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Aerobic oxidation of primary amines to amides catalyzed by an annulated mesoionic carbene (MIC) stabilized Ru complex†

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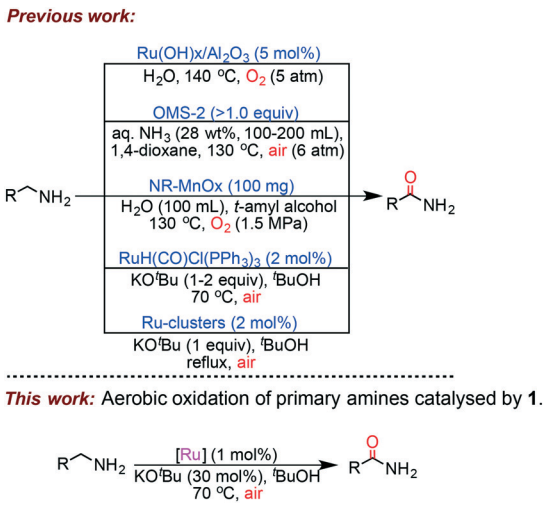
Catalytic aerobic oxidation of primary amines to the amides, using the precatalyst [Ru(COD)(L^1)Br_2] (**1**) bearing an annulated π-conjugated imidazo[1,2-*a*][1,8]naphthyridine-based mesoionic carbene ligand L^1, is disclosed. This catalytic protocol is distinguished by its high activity and selectivity, wide substrate scope and modest reaction conditions. A variety of primary amines, RCH_2NH_2 (R = aliphatic, aromatic and heteroaromatic), are converted to the corresponding amides using ambient air as an oxidant in the presence of a sub-stoichiometric amount of KO^{t}Bu in ^{t}BuOH. A set of control experiments, Hammett relationships, kinetic studies and DFT calculations are undertaken to divulge mechanistic details of the amine oxidation using **1**. The catalytic reaction involves abstraction of two amine protons and two benzylic hydrogen atoms of the metal–bound primary amine by the oxo and hydroxo ligands, respectively. A β-hydride transfer step for the benzylic C–H bond cleavage is not supported by Hammett studies. The nitrile generated by the catalytic oxidation undergoes hydration to afford the amide as the final product.

1. Introduction

The amide functionality is ubiquitous in biological and synthetic structures, such as proteins, polymers, pharmaceuticals, agrochemicals and fine chemicals.[1–7] For example, it is estimated that more than 25% of the available drugs[8] and 2/3 of the drug candidates surveyed in 2006[6] contain amide moieties. The acylation of amines is the most common reaction in the synthesis of pharmaceuticals, constituting approximately 16% of all the reactions performed in this field.[9] Amides are also synthesized by the coupling of carboxylic acids or their activated derivatives with amines or ammonia in the presence of inorganic or organic promoters.[10–21] Beckmann rearrangement of ketoximes is another conventional route to access amides.[22] However, these classical methods are not atom-efficient, employ hazardous reagents and generate copious chemical waste. The development of efficient and environment-friendly synthetic methodologies for amides is identified as one of the key green chemistry research objectives,[23–25] and extensive efforts have therefore been directed to this end.[26–37] The dehydrogenative amidation of alcohol,[26,38–54] amino carbonylation of haloarenes,[55–57] hydroamination of alkynes,[58,59] transamidation of primary amides,[60–63] oxidative amidation of aldehydes,[64–72] catalytic conversion of oximes to amides,[73–77] hydration of nitriles[78–81] and other methods[82–89] have been reported for the synthesis of amides. The direct oxygenation of the α-methylene group of primary amines to produce the corresponding amides is an attractive choice given the ready accessibility of amines through a wide variety of chemical transformations.[90–92] However, the higher reactivity of the $-NH_2$ group as compared to the methylene α-carbon poses a challenge. Further, the oxygenation of primary amines usually requires a stoichiometric amount of



Scheme 1 α-Oxygenation of primary amines to amides.

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different oxidants, for examples, ^{t}BuOOH,[52,93,94] iodosobenzene,[95] RuO_4,[96] MnO_2,[97] H_2O_2,[98] and $PhCO_3{}^{t}Bu$.[99] Using O_2/air as the terminal oxidant for the selective α-oxygenation of amines to amides where H_2O is the only by-product provides a powerful green synthetic alternative. Various heterogeneous catalytic systems, such as, $Ru(OH)_x/Al_2O_3$,[100] Au nanoparticles,[101–103] Au-nanoclusters,[104] PVP-stabilized nanogold,[105] MnO_2-based octahedral molecular sieves (OMS-2),[106] nanorod manganese oxide,[107] Au/Al_2O_3 (ref. 108) and ionic liquid[109] are known in the literature for the aerobic oxidation of amines to amides (Scheme 1). However, in these procedures, the reactions are either performed in an autoclave under pressurized oxygen (5–15 atm) at an elevated temperature (130–160 °C), and/or they are generally limited in substrate scope.

Reports on the direct oxidation of primary amines to amides employing homogeneous systems are scarce. In 2012, Fu and coworkers introduced a copper-catalyzed oxidation of (aryl)methanamines to primary amides using O_2 as an oxidant in DMSO–H_2O.[110] Latter in 2014, Milstein and co-workers reported Ru-catalyzed oxygenation of cyclic amines to lactams (15–85% yields) using water as oxygen atom source at 150 °C.[111,112] Lahiri and co-workers demonstrated the use of $[RuH(CO)Cl(PPh_3)_3]$ for the oxygenation of amines to amides using 1–2 equivalent of base.[113] Recently, Lin *et al.* employed trinuclear ruthenium carbonyl clusters for the aerobic oxidation of benzyl amine derivatives in the presence of 1 equivalent of base in refluxing ^{t}BuOH.[114] However, primary aliphatic amines could not be converted to the corresponding amides by this method. The available homogeneous catalytic methods for primary amine oxidation usually require harsh conditions, and employ high amounts of catalyst and base. Further, the mechanistic scheme offered is often sketchy. Clearly, the pursuit of an efficient and general catalytic protocol for the oxidation of amines using air, an ideal oxygen source, at low catalyst and base loadings is desired in terms of practicality, economic viability and environmental acceptability.

Mesoionic carbene (MIC) ligands are strong σ-donors and form robust transition metal complexes suitable for oxidation chemistry.[115–118] Moreover, annulated carbenes exhibit unique stereoelectronic properties which may result in improved catalytic activity and selectivity of their metal complexes.[119] We earlier reported the use of $[Ru(COD)(\mathbf{L^1})Br_2]$ (COD = 1,5-cyclooctadiene) bearing a fused π-conjugated imidazo[1,2-*a*][1,8]naphthyridine-based MIC ligand ($\mathbf{L^1}$) for catalyzing the oxidative scission of olefin to aldehyde.[120] The chelate-bound annulated MIC ligand was shown to stabilize the metal in higher oxidation state. In our ongoing efforts to widen the use of annulated carbene ligands in a range of catalytic transformations,[121–125] we herein report the catalytic activity of $[Ru^{II}(COD)(\mathbf{L^1})Br_2]$ (**1**) for the aerobic oxidation of primary amines to amides (Scheme 1). Catalyst **1** exhibits excellent activity for the oxidation of a range of primary aliphatic amines, benzyl amines and heteroaryl methanamines using air as an oxidant. Detailed mechanistic studies are undertaken which reveal valuable insight into the oxidation pathway. DFT calculations support a mechanistic proposal that involves abstraction of the two protons and two benzylic hydrogen atoms of the metal-bound amine by the oxo and hydroxo ligands, respectively.

2. Result and discussion

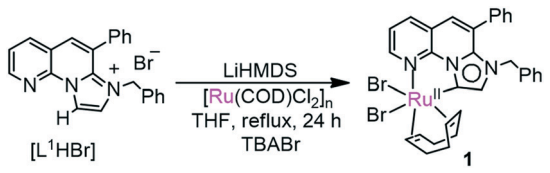
2.1. Synthesis of 1

The reaction of the MIC precursor $[\mathbf{L^1}H]Br$ with $Li[N(SiMe_3)_2]$ followed by 1 equiv of $[Ru(COD)Cl_2]_n$, and subsequent treatment with 1 equiv of $[^{n}Bu_4N]Br$ afforded the complex $[Ru(COD)(\mathbf{L^1})Br_2]$ (**1**) (Scheme 2).[120]

2.2. Catalytic studies

2.2.1. Reaction optimization. The catalytic utility of **1** was evaluated for the aerobic oxidation of amines to amides. An initial experiment using benzylamine (0.5 mmol), KO^{t}Bu (50 mol%) and catalyst **1** (2 mol%) in ^{t}BuOH (2 mL) at 80 °C under air afforded quantitative conversion with benzyl amide in 98% yield after 24 h (see, ESI†). The minor side product is benzonitrile. The use of 1 mol% of the catalyst and 30 mol% of KO^{t}Bu at 70 °C did not alter the product amount and selectivity for the model reaction. A further reduction of the catalyst loading, amount of KO^{t}Bu or temperature diminished the conversion as well as the selectivity. The amide product was not detected when the model reaction was carried out under the nitrogen atmosphere, implying the role of air as the oxidant. No amide product was obtained without the catalyst and the base. Screening of bases and solvents was carried out with the model reaction. Other bases, such as, NaO^{t}Bu, Na_2CO_3, K_2CO_3, Cs_2CO_3, Et_3N, KOH, and NaOH were found to be less efficient in terms of conversion and/or selectivity. Solvents EtOH, ^{i}PrOH, MeOH, toluene, *p*-xylene, DMF, DMSO, dioxane, THF, CH_3CN, EtOAc and $(CH_2)_2Cl_2$ proved to be ineffective. The best reaction condition for the aerobic oxidation of amine to amide, as obtained from the optimization studies, is: catalyst (1 mol%), amine (0.5 mmol) and KO^{t}Bu (0.15 mmol) in 2 ml ^{t}BuOH at 70 °C.

Catalyst screening was conducted with a host of commercially available Ru complexes for the model reaction under the optimized conditions. The results are summarized in Table S2.† Performing the reaction with $[Ru(COD)Cl_2]_n$, which is the precursor to catalyst **1**, afforded poor yield of the benzamide (34%). The previously reported amine oxidation catalyst $[RuH(CO)Cl(PPh_3)_3]$ gave benzamide in 40% yield under the optimized conditions for catalyst **1**,[113] though a higher yield could be obtained by increasing the catalyst and

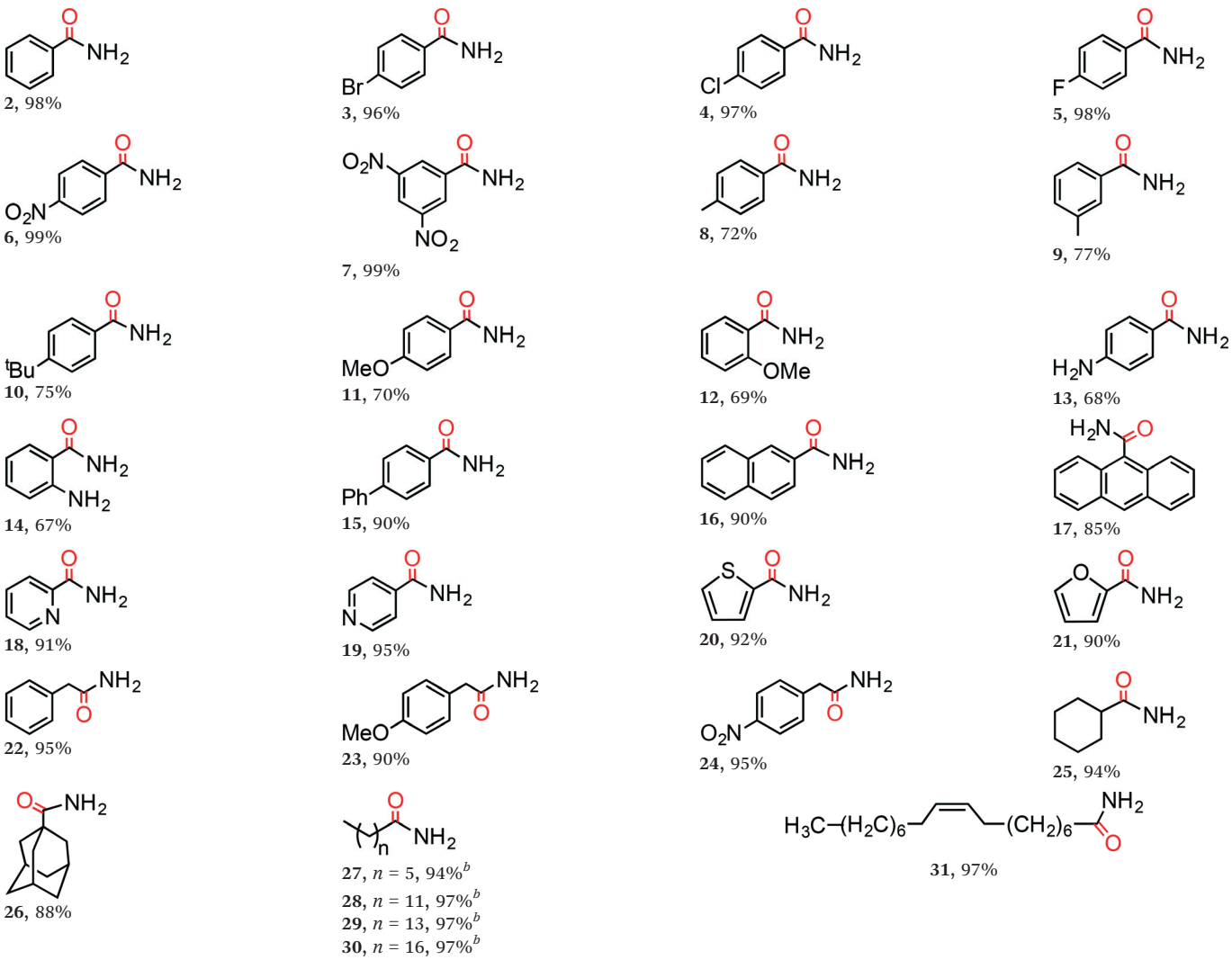


Scheme 2 Synthesis of complex **1**.

base loadings. $Ru(PPh_3)_3Cl_2$ also furnished benzamide in 40% yield. Compounds [Ru(IMe)(η^6-*p*-cymene)$(Cl)_2$] (IMe = 1,3-dimethylimidazol-2-ylidene)[126] and [Ru(py-NHC)$(CO)_2(Br)_2$] (py-NHC = 3-methyl-1-(pyridin-2-yl)imidazol-2-ylidene)[127] afforded benzamide in 40% and 55% yields, respectively. The significantly higher activity of **1** as compared to these Ru–NHC complexes reveals the role of the chelate-bound annulated MIC ligand in stabilizing higher metal oxidation state in catalytic oxidation pathway.

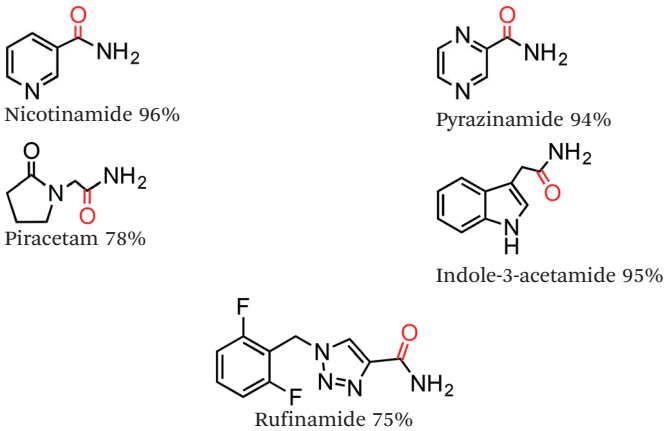
2.2.2. Substrate scope. The substrate scope for **1** was evaluated under the optimized reaction conditions, and the results are summarized in Table 1. Benzylamine afforded benzamide in 98% yield (entry **2**). The presence of electron-withdrawing groups (Br, Cl, F, NO_2) led to excellent yields of the corresponding products (96–99%; entries **3**–**7**). Electron-rich benzylamines gave lower yields (68–77%) of the respective amides (entries **8**–**14**). Notably, benzylamines substituted with OMe and NH_2 groups at the *o*-position (entries **12** and **14**) produced the corresponding amides in similar yields as to their para congeners (entries **11** and **13**), indicating no detrimental steric effect for *o*-substituted substrates. Biphenyl-4-carboxamide was obtained from the corresponding amine in 90% yield (entry **15**). 2-Naphthylmethylamine was oxygenated to the corresponding amide in 90% yield (entry **16**), whereas sterically demanding anthracen-9-ylmethanamine furnished the corresponding amide in 85% yield (entry **17**). (Heteroaryl)methanamines were converted to the corresponding amides in high yields (90–95%, entries **18**–**21**). The oxygenation of 2-phenethylamine afforded a 95% yield of 2-phenylacetamide (entry **22**). Electron-rich 2-(4-methoxyphenyl)ethanamine furnished the corresponding amide in lower yield (90%; entry **23**) as compared to relatively electron-poor 2-(4-nitrophenyl)-ethanamine (95%; entry **24**). The protocol was further

Table 1 Substrate scope[a]



[a] Amine (0.5 mmol), KO^{t}Bu (0.15 mmol) and catalyst **1** (1 mol%) in ^{t}BuOH (2 mL) under aerobic condition at 70 °C, 24 h, isolated yields. [b] GC-MS yield using mesitylene as an internal standard.

Table 2 Bioactive amides[a]



[a] Reaction conditions: amine (0.5 mmol), KO^{t}Bu (0.15 mmol) and catalyst **1** (1 mol%) in ^{t}BuOH (2 mL) under aerobic condition at 70 °C, 24 h, isolated yields.

extended to aliphatic amines. Cyclic aliphatic amine, cyclohexanemethylamine, was converted to cyclohexanecarboxamide in 94% yield (entry **25**). Sterically demanding 1-adamantanemethylamine afforded 88% yield of the corresponding amide (entry **26**). Notably, linear long-chain amines, which are difficult substrates,[114] could be smoothly transformed to the desired products without noticeable differences in yields and selectivity (entries **27–30**). Catalyst **1** selectively oxidized oleylamine to oleamide in 97% yield (entry **31**). The amide product was not detected when the reaction was conducted using a secondary (*N*-methylbenzylamine) or a tertiary amine (*N*,*N*-dimethylbenzylamine) as a substrate.

Further, a few bioactive amides were synthesized under the optimized reaction conditions using catalyst **1** (Table 2). Oxidation of 3-picolylamine produces nicotinamide in 96% yield, which is used to treat skin inflammation.[128,129] Pyrazinamide, a drug recommended for short-course treatment of pulmonary tuberculosis,[130] was obtained in 94% yield from the oxygenation of 2-aminomethylpyrazine. The same protocol was also used to access piracetam (2-oxo-1-pyrrolidineacetamide), a medicine that belongs to the category of cognitive enhancers.[130] Indole-3-acetamide, a plant metabolite, was synthesized from the oxygenation of tryptamine. Antiepileptic drug rufinamide, which is suggested as an adjunctive seizure medicine for children and for adults with the Lennox–Gastaut syndrome, was also synthesized in 75% yield.[131–136]

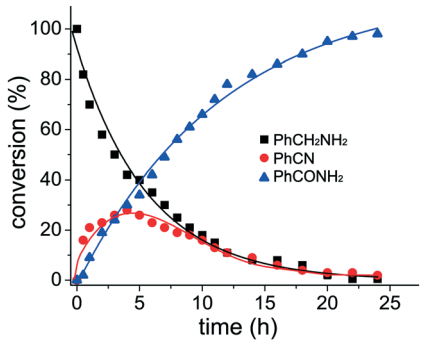


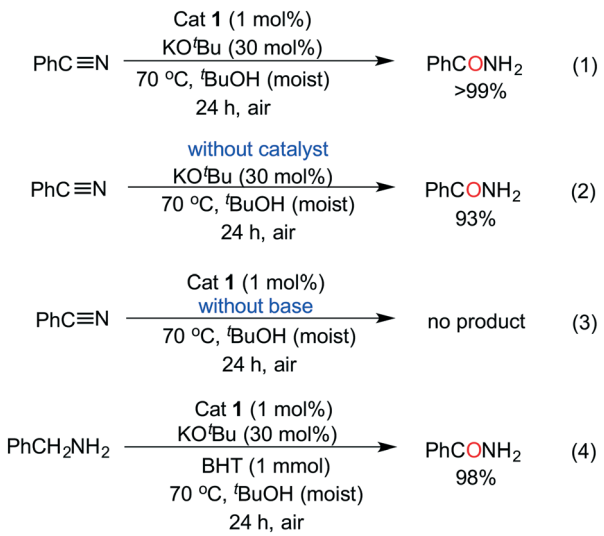
Fig. 1 Time–conversion plot of the oxidation of benzylamine.

2.3. Mechanistic studies

2.3.1. Reaction profile. The progress of the reaction was monitored by GC-MS under the optimized conditions using benzylamine as the model substrate (Fig. 1). The amount of benzylamine decreased gradually with time, and simultaneously, the amounts of benzonitrile and benzamide increased. The amount of benzonitrile reached a maximum (~25% of the starting material) after 4.5 h and decreased afterward. After 24 h, quantitative conversion of benzyl amine is observed with benzyl amide in 98% yield. This time–conversion profile suggests that benzonitrile is formed as a reaction intermediate, which hydrolyzes to give benzamide in the presence of a base.

2.3.2. Control experiments. A stoichiometric reaction of complex **1**, benzylamine and KO^{t}Bu (1 : 1 : 0.5 molar ratio) in ^{t}BuOH was carried out at 70 °C for 24 h under air. The reaction mixture was then filtered and all the volatiles were removed. The acetonitrile solution of the residue was subjected to ESI-MS analysis, which showed a signal at *m*/*z* 598.0180 (*z* = 1) corresponding to $[Ru(\mathbf{L^1})Br(CH_3CN)_2]^+$. The presence of metal-bound $\mathbf{L^1}$ after completion of the reaction suggests that the molecular integrity of the catalyst is maintained throughout the catalysis.

To probe the intermediacy of a nitrile, a set of control experiments was carried out. The results are summarized in Scheme 3. Subjecting benzonitrile to the standard catalytic conditions in moist ^{t}BuOH led to a quantitative formation of benzamide (Scheme 3, reaction 1). The same reaction



Scheme 3 Control experiments.

afforded 93% yield of the product in the absence of the catalyst (reaction 2), indicating the metal-free hydration of nitriles.[85] No product was obtained without the base (reaction 3). The conversion and selectivity were not affected when the reaction was carried out in the presence of 1 mmol BHT (reaction 4), possibly ruling out the involvement of any radical intermediate in the catalytic pathway.

2.3.3. Kinetic studies. The initial rate of the reaction (up to <10–15% conversion) was monitored to determine the reaction order with respect to catalyst **1**, amine and KO^{t}Bu. The initial rate varied linearly with [**1**] and [benzylamine] (Fig. 2a and b). Increasing [KO^{t}Bu] did not affect the rate of reaction and followed a zero-order kinetics (Fig. 2c). Accordingly, a rate law was established as shown in eqn (1). The results suggest the involvement of one molecule of benzylamine and catalyst **1** each in the reaction intermediates.

$$\text{rate} = k_{obs}[\text{catalyst}]^1[\text{amine}]^1[\text{KO}^t\text{Bu}]^0 \quad (1)$$

2.3.4. Eyring plot. The effect of temperature on the rate of benzylamine oxygenation catalyzed by **1** was also studied and the activation parameters were calculated from the plot of $\ln(k/T)$ *versus* $1/T$ (Fig. 3). The estimated entropy of activation ($\Delta S^{\ddagger}$) is −24.34 ± 0.84 cal mol^{-1} K^{-1}, and the enthalpy of activation ($\Delta H^{\ddagger}$) is 15.61 ± 0.60 kcal mol^{-1}. A negative $\Delta S^{\ddagger}$ value is indicative of an ordered transition state in the catalytic pathway.

2.3.5. Hammett study. The initial rates of the reactions of electronically varied *para*-substituted benzylamines (p-$YC_6H_4CH_2NH_2$; Y = OMe, Me, H, F, Cl) under optimized conditions were measured. A plot of relative rates $\log(k_X/k_H)$ *versus* substituent constant (σ) gave a fairly good linear relationship with a ρ value of +2.28 (Fig. 4). The positive ρ value

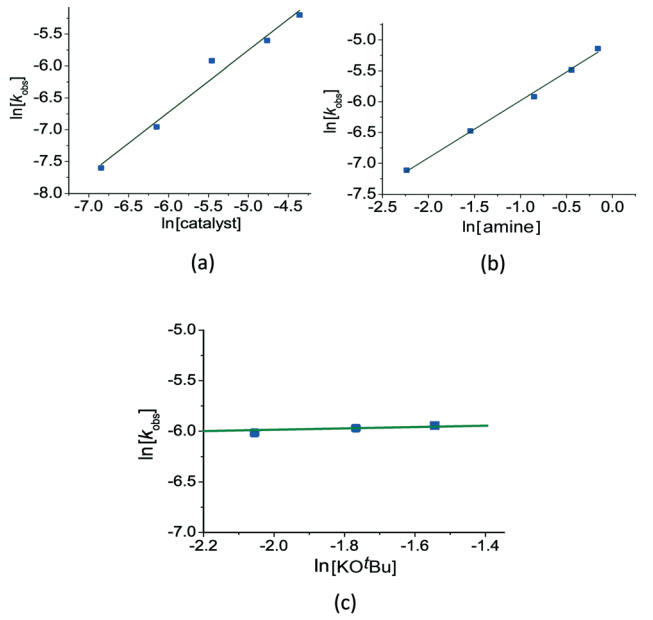


Fig. 2 $\ln[k_{obs}]$ *vs.* (a) [**1**], (b) [amine], and (c) [KO^{t}Bu].

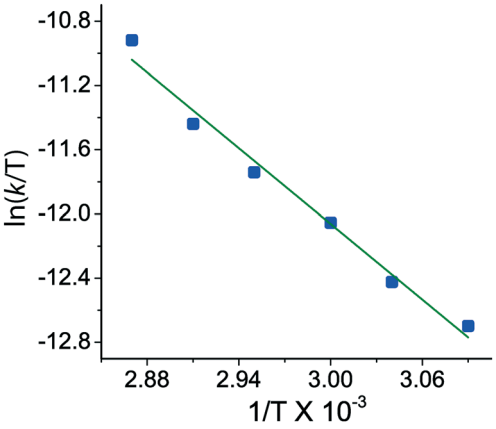


Fig. 3 Eyring plot for the oxidation of benzylamine with catalyst **1**.

shows that the electron-donating substituents should decrease the rate of the reaction, which is consistent with the results discussed in the substrate scope. In contrast, Yamaguchi and Mizuno reported a linear relationship of $\log(k_X/k_H)$ *versus* Brown–Okamoto σ^+ constant for the oxidative dehydrogenation of amines over RuO_2/Al_2O_3 catalysts. A ρ value of −0.154 obtained in this case suggested a carbocation-type intermediate involved in the rate-determining step (rds).[137] Further, a smaller ρ value indicated a weak electronic effect. In a related continuous flow system, Fehrmann and coworkers reported a linear relationship between $\log(k_X/k_H)$ and the Hammett σ constants with a ρ value of −1.04.[138] For catalyst **1**, a linear relationship between $\log(k_X/k_H)$ with the Hammett σ constants with a ρ value of +2.28 suggests the development of partial negative charge at the α-carbon atom adjacent to the phenyl ring in catalytic pathway.

2.3.6. KIE study. The kinetic isotope effect (KIE) was obtained by comparison of the initial rates of oxidation of $PhCH_2NH_2$ and $PhCD_2NH_2$, and the value of k_H/k_D = 2.9 ± 0.04 (Fig. 5). This result indicates that the removal of the benzylic hydrogen atom is involved in one of the slow steps of the reaction.

2.3.7. Proposed reaction mechanism. A mechanism is proposed based on the controlled experiments, kinetic studies and literature precedents (Scheme 4).[113,139,140] Initially, the reaction of the precatalyst **1** with molecular oxygen in air generates the active catalytic Ru–oxo species, **A**.

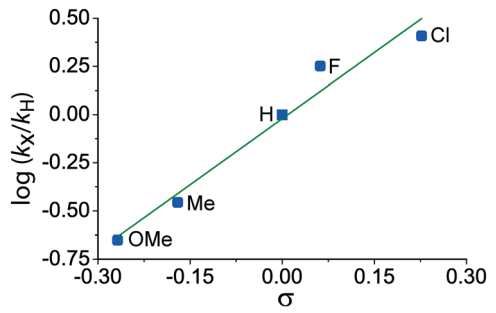


Fig. 4 Hammett plot for the comparative oxidation of benzylamine and *para*-substituted derivatives catalyzed by **1**.

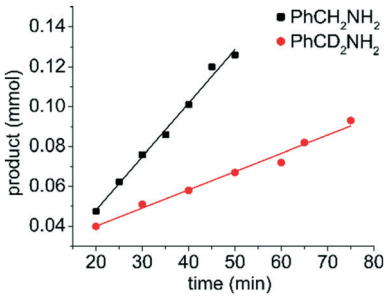
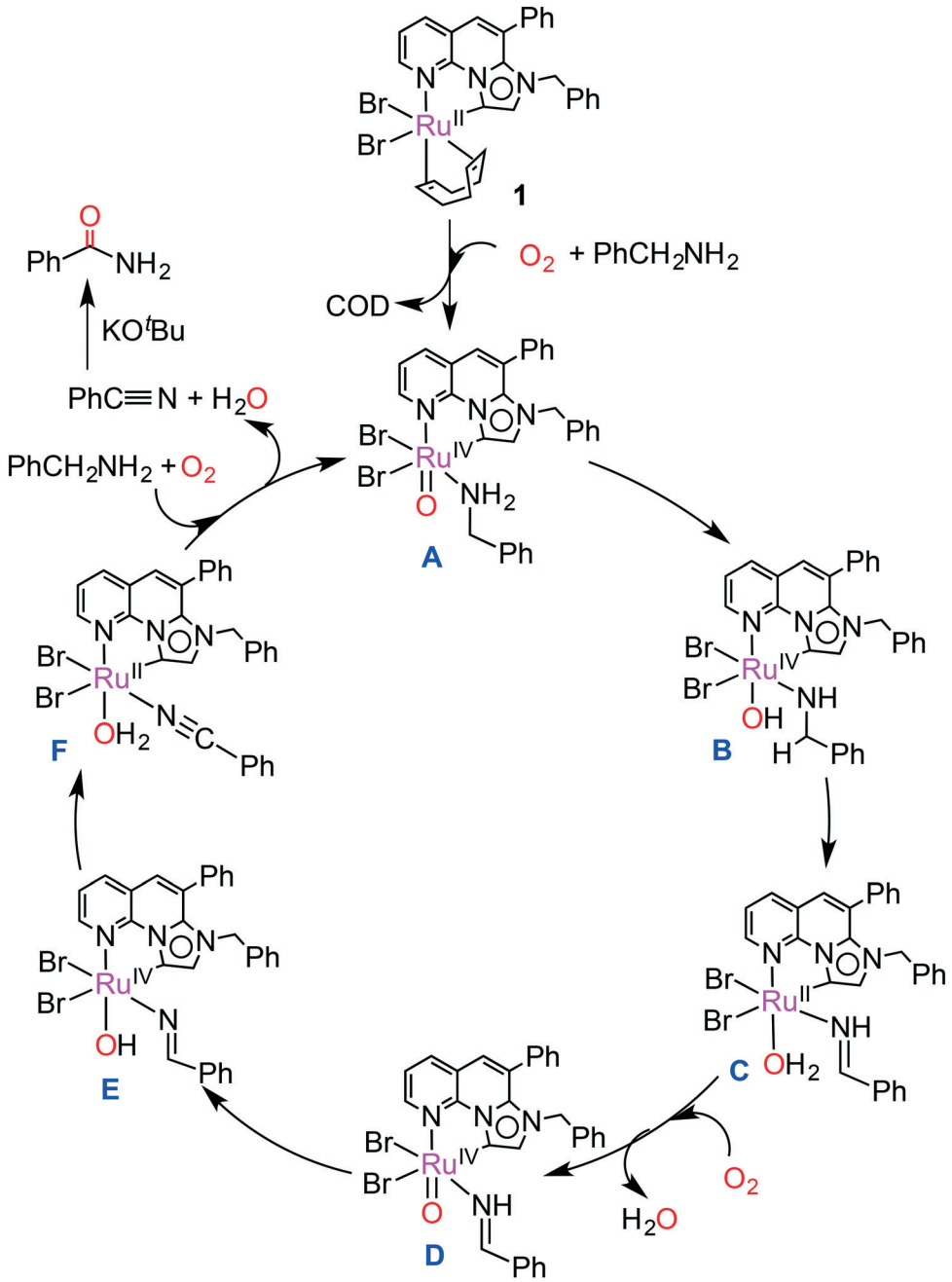


Fig. 5 Product formation plot for the oxidation of $PhCH_2NH_2$ and $PhCD_2NH_2$.

The loss of COD in the process provides a vacant site for binding of the amine substrate to the metal center. The formation of the Ru^{IV}=O in the presence of oxygen is precedented and such Ru–oxo complexes have been widely invoked as active species in the oxidation catalysis.[113,141–144] To substantiate this proposal, oxygen gas was passed through a solution of catalyst **1** in CH_3CN at room temperature for 30 min. The ESI-MS spectrum of the resultant reaction mixture exhibits a signal at *m*/*z* 573.9969 corresponding to $[Ru(\mathbf{L^1})Br(O)(CH_3CN)]^+$. The FT-IR spectrum of this mixture shows a new absorption at 808 cm^{-1} for ν(Ru=O) (see, ESI†),



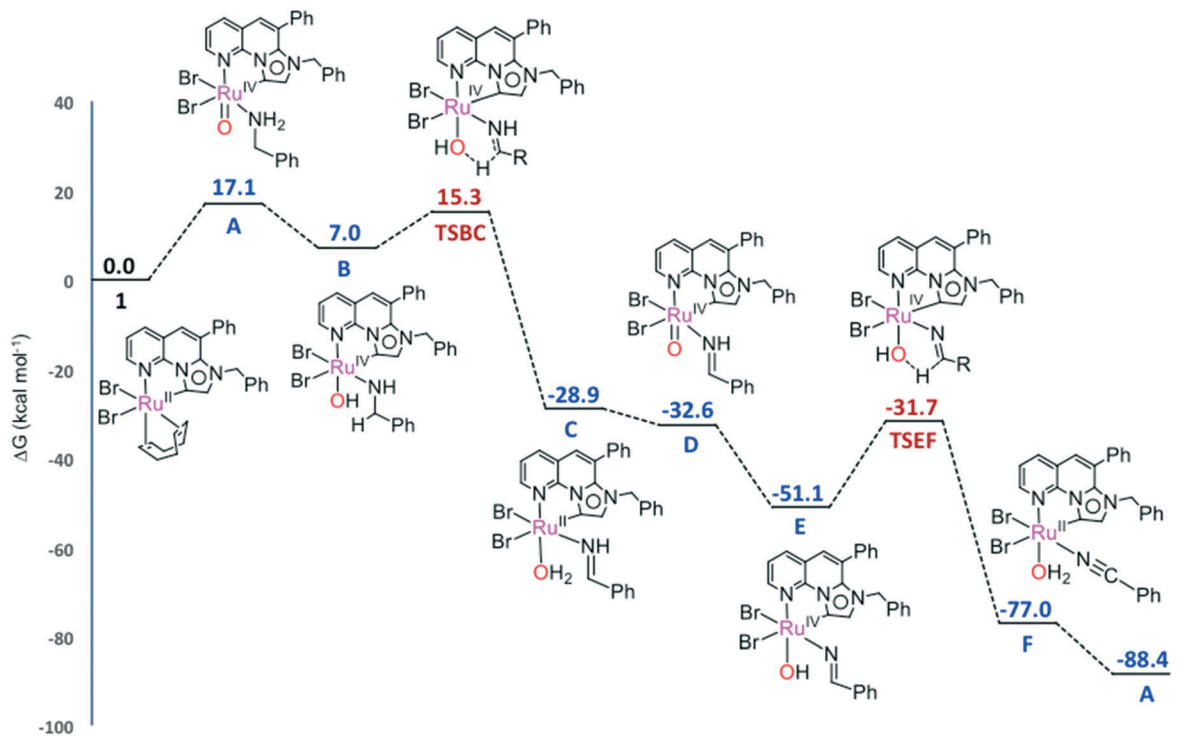
Scheme 4 Proposed mechanism for the α-oxygenation of amine to amide catalyzed by **1**.

strongly suggesting the formation of species **A** in the presence of amine. A proton is transferred from the coordinated amine to the oxo ligand in **A** to form the Ru–amido intermediate **B**.[113,145] Next, the metal-bound –OH group abstracts the benzylic hydrogen atom to form an imine-coordinated intermediate **C**. Fehrmann demonstrated similar benzylic hydrogen abstraction of amine by the hydroxide groups present on the surface of the RuO_2/Al_2O_3 catalysts.[138] The intermediate **C** is then reoxidized by dioxygen to give **D** with the elimination of a water molecule.[146] A proton is transferred from the coordinated imine to oxo ligand forming a Ru–imido intermediate **E**. Subsequently, the abstraction of second benzylic hydrogen atom from the imido ligand (–N=CH–Ph) gives intermediate **F**. The nitrile is then released and **A** is regenerated by reacting with oxygen and amine completing the cycle. The overall catalytic cycle shows the elimination of two water molecules, which promote the hydration of nitrile to amide under the basic reaction conditions. Although the reaction of the coordinated or free imine PhCH=NH with the amine substrate to form $PhCH_2N{=}CHPh$ as a side-product is a possibility, this process does not appear to be favored in the present catalytic system.

An alternative mechanism could be proposed that involves direct β-hydride transfer to the metal. Lahiri proposed a β-hydride elimination step of the Ru–amido intermediate giving a Ru–H species during catalytic oxygenation of amines using $[RuH(CO)Cl(PPh_3)_3]$ as precatalyst.[113,147] A similar step was also invoked in catalytic oxidations at the surface of supported Ru catalysts.[137,139,140] However, it is unlikely for catalyst **1** given the results of the Hammett study. It is reasonable to expect that the β-hydride transfer step would develop a positive charge on the α-carbon, so that the rate of the reaction would be diminished with electron-poor benzylamines, which is in line with the observations made in the above examples.[137,139,148] The Hammett study for **1**, however, reveals a contrasting behavior where electron-withdrawing substituents accelerate the rate of the reaction. Hence, the β-hydride transfer step can be ruled out in this case.

2.3.8. DFT studies. To corroborate the proposed mechanism, DFT calculations were performed for the **1**-catalyzed oxygenation of benzylamine as a model reaction. The free energy profile of the catalytic cycle is given in Scheme 5 and the optimized structures of all intermediates and transition states are provided in the ESI.† The calculations were performed using M06 hybrid meta-GGA functional.[149] LanL2DZ basis set by Hay and Wadt with effective core potentials[150] was used for Ir and 6–31+G(d,p) basis set was used for other atoms.[151,152] Technical details of the computations are provided in the experimental section.

The formation of **A** from **1** is an endothermic process (ΔG = 17.1 kcal mol^{-1}), whereas the proton transfer step (**A** → **B**) is thermodynamically downhill (ΔG = −10.1 kcal mol^{-1}). The transition state for **B** → **C** (**TSBC**) involves an intramolecular hydrogen transfer from the benzylic position of the primary amine to the metal-coordinated –OH group. The Gibbs free energy barrier for this step is 8.3 kcal mol^{-1}. This is followed by the formation of a second Ru–oxo species **D**. The second proton transfer (**D** → **E**) is also thermodynamically facile (ΔG = −18.5 kcal mol^{-1}). The subsequent hydrogen abstraction



Scheme 5 Free energy profile for the α-oxygenation of amine to amide catalyzed by **1**.

from the benzylic position of the metal-coordinated imido group proceeds *via* **TSEF** and involves a Gibbs free energy barrier of 19.4 kcal mol^{-1}. Species **A** is then regenerated from intermediate **F** by reaction with O_2, which is a thermodynamically downhill step. A comparison of the free energy barriers for **B** → **C** and **E** → **F** indicates that the second hydrogen abstraction is the slower step. Nevertheless, both steps involve the breaking of benzylic C–H bond. Overall, the proposed mechanism is thus consistent with KIE results, control experiments and kinetic studies, which is further supported by DFT calculations.

3. Conclusions

A Ru(II)–MIC complex was employed for catalyzing the oxygenation of primary amines to amides using ambient air as an oxidant in the presence of a sub-stoichiometric amount of base. The complex is found to be an excellent catalyst for the aerobic oxidation of a library of primary aliphatic amines, benzyl amines and heteroaryl methanamines in high yields and with excellent selectivity. The transformations are clean and do not produce unwanted byproducts. Mechanistic studies indicated the formation of nitrile as the reaction intermediate, which hydrolyzes to amide under the reaction conditions. The two amine protons and two benzylic hydrogen atoms of the metal-bound amine are abstracted by the oxo and hydroxo ligands, respectively. A β-hydride transfer to the metal is ruled out for the breaking of the C–H bond on the basis of Hammett studies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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