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C_α–H Oxidations of Amines to Amides: Expanding Mechanistic Understanding and Amine Scope through Catalyst Development

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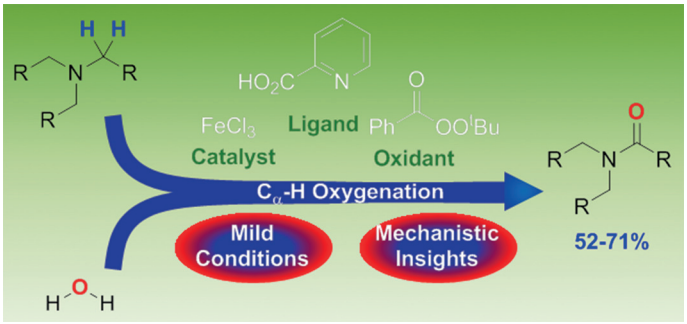


Received: 21.03.2016
Accepted after revision: 21.04.2016
Published online: 13.05.2016
DOI: 10.1055/s-0035-1561863; Art ID: st-2016-p0199-sp

Abstract This highlight provides a general overview of C_α–H oxidations of amines to form amides. Initial as well as recent examples are reviewed with a particular focus on existing challenges regarding substrate scope and reaction conditions. Finally, one very recently established catalyst system is described in detail which achieves the iron-catalyzed, C_α–H oxidation of amines under mild conditions.

1 Introduction
2 First C–H Oxygenations
3 State of the Art: Oxidations of Primary, Secondary, Cyclic, Benzylic, and Aromatic Amines
4 General Iron-Catalyzed C–H Oxidations under Mild Conditions
5 Conclusions

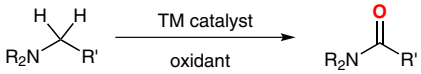
Key words amides, catalysis, iron, oxidation, amines, biomimetic synthesis

1 Introduction

Amide substructures can be found in a wide variety of chemical target compounds, such as pharmaceuticals, natural products, and materials (e.g., in nylons) that are critical to our society. Although many well-established synthetic methodologies exist that afford amides,[1] the majority of these protocols suffer from shortcomings such as low atom economies, harsh conditions, and the generation of stoichiometric amounts of chemical waste. These deficiencies have not gone unnoticed in the pharmaceutical industry, which heavily relies on amide syntheses. Thus, several of the world's largest pharmaceutical companies participating in the ACS Green Chemistry Roundtable have called for research to discover more efficient — preferably catalytic — methodologies for amide formations and define it as one of the most important and challenging problems in the industry.[2]

Marion H. Emmert received her PhD from the University of Münster (Germany) working with Gerhard Erker on model compounds for zirconium-based polymerization catalysts. Following postdoctoral work at the University of Michigan with Melanie Sanford as a DFG (German Research Foundation) and NSF CCI CENTC postdoctoral fellow, she joined the faculty at Worcester Polytechnic Institute in 2011 as assistant professor of chemistry, with joint appointments in Materials and Chemical Engineering since 2012. Her research interests focus on the development of sustainable reactions and processes. Current projects include nondirected C–H functionalizations, aerobic oxidations at low oxygen concentrations, catalyst development for biomass deconstruction, and recovery processes for rare-earth materials.

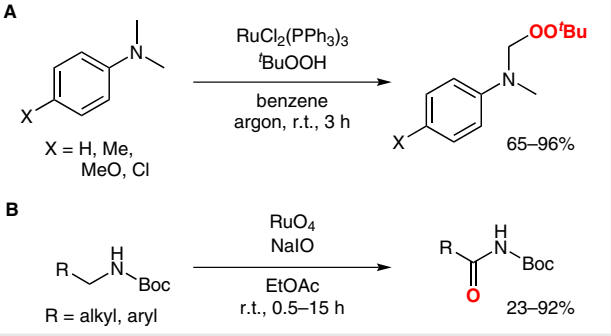
As an alternative to classical coupling reactions, transition-metal-catalyzed C–H oxidations have recently been employed for the synthesis of amides. This approach is highly attractive due to the inherently high atom economies that are possible (Scheme 1) when employing sustainable oxidants (e.g., O_2 or air).



Scheme 1 Transition metal (TM)-catalyzed C_α–H oxidation of amines to form amides

2 First C–H Oxygenations

Methodologies for transition-metal-catalyzed, high-yielding C_α–H oxygenations of amines were first reported by Murahashi and coworkers.[3,4] These systems typically utilize ruthenium catalysts to achieve methyl C_α–H oxidation and are effective at oxidizing aniline derivatives (Scheme 2,A). In the same year (Scheme 2,B), a ruthenium-catalyzed oxidation of *tert*-butoxycarbonyl (Boc)-protected primary amines was reported (Scheme 2,B).[5] Although these early examples did not result in direct amide formation, they pioneer new procedures for amine C_α–H oxidation and established that it is feasible to oxidatively install C–O bonds in these positions.

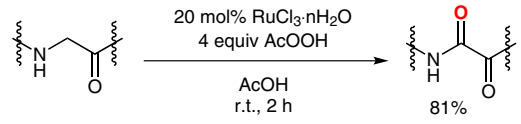


Scheme 2 Early ruthenium-catalyzed C_α–H oxidations

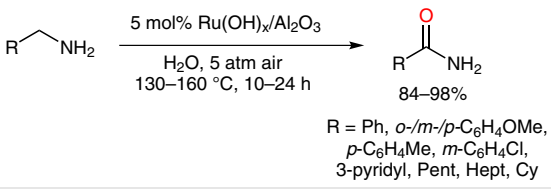
An even earlier example of the C_α–H oxidation of amines has been reported using the Gif IV oxidation system ($FeCl_3$, Zn, pyridine, O_2) and achieves formation of amides.[6] However, in contrast to the Murahashi system, the obtained yields are very low (<15%) and the oxidations do not proceed chemoselectively, providing side products of methylene oxygenation.

3 State of the Art: Oxidations of Primary, Secondary, Cyclic, Benzylic, and Aromatic Amines

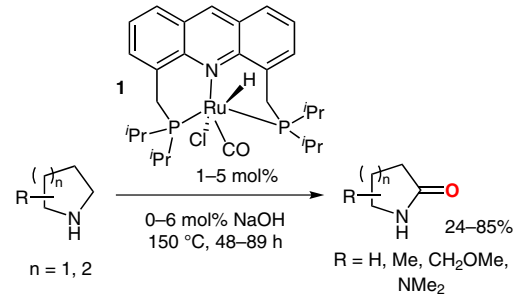
In more recent years, significant progress has been made in an effort to establish efficient, transition-metal-catalyzed amide syntheses; however, many of the known methodologies have significant limitations. Examples for this are the use of expensive transition-metal catalysts based on ruthenium[7–9] or gold.[10] For example, $RuCl_3$ has been employed in the C_α–H oxidation of glycine residues for peptide backbone modification (Scheme 3).[7] This methodology affords high amide yields, but only one substrate type can be oxidized. Other protocols use supported, heterogeneous catalysts [$Ru(OH)_x/Al_2O_3$; Scheme 4][8] or a pincer-type ruthenium catalyst **1** (Scheme 5).[9] Although more versatile than $RuCl_3$-catalyzed reactions, these methodologies also suffer from relatively narrow substrate scopes (primary aryl amines and secondary cyclic amines, respectively). Lastly, both systems require high temperatures.



Scheme 3 $RuCl_3$-catalyzed glycine-selective C_α–H oxidation of peptide backbones

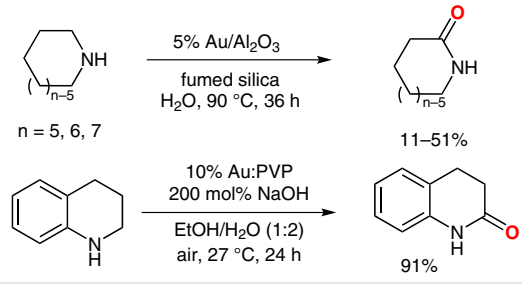


Scheme 4 $Ru(OH)_x/Al_2O_3$-catalyzed C_α–H oxidation of primary amines



Scheme 5 C_α–H oxidation of cyclic secondary amines catalyzed by ruthenium pincer complex **1**

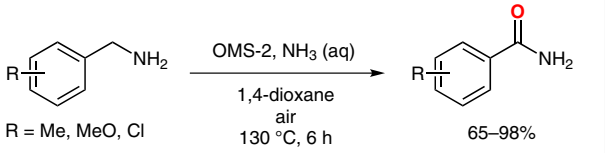
Generally, gold-catalyzed amine C_α–H oxidations require lower temperatures, but even these protocols are limited by their ability to oxidize only cyclic secondary amines (Scheme 6).[10,11] Furthermore, these methodologies employ heterogeneous catalysts whose rational optimization based on mechanistic studies is more challenging that in homoge-



Scheme 6 Gold-catalyzed C_α–H oxidation of cyclic secondary amines

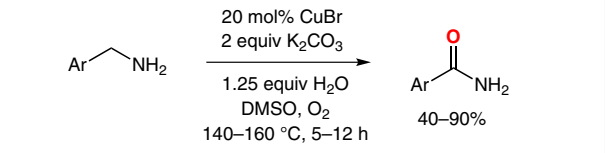
neous systems. Lastly, industrial applications of costly gold catalysts seem even more unlikely than the use of ruthenium-based systems.

As a major improvement towards the use of more earth-abundant catalysts, manganese oxide octahedral molecular sieves (OMS-2) have been reported to oxidize C_α–H bonds of primary benzylic amines aerobically (Scheme 7).[12] However, like many other examples of amide formation via transition-metal-catalyzed amine C_α–H oxidation, this protocol requires high temperatures, and lacks substrate versatility. Moreover, due to the heterogeneous nature of the used catalysts, improvements based on mechanistic understanding of catalytic pathways are challenging.

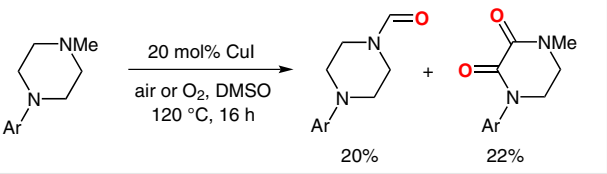


Scheme 7 C_α–H oxidation of primary benzylic amines catalyzed by a manganese-based molecular sieves catalyst

Other methodologies utilize copper catalysts to achieve amide formations via C_α–H oxidation as shown in Scheme 8,[13] and Scheme 9.[14] Although these methodologies utilize copper – a far cheaper alternative to ruthenium or gold – and molecular oxygen as oxidant (a mild alternative to more harsh chemical oxidants such as *t*-BuOOH), both protocols suffer from high reaction temperatures, a narrow substrate scope (benzylic primary or cyclic tertiary amines) and a lack of mechanistic understanding. The latter, CuI-catalyzed methodology produces a variety of different oxidation products, suggesting that the chemoselectivity is difficult to control under the established conditions.



Scheme 8 CuBr-catalyzed C_α–H oxidation of primary arylamines

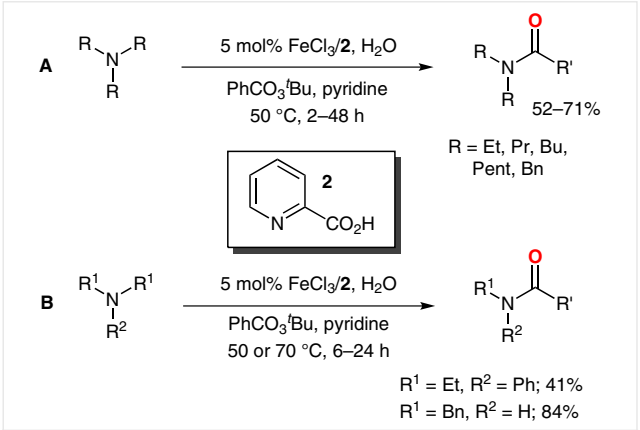


Scheme 9 CuI-catalyzed C_α–H oxidation of cyclic tertiary amines

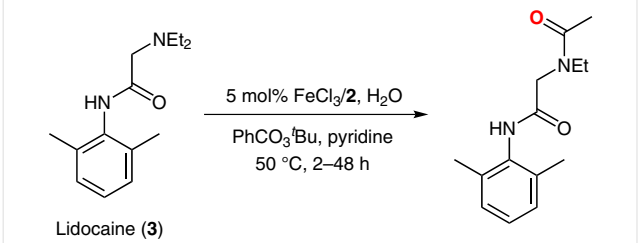
Based on the described state-of-the-art examples, we conclude that relatively few methodologies for efficient C_α–H oxidation of amines to form amides are known. Typical drawbacks are mostly associated with high reaction temperatures, lack of chemoselectivity, limited substrate scopes (primary, secondary, or cyclic tertiary amines), often low yields, and a lack of mechanistic information.

4 General Iron-Catalyzed C–H Oxidations under Mild Conditions

Thus, research in our group has been aimed at addressing these shortcomings to develop a versatile and mild methodology for oxidative amide synthesis. Using an iron catalyst, our work has achieved general C_α–H oxidations of acyclic tertiary amines to afford amides in synthetically useful yields (Scheme 10)[15]. In addition to expanding the substrate scope of catalyzed amine oxidation protocols, our system uses an iron-based system as a cheap and relatively nontoxic catalyst and temperatures well below 100 °C, which increases the overall sustainability of the reaction. Additionally, we have demonstrated our system's ability to oxidize the pharmaceutical drug lidocaine (**3**), which showcases the versatility of the new protocol (Scheme 11).



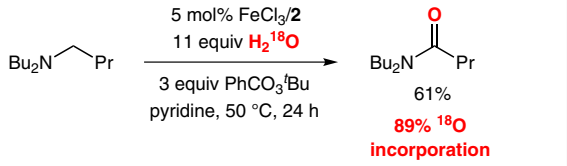
Scheme 10 Fe-catalyzed C_α–H oxidation of tertiary alkyl amines **A** and asymmetric/secondary amines **B**



Scheme 11 Oxidation of lidocaine (**3**) catalyzed by $FeCl_3$/**2**

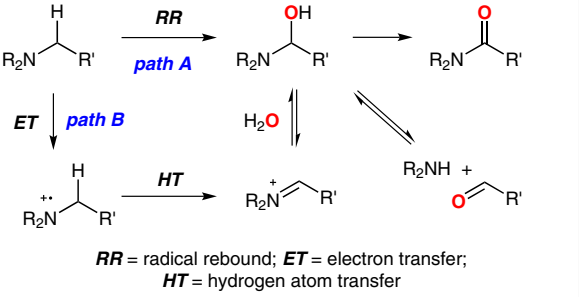
The unique dependence of the catalytic system on the concentration of water in the reaction mixture was a major area of investigation in the development of this protocol, as deviation from water loadings resulted in a steep reduction in amide yield. Interestingly, the concentration of H_2O in

the reaction mixture had to be optimized for each substrate independently in order to achieve the reported yields. Furthermore, exclusion of water from the reaction afforded no trace of amide products even under aerobic conditions. A study using ^{18}O-labeled water suggested that the source of the newly introduced O atom in the amide products is H_2O and not the oxidant (Scheme 12). In contrast, a background study exposing the independently synthesized amide product to $H_2{}^{18}O$ did not result in significant ^{18}O incorporation.



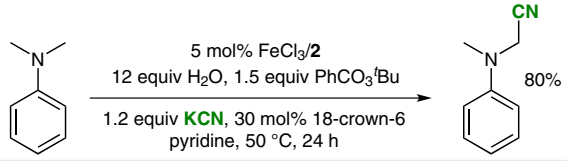
Scheme 12 Incorporation of ^{18}O into amide product

Based on these data, two mechanisms that have been previously proposed for cytochrome P_{450} catalyzed oxidations of amines[16] could be responsible for the incorporation of ^{18}O from H_2O (Scheme 13): path A proceeding through a radical rebound-type oxygenation of the C_α–H bond or path B, which proposes sequential electron and hydrogen-atom transfers. Path B would result in the formation of an iminium intermediate, which in turn would react with H_2O as nucleophile. In path A, ^{18}O incorporation could occur if the putative iron-oxo intermediate attacking the C_α–H bond is formed through reaction with H_2O or if exchange between the oxo ligand and external H_2O is possible. As such pathways have been documented in previous studies,[17] both pathways A and B are possible for the discussed amine oxidation. This first oxidation step would lead to a hemiaminal intermediate, which in turn either undergoes reversible dealkylation or a second oxidation step.



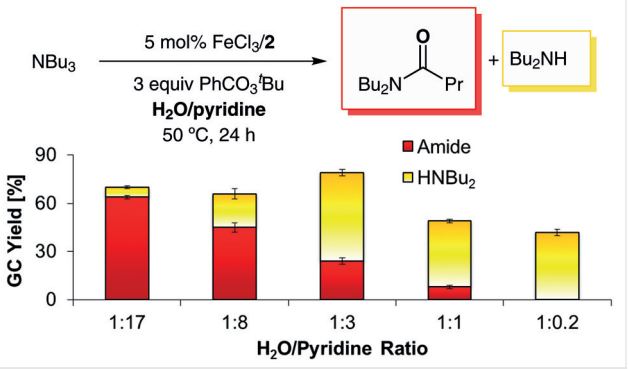
Scheme 13 Mechanistic hypotheses for iron-catalyzed C_α–H oxidation of amines

The proposed iminium ion intermediate would be a highly useful synthetic intermediate, as its reaction with a variety of different nucleophiles could be imagined. Indeed, several methodologies in the literature are known that realize such amine C_α–H functionalizations to form new C_α-alkyl,[18,19] C_α-alkynyl,[20] C_α-Ar,[21] C_α-Ac,[22] and C_α-CN[23] bonds. We hypothesized that the addition of CN^- as nucleophile to the developed system would analogously trap a potential iminium intermediate and enable C_α–CN bond formations with tertiary amine substrate. Thus, KCN was added to the reaction mixture, which resulted in traces of the desired α-amino nitrile. However, in the presence of 18-crown-6 to increase the solubility of KCN, C_α–H cyanation of dimethylaniline was observed in high yield (Scheme 14). In addition to expanding the versatility of the established catalytic system, this result suggests that different nucleophiles can react with a common reaction intermediate and further supports our hypothesis that iminium ions are accessible under the reaction conditions.



Scheme 14 C_α–H cyanation of dimethylaniline

Finally, the proposed mechanism suggests that dealkylated amines should be accessible through decomposition of hemiaminal intermediates. This is a particularly relevant reaction when considering that C_α–H oxidation of amines to amides and oxidative dealkylation are both reactions that are often observed in the metabolism of drugs, which is catalyzed by cytochrome P_{450} and other enzymes. Therefore, establishing a general methodology to synthetically access oxidative metabolites of amines is an important challenge for the pharmaceutical chemistry community. We hypothesized that the product selectivity of amide formation vs. dealkylation should be dependent on the concentration of H_2O in the reaction mixture: H_2O could remove the aldehyde byproduct resulting from hemiaminal cleavage from the equilibrium by forming an aldehyde hydrate, thus driving the reaction towards dealkylation. In order to test this hypothesis, we measured the yields of dealkylated and amide products in dependence on the H_2O con-



Scheme 15 Product selectivity in dependence on the H_2O concentration of the reaction mixture

centration of the reaction mixture (Scheme 15). Remarkably, product selectivity behaves as predicted, forming dialkylamine more selectively with rising H_2O concentrations.

5 Conclusions

In conclusion, catalytic systems that enable C_α–H oxidations of amines provide a versatile platform for functionalizing the C_α–H bonds in amine substructures. Many advances have been made in recent years to improve catalytic efficiencies, understand catalytic mechanisms, increase yields, and enable milder reaction conditions. Thus, newly designed protocols, including the herein highlighted iron-catalyzed system, allow for broadly applicable functionalizations of C_α–H bonds mimicking oxidative, enzyme-catalyzed transformations such as the ones found in metabolic pathways. In order to further broaden the scope of these reactions, a thorough understanding of the nature of the used transition-metal catalysts would be highly desirable, in particular, since changes in the ligand framework of the catalysts can be expected to modulate and control reactivity achieved with these systems. Major challenges that can be addressed through such catalyst design approaches would be the typically low yields achieved with sterically bulky amines, site selectivity of C_α–H oxidation for nonsymmetrical amines, and the application of these catalytic systems in complex molecule settings.

Acknowledgment

We thankfully acknowledge helpful discussion with Dr. Dominique Hebrault (Mettler Toledo) regarding identification of the proposed hemiaminal intermediate by in situ FTIR measurements. M.H.E. acknowledges funding of the work described in the latter part of this manuscript through start-up funds provided by Worcester Polytechnic Institute.

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