed during each subsequent cycle. It was argued that deactivation during successive catalytic cycles was not due to an inefficient catalyst separation, but typical of gold-based catalysts for these reactions, and that in spite of the straightforward preparation procedure, the magnetically separable catalyst was much more stable against deactivation than those prepared by dedicated preparation procedures. In fact, by examining the literature it is clear that deactivation is a common theme for heterogeneous gold catalysts during amine ODH.[64−66,68] Although leaching is a possible reason for deactivation, each report describes that leached gold species are below the ICP detection limit (∼ppb). A more likely reason for deactivation is sintering of the gold nanoparticles under the influence of the amine at reaction temperature. This can lead to irreversible particle growth and a corresponding decrease in catalytic activity. In fact, severe sintering during the ODH of secondary amines was later reported by Miyamura et al., based on a combined activity-microscopy study.[69]

In a subsequent publication, the in situ synthesis procedure was further extended to a number of additional gold precursors ($Au(PPh_3)_3$, $HAuCl_4$, and $Au(OAc)_3$) and support materials (C, Al_2O_3, TiO_2 and SiO_2).[67] From these investigations, a unique synergy between gold and ceria was concluded as this was the only combination to provide any significant (>5%) activity (entry 5, Table 2). Aurochloric acid ($HAuCl_4{\cdot}3H_2O$) was identified as most suitable gold precursor, and thus a combination of $HAuCl_4{\cdot}3H_2O$ and CeO_2 afforded an in situ prepared catalyst which exhibited TOFs as high as 82 h^{-1} at a selectivity of 87%.

The ability of supported gold nanoparticles to catalyze the formation of dibenzylimine was also investigated by Corma, Garcia, and co-workers.[68] Among a number of TiO_2-supported noble metal catalysts (i.e., Au, Pd, and Pt), the highest TOFs were observed for gold nanoparticles (entry 7, Table 2), which produced the corresponding imine at a selectivity above 90% and TOFs of 3.1 h^{-1}. In spite of this intrinsic activity, the best yield was in fact obtained with the Pt-based analogue, with quantitative yield reached in only 22 h (vs. 30 h for gold). A clear particle size-activity relationship was displayed, as an

Scheme 8. Potential Reaction Pathway for the Production of Imines via Oxidation of Primary Amines over Au-Based Catalysts



exponential increase in catalytic activity was observed with decreasing particle size. However, in spite of its increased average particle size (10 nm vs 3.5 nm), 0.8 wt % Au/activated carbon catalyst was found to be over 30 times more active than the best TiO_2-supported analogue (entry 6, Table 2), clearly demonstrating that particle size effects alone do not account for catalytic activity. An interesting feature of this catalyst was its bifunctionality, as the coupled imine product was reportedly hydrogenated by the same catalyst in a two step, one-pot procedure. This process, which readily yielded the corresponding secondary amine at high yields (98%), provides an alternative and much more selective route toward the *N*-alkylation of amines. Graphite-supported gold nanoparticles (AuNP/C) were also investigated for the aerobic oxidation of amines by So et al.[60] The catalyst, containing 2 wt % gold at an average particle size of 14.5 nm, was found to be active and highly selective for the liquid-phase oxidation of dibenzylamine with bubbled dioxygen or air (entry 8, Table 2). Interestingly, this system was also capable of yielding cross-dehydrogenative coupling products when the oxidation was performed in the presence of a suitable nucleophile.

Mechanistic Aspects of Au-Based ODH. Although Au-based systems are active for the ODH of amines, it is notable that unlike Ru-based systems, they are unable to completely dehydrogenate primary amines to the corresponding nitrile; the process instead stops at the intermediate imine stage (Scheme 8). This seems curious, given that a similar β-hydride elimination mechanism to the one proposed for ruthenium is widely accepted for gold-catalyzed amine and alcohol oxidation.[60,70] It has been proposed that the formation of coupled imines from primary amines either occurs via the condensation of the hydrolyzed intermediate imine and the amine substrate, or more likely via coupling of the imine intermediate and a second molecule of amine, thus forming an intermediate aminal which undergoes NH_3-removal.[63] In either case, the rate of the second dehydrogenation step should be significantly lower for Au than for Ru, allowing condensation or aminal formation to prevail under the reaction conditions. To date however, the exact reasons for this difference have not been investigated.

Alternative Transition Metals. In addition to the more well-studied Au and Ru systems, a number of other transition metals are also able to ODH various amine substrates. In fact, one of the earliest reported transition metal catalysts for the conversion of primary amines into nitriles was described by Kametani et al. It was reported that Cu(I)Cl in pyridine effectively catalyzed the aerobic oxidation of primary amines at ambient temperature to the corresponding nitriles at moderate yields (≤50%).[71] In a subsequent paper, Capdevielle et al. proposed that the interaction between the solvent (pyridine), Cu(I)Cl, and oxygen yielded in situ the active oxidative species, namely, $(pyridine)_4Cu_4Cl_4O_2$, a species that contained two μ-oxo ($-Cu^{II}-O-Cu^{II}-$) moieties at its core.[72,73] This system was subsequently shown to be active for a range of aliphatic and aromatic amine substrates, and in all cases, the corresponding nitrile was obtained at greater than 90% selectivity. However, although a similar selectivity pattern to the ruthenium-catalyzed systems was observed, a fundamentally different reaction mechanism was proposed from both kinetic evaluations and isotope effects. The first step of the reaction was proposed to involve slow one-electron transfer from the amine substrate to the Cu(II) center, thus yielding an aminium radical.[73] This radical subsequently underwent α-proton release to yield an intermediate imine species, which subsequently converted to the nitrile. The proposed radical mechanism was supported by the decreased rate of oxidation upon the addition of radical scavengers. It is important to note that this is in clear contrast to both the gold- and ruthenium-based systems, which are reported to be unaffected by radical scavengers.

This system was also investigated by Maeda et al.[74] During these investigations, it was discovered that by substituting the pyridine solvent for toluene, up to a 12-fold increase in catalytic rate could be obtained for aromatic and aliphatic amine substrates. This investigation also supported the radical-based nature of the catalytic system, and agreed that ammoniumyl and alkylideneaminyl radicals were likely reaction intermediates. However, it must be noted that the nitrile selectivities observed within this report were typically much lower than those reported by Capdevielle, with a maximum selectivity of 75% observed for benzonitrile. In fact, a diminished nitrile selectivity (and a corresponding increase in imine and aldehyde selectivity) is typical of most reports of Cu-catalyzed amine oxidation,[75] and clearly demonstrates the decreased rate of imine dehydrogenation with respect to the ruthenium-catalyzed systems.

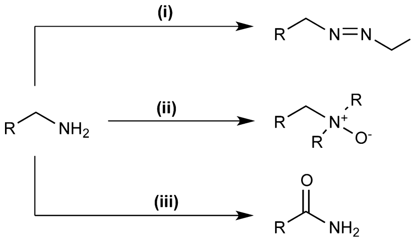
Along with ruthenium, gold, and copper systems, a number of other transition metals have also been investigated for the aerobic oxidation of amines. One of the earliest catalytic systems for the conversion of amines to the corresponding imines was based upon a cobalt Schiff base complex with molecular oxygen.[76] Under optimized reaction conditions, this system was found to dehydrogenate a range of secondary benzylanilines at high selectivity (>80%). Mixed metallophosphates containing vanadium and molybdenum were also found to be active catalysts for the oxidative dehydrogenation of benzylic amines.[77] Similar selectivity patterns to the gold-based systems were observed, with primary amines (e.g., benzylamine) being converted to the corresponding Schiff-base imines with molecular oxygen at 100% selectivity.

Metal organic frameworks (MOFs) are a class of crystalline materials consisting of both metal ions and organic molecules that are joined together into rigid 1-, 2-, or 3-dimensional porous frameworks.[78] Although typically utilized in gas-storage or as adsorbants, MOFs are receiving increasing attention for their catalytic potential.[79−81] As such, the ability of an Fe-based MOF (NHPI/Fe(BTC)) to catalyze the solvent-free aerobic oxidation of amines deserves attention.[82] This catalyst was reported to be active for the oxidation of a number of primary and secondary amines, featuring high imine selectivity (>90%). Although Fe leaching was detected in solution, the crystal structure of the MOF was found intact after the catalytic reaction. Whether the material is also stable under continuous reaction conditions (e.g., in a fixed bed reactor) remains to be examined.

■ OTHER OXIDATIVE TRANSFORMATIONS; N-OXIDES, AZO COMPOUNDS, AND AMIDES

Although significantly less investigated than the oxidative conversion of amines to oximes, imines and nitriles, a number of other important chemicals may also be obtained through oxidation of the nitrogen center (Scheme 9).

Scheme 9. Alternative Oxidative Transformations of Amines

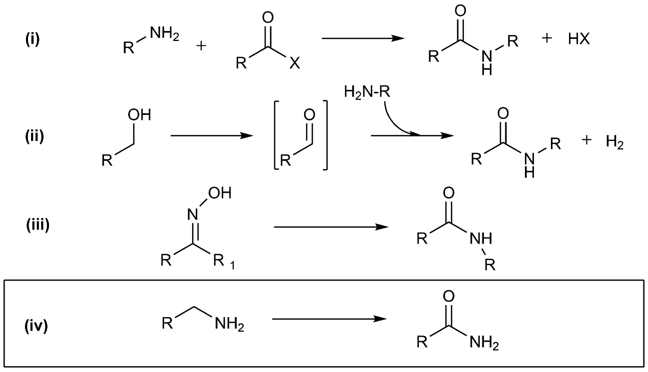


Azo compounds (Scheme 9.i) are highly important components of dyes, pigments, and therapeutic agents. To date, however, there remains few catalytic methods for their preparation in high yields and selectivity.[83] It was recently reported by Grirrane et al. that Au/TiO_2 was able to catalytically convert aromatic anilines to aromatic azo compounds.[84] Unlike traditional synthesis routes, which typically produce large quantities of transition metal or nitrite waste, the gold-catalyzed aerobic route afforded the desired azo compounds at high yields (>98%) under mild reaction conditions (3−5 atm O_2, 100 °C). Furthermore, the catalyst was also able to yield azo compounds directly from nitro-aromatics, via a two-step, one-pot reaction involving the gold-catalyzed reduction of nitro-aromatics with hydrogen. More recently, Zhang et al. demonstrated the Cu(I)Cl/pyridine/O_2 system, pioneered by Kametami et al.,[71] was also able to yield symmetric and asymmetric azo compounds from aniline precursors.[85] A one-electron transfer mechanism between the aniline and the in situ formed copper complex was proposed to initiate the reaction, with the azo compound eventually forming via oxidation of the hydrazine intermediate.

Another important group of amine derivatives are the *N*-oxides (Scheme 9.ii), major components in various domestic, medicinal, and commodity chemicals, and valuable oxidants in fine chemistry.[86] *N*-oxidations are also important industrial procedures, one major example being the *N*-oxidation of acetone imine to acetone azine, a key step in the state-of-the-art process for hydrazine manufacture. Although a number of systems are known to oxidize tertiary amines to the corresponding *N*-oxides,[87−90] very few reports describing catalytic, aerobic *N*-oxidation are available. However, in a series of publications, Jain et al. described the ability of ruthenium ($RuCl_3$)[91] and cobalt (Schiff base complexes) to catalyze the aerobic *N*-oxidation of a variety of tertiary amines. Under the influence of these catalysts, quantitative *N*-oxide yields could be obtained in as little as 6 h, at atmospheric pressure and at room temperature. However, although cobalt Schiff base complexes have been proposed to activate dioxygen, the ability of ruthenium to catalyze this reaction is in contrast to the reports described above, which state that tertiary amines are not oxidized by ruthenium-based catalysts. It must therefore be considered whether this system also involves more reactive oxygen donors via co-oxidation of the organic solvent (dichloroethane).[92] However, it should be noted that although co-oxidation of the organic solvent may be a factor in these systems, recent work by della Pina et al. demonstrated that the aerobic *N*-oxidation of tertiary amines may also be performed in an aqueous medium.[93] In this case, a series of mono- and bimetallic gold catalysts were found to efficiently *N*-oxidize a number of tertiary amines under an aerobic atmosphere. The best activity was found for a 0.5% Au-0.5% Rh/C catalyst, which afforded a quantitative yield of triethylamine *N*-oxide within only 2 h at 90 °C.

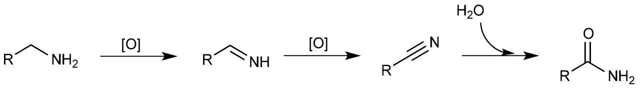
Amides (Scheme 9.iii) are hugely important intermediates within the fields of biology and chemistry, within which they are utilized as versatile synthetic intermediates or raw materials for plastics. Although they are readily prepared by reacting amines with activated carboxylic acid derivatives (Scheme 10.i), this dated chemistry is rather inefficient (cf. low atom efficiency) and limited by additional environmental and toxicity issues. Therefore, there is currently much interest in the development of alternative, sustainable routes for amide production. Alternative routes currently under investigation include the oxidative condensation of alcohols and amines[94−97] (Scheme 10.ii), or the rearrangement of oximes (cf. Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam) to the corresponding amide (Scheme 10.iii). However, the production of stoichiometric quantities of coproducts or poor general applicability have somewhat limited these approaches.

Scheme 10. Potential Routes for the Preparation of Amides



A more preferable route involves the direct oxyfunctionalization of amines to amides (Scheme 10.iv). However, although amides have occasionally been reported as byproduct during amine oxidation, few publications have reported the direct oxidation of amines to amides in high yield or selectivity. This likely emanates from the significantly higher reactivity of the amine functionality over the methylene α-carbon, which necessitates functional-group protection and a significant decrease in atom efficiency. Recent research has, however, developed a promising alternative route for the direct conversion of amines to amides. This process, known as oxidative hydration, involves the hydrolysis of an in situ produced nitrile, in a highly atom-efficient process that produces water as the sole byproduct (Scheme 11).

Scheme 11. Oxidative Hydration of Amines to Amides via Intermediate Nitrile Hydrolysis



Given its rather unique ability to selectively oxidize primary amines to nitriles, it is unsurprising that a ruthenium-based catalyst accounts for the first report of such a transformation. As an extension to their highly efficient ODH catalyst, $Ru(OH)_3/Al_2O_3$, the Mizuno group found that by performing the ODH of primary amines in an aqueous medium, high yields of amides could be obtained under relatively mild reaction conditions (140 °C, 6 h, air oxidant).[98] Mechanistic studies demonstrated that the oxygen atom present in the amide originated from H_2O, and that the amide was thus formed through in situ hydrolysis of an intermediate nitrile. This accounts for the increased reaction times required for good selectivity, as the reported hydration activity of $Ru(OH)_3/Al_2O_3$ is rather poor.[95] However, in spite of the high selectivity reported for certain substrates and catalysts, it must be noted that in general, the reaction was rather non selective, and a mixture of amide, nitrile, aldehyde, carboxylic acid, and imine products were observed. Indeed, the rather poor efficiency of the catalyst was recently exemplified by the same research group, who demonstrated that a manganese-based molecular sieve (OMS-2) was orders of magnitude more selective to amides than $Ru(OH)_3/Al_2O_3$ under similar reaction conditions.[99] Curiously, this catalyst was found to be very poorly selective to amides in the absence of ammonia; it was proposed that ammonia limited the production of the undesirable byproduct, dibenzylimine, which could lead to an irreversible reduction in yield.

PERSPECTIVES AND PERTAINING CHALLENGES

While it is true that a great deal of success has been achieved in recent times toward the aerobic oxidation of organic substrates, it is clear that the aerobic oxidation of amines is far less developed than the corresponding alcoholic substrates. However, it is apparent that many catalytic systems capable of aerobic alcohol oxidation are also applicable to amines substrates. As such, given that the available literature clearly illustrates that the oxidative upgrading of amines offers potentially interesting new sustainable routes to important chemical building blocks, it is likely that interest in selective amine oxidation is to increase over the coming years. In view of this, it is worth highlighting some of the pertinent challenges that remain within this premature field, and set targets for future research.

It is clear from this review that catalyst design has, to date, been the most fruitful focus of investigation. Indeed, great progress has been made toward the design of efficient homogeneous and heterogeneous catalytic systems that can transform amines into a number of important chemical building blocks. In spite of this, it is clear that there is still significant room for improvement; the catalytic efficiencies achieved to date remain quite low (i.e., TOFs), in particular when compared to various alcohol substrates, which in many cases are selectively oxidized at rates many orders-of-magnitude faster than the more reactive amine substrates. Although promising results have also been obtained with monometallic Au, Ru, and Cu-based systems for amine oxidative dehydrogenation, other catalytic elements, for example, Pd, are barely investigated for amine substrates. It may also be desirable to move to bimetallic catalytic systems, particularly given the advancements such systems have provided for alcohol and C-H oxidation, in terms of activity and selectivity. It is also worth noting that in spite of the progress made thus far, there is little understanding over the nature of catalytically active species within these systems. Greater emphasis should be placed on the elucidation of the active components within catalytic system, so that rational catalytic design can be performed based on scientific and not empirical observations.

It is also apparent that significant effort should also be made to reduce the amounts of catalyst, particularly for precious metal based systems. Moreover, many catalytic systems also require cocatalyst, toxic additives, or additional substoichiometric reagents at high (20 mol. %) loadings. This is undesirable from both an economic and an environmental aspect. In addition, attention should be placed on performing the desired reactions under solvent-free conditions, or utilizing oxidatively stable solvents. This could also lead to increased space-time yields, and the prevention of undesirable co-oxidation. However, a significant issue with this goal is overcoming the corrosive nature of amines, which may lead to alternative problems, such as catalyst stability and reactor design.

An additional pertinent challenge involves the mechanistic understanding of the underlying chemistry. Further investigations of the reaction mechanisms through a combination of kinetic evaluations and molecular modeling will also allow for the design of more efficient catalytic systems based on molecular understanding. Key examples are the contrasting reactivities of Ru and Au for primary amine ODH (*why does Au not fully dehydrogenate primary amines to nitriles given the similarly reported* reaction *mechanisms?*), and the radical-mediated oximation of cyclohexyl amine (*should the catalyst be a Lewis acid-based epoxidation catalyst?*). Answering such questions will hopefully accelerate the discovery of novel catalytic materials that afford more satisfying space-time-yields.

A final challenge involves the general applicability of such catalytic systems to substrates other than activated benzylic amines or sterically strained cyclic amines. Additionally, although examples showing the preferential oxidation of amine functional groups over alcohols have been demonstrated, the preferential oxidation of particularly amine groups in substrates containing more than one amine group, or indeed substrates containing multiple functional groups, is potentially the biggest challenge facing this field.

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Author Contributions

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Notes

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