

PAPER

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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)(L¹)Br₂] (**1**) bearing an annulated π -conjugated imidazo[1,2-*a*][1,8]naphthyridine-based mesoionic carbene ligand L¹, 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, RCH₂NH₂ (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^tBu in ^tBuOH. 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.

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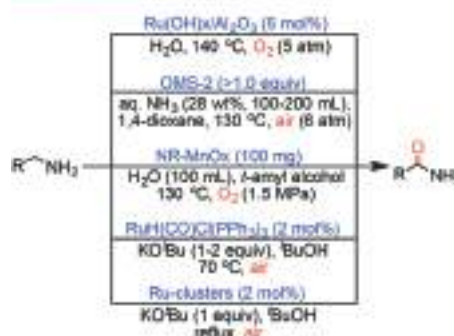
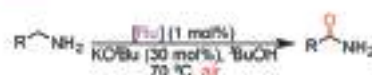
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1. Introduction

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 drugs⁸ and 2/3 of the drug candidates surveyed in 2006⁶ 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 –NH₂ group as compared to the methylene α -carbon poses a challenge. Further, the oxygenation of primary amines usually requires a stoichiometric amount of

Previous work:

This work: Aerobic oxidation of primary amines catalysed by **1**.Scheme 1 α -Oxygenation of primary amines to amides.Department of Chemistry and Centre for Environmental Sciences and Engineering,
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