Insights into the Oxidative Dehydrogenation of Amines with Nanoparticulate Iridium Oxide

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Abstract: The aerobic oxidation of amines offers a promising route towards many versatile chemical compounds. Within this contribution, we extend our previous investigations of iridium oxide-catalyzed alcohol oxidation to amine substrates. In addition to demonstrating the versatility of this catalyst, particular attention is focused on the mechanisms of the reaction. Herein, we demonstrate that although amines are oxidized slower than the corresponding alcohols, the catalyst has a preference for amine substrates, and oxidizes various amines at turnover frequencies greater than other systems found in the open literature. Furthermore, the competition between double amine dehydrogenation, to yield the corresponding nitrile, and amine–imine coupling, to yield the corresponding

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coupled imine, has been found to arise from a competitive reaction pathway, and stems from an effect of substrateto-metal ratio. Finally, the mechanism responsible for the formation of *N*benzylidene-1-phenylmethanamine was examined, and attributed to the coupling of free benzyl amine substrate and benzaldehyde, formed in situ through hydrolysis of the primary reaction product, benzyl imine.

Introduction

Selective oxidations are some of the most important processes across all levels of the chemical industry, and they play a vital role in the functionalization of molecules. Nevertheless, in spite of their importance, they remain problematic transformations, from both a mechanistic and environmental point of view.^[1] Typically, selective oxidations are performed with inorganic salts of high-valent transition metals, such as Cr^{VI} or Mn^{VII}, or organic metal-free oxidants, such as the Dess-Martin periodinane or various hydroperoxides. Although allowing for high levels of selectivity, the use of these oxidants is often accompanied by the coproduction of large amounts of organic and/or toxic waste, leaving each oxidant rather undesirable from a sustainable chemistry standpoint.^[2] In recent times, research has, therefore, focused on the development of catalysts and catalytic systems that are capable of selectively oxidizing hydrocarbons with green and atom-efficient oxidants, such as dioxygen and hydrogen peroxide.^[1,3] Nevertheless, achieving sufficient spacetime-yield with these more sustainable oxidants, while maintaining high levels of selectivity, remains a challenge.

In spite of the successes achieved in recent years with regards to the aerobic oxidation of alcohols,^[4] considerably less attention has focused upon the aerobic oxidation of analogous amine substrates. This lack of attention is rather

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 E-mail: ive.hermans@chem.ethz.ch surprising, considering that amines can act as versatile platform molecules for the synthesis of a number of important chemical species, such as oximes, imines, nitriles and azocompounds (Scheme 1).^[5] The development of catalysts that are active for the selective oxidation of amines, in addition to alcohols, is thus a key challenge for the future.



Scheme 1. Some important target molecules that can be obtained through selective oxidation of amines.

Recently, we have shown that a heterogeneous catalyst, comprised of ceria-supported nanoparticulate iridium oxide, is an active catalyst for the selective oxidation of alcohols with molecular oxygen.^[6] The formation of iridium(III) oxide was found to be critical to the function of this catalyst, which was able to oxidize alcohols to aldehydes through cleavage of C–H bonds, in a β -hydride elimination mechanism. Rapid reoxidation of the so-formed metal-hydroxide species was achieved through the efficient transport of O₂ by the collaborative support, CeO₂, which allowed a catalytic cycle to be achieved. Herein, we demonstrate the applicability of this catalyst for the selective oxidation of amines, and pay particular attention to the numerous competing mechanisms possible in this unique case.

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Results and Discussion

Initial amine oxidation studies: Our preliminary studies focused on the aerobic oxidation of benzyl amine, under conditions analogous to those previously employed for the aerobic oxidation of benzyl alcohol (Figure 1).

Figure 1 compares the temporal evolution of conversion for benzyl alcohol and benzyl amine. As can be seen, the se-



Scheme 2. General mechanism accounting for the formation of *N*-benzylidene-1-phenylmethanamine and benzonitrile from benzyl amine.



Figure 1. Temporal evolution of conversion for (A, hollow triangles) benzyl alcohol and (B, filled triangles) benzyl amine. The inset is an expansion of the conversion vs. time profile for the first 30 min of reaction. Reaction conditions: substrate (0.2 M), catalyst (0.5 mol % relative to substrate), O₂ (1 bar), 90 °C.

lective oxidation of benzyl amine proceeds smoothly under the influence of 0.5 wt % Ir/CeO₂, prepared by depositionprecipitation and reduced at 400 °C prior to use (henceforth 0.5Ir/CeO_{2(DP400R)}). In contrast to the selective oxidation of benzyl alcohol,^[6] a typical kinetic profile is observed, which is free from both an induction period and a deactivation mechanism. Therefore, despite being oxidized at a lower initial rate $(6.0 \text{ mmmin}^{-1} \text{ benzyl} \text{ amine converted vs.}$ 9.1 mmmin⁻¹ benzyl alcohol), benzyl amine is quantitatively converted within six hours reaction at 90 °C. In contrast, benzyl alcohol rapidly reaches approximately 50% conversion within one hour, before a severe deactivation process is observed, thereby limiting further conversion. We have previously attributed this deactivation process in the case of aerobic alcohol oxidation to the radical-based by-production of benzoic acid,^[6] and thus do not expect a similar event to poison the catalyst in the case of benzyl amine oxidation. Nevertheless, the lack of deactivation suggests that none of the products formed during the reaction lead to deactivation of the catalyst in this case.

The major product formed (more than 90% selectivity) during the aerobic oxidation of benzyl amine is *N*-benzyli-

dene-1-phenylmethanamine (Scheme 2), although small amounts (ca. 5-10% selectivity) of benzonitrile are also observed, regardless of the conversion level. The presence of benzonitrile can be rationalized by the consecutive oxidative dehydrogenation of in situ formed benzyl imine, with two oxidative steps resulting in the doubly dehydrogenated nitrile. In contrast, the formation of N-benzylidene-1-phenylmethanamine can most likely be attributed to a self-coupling reaction between an unconverted molecule of benzyl amine and the in situ formed imine.^[5] Given that we failed to detect any benzyl imine through conventional chromatographic or mass-spectrometric techniques, we presume that this self-coupling step is much faster than the initial oxidative dehydrogenation process. To date, the mechanism of formation of N-benzylidene-1-phenylmethanamine has not yet been elucidated; this topic is discussed in the second part of the publication.

The observation of *N*-benzylidene-1-phenylmethanamine as the major product further confirms that 0.5Ir/CeO_{2(DP400R)} is much more active for the selective oxidation of alcohols as opposed to amines. Although the initial substrate conversion rate is higher for benzyl alcohol than for benzyl amine (9.1 vs. 6.0 mmmin^{-1}), the conversion rate for benzyl amine is exaggerated by the (homogeneous) removal of one equivalent of benzyl amine through the self-coupling reaction. To gain a better understanding of the activity of this catalyst toward amine oxidative dehydrogenation, we investigated the oxidation of dibenzyl amine, an frequently investigated substrate in the open literature.

As can be seen (Table 1), $0.5Ir/CeO_{2(DP400R)}$ is a remarkably active catalyst for this transformation, and performs

Table 1. Comparison of the catalytic activity of $0.5 Ir/CeO_{2(DP400R)}$ and various reported catalysts for the selective oxidative dehydrogenation of dibenzyl amine.

N N	$\square \longrightarrow \square ^{\times N'}$	
Catalyst	Total TOF [h ⁻¹] ^[a]	Reference
0.5Ir/CeO _{2(DP400R)}	88	this work
HAuCl ₄ ·3H ₂ O/CeO ₂	82	[7]
Au/C (activated)	99	[8]
Ru/Al ₂ O ₃	1.6	[9]

[a] Turnover frequency calculated as moles (*N*-benzylidene-1-phyenylmethanamine) produced per mole (metal) per hour. this reaction at TOFs equal to, or indeed better than, the most active catalysts reported to date. Surprisingly, we observe that the initial TOF (at 15 min) obtained for dibenzyl amine (468 moles dibenzyl amine converted per mole of Ir per hour) is, in fact, higher than those obtained for benzyl amine (360 h⁻¹) under analogous conditions, despite the homogeneous coupling reaction overestimating the TOFs by a factor of two in the second case. We propose that the availability of two β -hydrides, that is, two N–H bonds, accounts for this increased activity. Nevertheless, even compared to this easily oxidized substrate, the TOFs obtained for alcohol oxidation remain higher (significantly greater than 500 h⁻¹).^[6]

Mechanistic studies: Having benchmarked the activity of the catalyst for the aerobic oxidation of amines, we subsequently turned our focus to the elementary reaction mechanism and the overall mechanistic pathway. In particular, several questions prevail: 1) Is the reaction mechanism the same as previously observed for the aerobic oxidation of al-cohols? 2) What is the mechanism of formation of *N*-benzy-lidene-1-phenylmethanamine? 3) Why is it that some catalysts reported in the literature are selective to nitriles, whereas others preferentially form the self-coupled imine?

We previously observed that the aerobic oxidation of alcohols with this catalyst proceeded through a β -hydride elimination mechanism, in which the cleavage of the benzylic C–H bond was rate determining.^[6] Rapid re-oxidation of the metal-hydroxide species closed the catalytic cycle and allowed the relevant aldehyde to be obtained with high selectivity. Key catalytic evidence, namely a zero-order dependence on O₂ concentration (Figure 2), and a first-order de-



Figure 2. Effect of O_2 partial pressure on the initial rate of oxidation of benzyl amine. Reaction conditions: Substrate (0.2 M), catalyst (0.5 mol% relative to substrate), O_2 (1 bar), 90 °C, 15 min.

pendence on catalyst concentration (Figure 3) indicates that the same elementary reaction mechanism is at play in this case. Furthermore, as we previously observed for alcohol substrates, a Langmuir–Hinshelwood relationship between

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Figure 3. Effect of metal molar loading (relative to substrate) on the initial rate of benzyl amine oxidation. Reaction conditions: Substrate (0.2 μ), catalyst (various mol% relative to substrate), O₂ (1 bar), 90°C, 15 min.



Figure 4. Effect of substrate concentration on the initial rate of oxidation for (filled triangles) benzyl alcohol, and (hollow triangles) benzyl amine. Reaction conditions: Substrate, O_2 (1 bar), catalyst (0.5 mol % relative to substrate), 90 °C, 15 min.

amine concentration and reaction rate is also observed in this case (Figure 4). From these experiments, we conclude that the aerobic oxidation of amines proceeds analogously to the aerobic oxidation of alcohols, and a β -hydride elimination mechanism is also prevalent for the reaction investigated herein.

As expected from the initial experiments (Figure 1), it is clear that the aerobic oxidation of benzyl amine proceeds at a lower rate than that of benzyl alcohol, and this is observed at all substrate concentrations investigated. This further confirms that the catalyst is more reactive towards the alcohol substrate. Curiously however, the maximum achievable rate of oxidation (V_{max}) for benzyl amine, albeit lower than the V_{max} for benzyl alcohol, is obtained at a substrate concentration significantly lower than that required for the alcohol (ca. 100 vs. 200 mM, for benzyl amine and benzyl alcohol, re-

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spectively, see Figure 4). This demonstrates that the equilibrium between adsorbed, activated substrate, and the free substrate in solution is more readily achieved with the amine, and suggests that the amine substrate would be more readily coordinated in the case of a competitive oxidation experiment.^[10]

If added amine was poisoning the catalyst, then the initial conversion rate would be expected to decrease again at higher concentrations, that is, a volcano-type plot should be observed. To investigate whether the amine was preferentially oxidized over the alcohol substrate, we subsequently investigated the effect of adding benzyl amine to a reaction solution primarily containing benzyl alcohol.

As can be seen (Figure 5), the addition of even small amounts of benzyl amine leads to remarkable decreases in the rate of alcohol oxidation, confirming that the catalyst preferentially oxidizes the amine substrate in the case of a competitive oxidation experiment. It is likely that the extra basicity of the amine functional group enhances its coordination to the active sites of the catalyst, and thereby prevents those same sites from oxidizing the more weakly coordinating alcohol.



Figure 5. Influence of benzyl amine addition on the initial rate of benzyl alcohol oxidation. Reaction conditions: benzyl alcohol (100 mM), benzyl amine, catalyst (0.5 mol% relative to alcohol), O_2 (1 bar), 90 °C, 15 min.

Investigating the influence of benzyl amine concentration (Figure 6) also provided some insight regarding the ability of some catalysts to selectively oxidize amines to nitriles,^[9,11] whereas others, such as 0.5Ir/CeO_{2(DP400R)} lead to the formation of the coupled imine product.^[6-8,12] By performing reactions at various benzyl amine concentrations, we observed a considerable increase in nitrile selectivity at lower amine concentration (Figure 6). As can be seen, decreasing the concentration of benzyl amine by one quarter leads more selectively to benzonitrile, that is, the doubly dehydrogenated product, increased by a factor of ten, despite the fourfold decrease in conversion.

Clearly, kinetic competition occurs during the reaction, whereby the imine intermediate (Scheme 2) can either be



Figure 6. Effect of benzyl amine concentration on the selectivity towards benzonitrile. Reaction conditions: benzyl amine, catalyst (0.5 mol% rela-

tive to substrate), O₂ (1 bar), 90 °C, 6 h.

further oxidized by the catalyst, thus leading to the corresponding nitrile, or be attacked by a free molecule of benzyl amine (Scheme 3), eventually yielding N-benzylidene-1-phenylmethanamine. The balance between these two steps appears to be dependent on the concentration of free benzyl amine and/or the catalyst. At high amine concentrations (or low catalyst loadings), coupling is favored over the second dehydrogenation step. However, in the absence of sufficient benzyl amine, that is, when the amount of imine and the catalyst surface dominates, consecutive dehydrogenation can take place. It is notable that despite only a fourfold increase in amine concentration (i.e., an increase from 50 to 200 mM benzyl amine concentration), a tenfold decrease in nitrile selectivity is observed. This suggests that the additional amine substrate actively plays a role in displacing the imine intermediate, and greatly enhances the coupling route by releasing benzyl imine into solution.

In the context of the available literature, these observations explain why some catalysts-notably based on Ru^[9,11]— are so selective to nitriles, whereas others—such as Au-based catalysts^[7,8,12]— are primarily selective to the coupled product. To date, most investigations based on Ru catalysts have been performed at low substrate/metal ratios of approximately 20-40, that is, a large amount of catalytic element has been utilized. Under such conditions, the reaction appears to be dominated by the available catalyst surface, and the relative concentration of free amine substrate is low. As such, it is unsurprising that a large selectivity for nitrile products can be achieved. Conversely, most reactions involving Au have been performed at much higher substrate/metal ratios (more than 100). Under such conditions, the relative concentration of free benzyl amine is higher, and thereby the self-coupling route is favored. We note here that for 200, 100, and 50 mm starting concentrations the substrate/metal ratios in Figure 4 are 200, 100 and 50, respectively. The clear increase in nitrile selectivity as the substrate/metal ratio decreases correlates well with this competition. We note that it

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Scheme 3. Competition between oxidative dehydrogenation and self-coupling during the aerobic oxidation of benzyl amine.

is only by investigating this Ir-based catalyst, which produces *both* benzonitrile and *N*-benzylidene-1-phenylmethanamine, that this insight has become apparent.

Mechanism of N-benzylidene-1-phenylmethanamine formation: At this stage, we are still left with the question of precisely how N-benzylidene-1-phenylmethanamine is formed.^[5] To date, two competing pathways for the formation of this product have been put forth (Scheme 4); either the benzyl imine intermediate is directly attacked by benzyl amine, leading to the formation of a hemiaminal intermediate and subsequently the coupled imine, or benzyl imine is hydrolyzed in situ by traces of water; rapid coupling of the amine and aldehyde would then produce the coupled imine product. Nevertheless, although these competing pathways have been proposed, little effort has been expended to elucidate which pathway is dominant. The first indication as to which reaction pathway prevails was provided by the competitive oxidation experiments (Figure 3). During these experiments, we noted that while benzyl alcohol was converted by the catalyst, no free benzaldehyde was detected until all of the amine substrate had also been consumed. This indicates that if benzaldehyde is formed, it is immediately captured by the remaining amine substrate in situ, and rapidly yields the coupled product. Indeed, by stirring a solution of benzaldehyde and benzyl amine at room temperature, *N*-benzylidene-1-phenylmethanamine was detected in quantitative yield within 5 min, clearly demonstrating the efficiency and rate of this reaction.

To further investigate which pathway is responsible and/ or dominant for the formation of N-benzylidene-1-phenylmethanamine, we subsequently investigated the influence of water on the reaction rate and selectivity. By performing experiments in the presence of dehydrated molecular sieves (3 Å Zeolite), we observed a large decrease in the final vield of N-benzylidene-1-phenylmethanamine. This suggested that if the hydrolysis of benzyl imine is inhibited by the removal of water, then the formation of N-benzylidene-1phenylmethanamine proceeds much less smoothly and the reaction becomes trapped at the first step, that is, the formation of benzyl imine. We note that although an increase in benzonitrile selectivity was observed following the addition of molecular sieves, again confirming the competition between oxidative dehydrogenation and coupling, we were still unable to detect any intermediate benzyl imine by conventional chromatographic techniques; however, its absence from the GC-FID/MS spectra could be due to the poor stability of the compounds, rendering typical gas chromato-



Scheme 4. Potential routes for the formation of N-benzylidene-1-phenylmethanamine from the oxidative dehydrogenation of benzyl amine.

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graphic analysis useless. These observations lead us to conclude that pathway A (i.e., hydrolysis of benzyl imine and subsequent coupling of benzaldehyde and benzyl amine) is the dominant pathway for the formation of *N*-benzylidene-1-phenylmethanamine. We note that this conclusion is in full agreement with the recent work of Jones and co-workers, who also observed that the addition of water both accelerated the rate of reaction and increased the maximal yield obtained during the aerobic oxidation of benzyl amine with nonpromoted CeO₂.^[13]

Conclusion

We have demonstrated that ceria-supported iridium oxide nanoparticles are an efficient, heterogeneous catalyst for the aerobic oxidation of amines. Although oxidized at a lower rate than the corresponding alcohol substrates, the greater coordinating power of the amine substrate ensures their preferential oxidation in a competitive oxidation experiment. We have noted that the TOFs exhibited by this catalyst for the aerobic oxidation of dibenzyl amine are among the highest reported in the open literature.

Whereas other catalysts examined for this reaction are typically highly selective towards a single reaction product, uniquely, during the aerobic oxidation of benzyl amine, the catalyst examined herein produces both *N*-benzylidene-1phenylmethanamine and benzonitrile. Due to this peculiarity, we have discovered that two competing pathways act during the aerobic oxidation of amines. At high substrateto-metal ratios the excess of free amine in solution leads to the formation of an imine, *N*-benzylidene-1-phenylmethanamine, through the coupling of free benzyl amine with in situ formed benzyl imine. Conversely, at low substrate-tometal ratios, the reaction is dominated by the available catalyst surface, and benzyl imine undergoes further oxidative dehydrogenation to benzonitrile.

In closing, we have investigated the mechanism of formation of *N*-benzylidene-1-phenylmethanamine and have concluded that its formation is due to the coupling of free benzyl amine and benzaldehyde, formed in situ through the hydrolysis of the primary reaction product, benzyl imine.

Experimental Section

The aerobic oxidation of benzyl amine or benzyl alcohol was performed in a 50 mL round-bottomed flask, which was sealed with a balloon of O_2 or air as appropriate. The flask was charged with the desired amount of catalyst (corresponding to 0.5 mol% Ir relative to substrate) and the reactant solution (0.2 m benzyl amine or benzyl alcohol in toluene, 5 mL total volume). Reactions were performed at 90 °C for 6 h. When appropriate, a mixed solution of benzyl amine and benzyl alcohol was employed, again at a total substrate concentration of 0.2 m. High-pressure experiments were performed in a stainless steel Parr Autoclave (100 mL) equipped with a Teflon liner (working volume 70 mL). Product analysis and quantification was performed by GC-FID/MS analysis (30 m FFAP column) against a biphenyl internal standard.

The catalyst investigated, 0.5Ir/CeO_{2(DP400R)}, was prepared by a deposition-precipitation methodology and fully characterized, as described elsewhere.^[6]

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