Amine Oxidation

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Iron-Catalyzed C_α–H Oxidation of Tertiary, Aliphatic Amines to Amides under Mild Conditions

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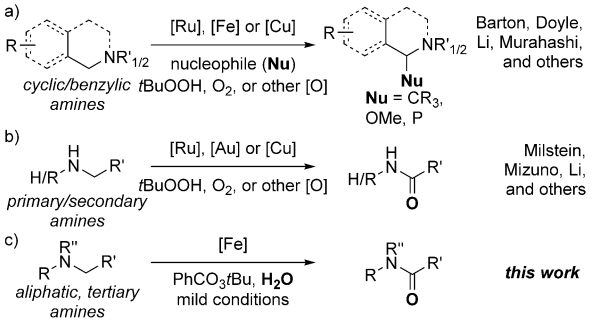
Abstract: *De novo syntheses of amides often generate stoichiometric amounts of waste. Thus, recent progress in the field has focused on precious metal catalyzed, oxidative protocols to generate such functionalities. However, simple tertiary alkyl amines cannot be used as starting materials in these protocols. The research described herein enables the oxidative synthesis of amides from simple, noncyclic tertiary alkyl amines under synthetically useful, mild conditions through a biologically inspired approach: Fe-catalyzed C_α–H functionalization. Mechanistic investigations provide insight into reaction intermediates and allow the development of a mild C_α–H cyanation method using the same catalyst system. The protocol was further applied to oxidize the drug Lidocaine, demonstrating the potential utility of the developed chemistry for metabolite synthesis.*

The synthesis of amides is one of the most important organic reactions, due to their prevalence in materials (e.g. Kevlar), biopolymers (e.g. proteins), and biologically active compounds. However, classical syntheses of amides require the activation of carboxylic acids to achieve the desired bond formation and thus lack in atom economy.[1,2] Owing to the importance of amides and the shortcomings of classical methods, protocols for greener amide formations are highly desirable.[1] In contrast to chemical syntheses, biological pathways catalyzed by Cytochrome P_{450} (CYP) achieve amide formations through amine C_α–H functionalizations.[3,4] Recent efforts to synthetically mimic this reactivity and achieve direct amine-to-amide conversions have employed Cu or supported Ru catalysts for primary amines as substrates.[5,6] Secondary cyclic amines can be converted into the corresponding lactams by Au nanoparticles[7] or a Ru pincer catalyst.[8] However, efficient amine-to-amide oxidations have only been realized for primary, secondary, cyclic, or benzylic amine substrates (Scheme 1).[5–10] Notably, these protocols lack generality and are unreactive for functionalizations of simple, acyclic tertiary alkyl amines.[11] Because of this gap in the knowledge, our studies aimed at establishing a methodology for the challenging oxidation of tertiary, aliphatic amines to amides. We report herein a versatile and tunable iron-based catalyst system which imitates the reactivity of CYP enzymes with respect to tertiary alkyl amines, resulting in amide synthesis, oxidative dealkylation, or C_α–H cyanation depending on the chosen water content, oxidant loading, and nucleophile in the reaction mixture.

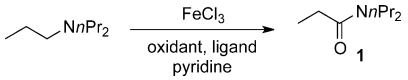


Scheme 1. Fe-catalyzed synthesis of amides from aliphatic trialkylamines.

To mimic the biological oxidant combination O_2/NAD(P)H,[12] various oxidants were initially evaluated in combination with $FeCl_3$ as catalyst precursor. Several common oxidants with peroxide substructures and hypervalent iodine reagents (see SI)[11a,13–27] were not effective in promoting the desired transformation. However, employing the peroxide esters $PhCO_3tBu$ or H_3CCO_3tBu resulted in low yields of the desired amide **1** (Table 1, entries 1 and 2).

Further studies were aimed at identifying suitable ligands for Fe to promote the desired reactivity, which resulted in identification of picolinic acid (**2**; Figure 1) as additive, which

Table 1: Reaction optimization and background.[a]



Entry	Conditions	Yield [%]
1	$MeCO_3tBu$ (2 equiv), 100 °C	3
2	$PhCO_3tBu$ (2 equiv), 100 °C	3
4	$PhCO_3tBu$ (4 equiv), 100 °C	10
5	$PhCO_3tBu$ (4 equiv), **2** (5 mol%), 100 °C	16
6	$PhCO_3tBu$ (3 equiv), **2** (5 mol%), 100 °C	15
7[b]	$PhCO_3tBu$ (3 equiv), **2** (5 mol%), 100 °C	35
8	$PhCO_3tBu$ (3 equiv), **2** (5 mol%), 50 °C	13
9[c]	$PhCO_3tBu$ (3 equiv), **2** (5 mol%), H_2O (11 equiv), 50 °C	58
10	no oxidant, **2** (5 mol%), H_2O (11 equiv), 50 °C	0
11	no $FeCl_3 \cdot 6H_2O$, 50 °C	15
12[c]	no $FeCl_3 \cdot 6H_2O$, 50 °C	0

[a] Conditions: Tri(*n*-propyl)amine (95 μL, 71 mg, 0.50 mmol, 1.00 equiv), $FeCl_3 \cdot 6H_2O$ (6.8 mg, 0.025 mmol, 5.0 mol%), pyridine (1.80 mL), 24 h. [b] 5.0 mL pyridine. [c] Under N_2 atmosphere.

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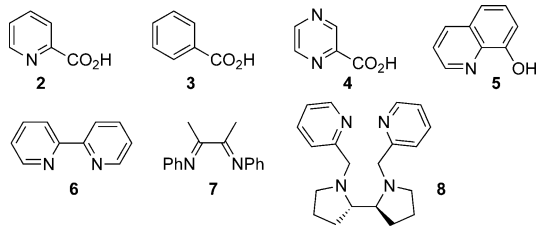
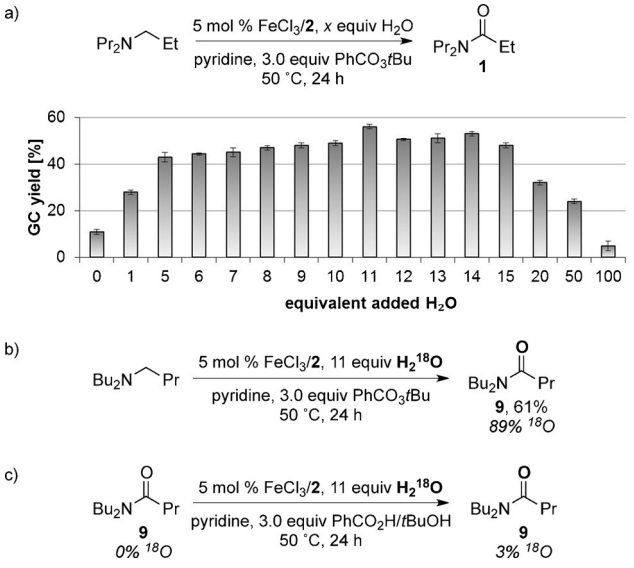


Figure 1. Ligands used in optimization.

provided 16% yield when used in a 1:1 ratio with $FeCl_3$ (Table 1, entry 5). Lower or higher loadings of **2** resulted in lower yields (Table S2 in the Supporting Information (SI)), while other ligands (see Figure 1 and the SI) did not improve the observed yield of amide (7–9%).

Interestingly, the $FeCl_3$/**2** catalyst system does not require high temperatures and is active at 50 °C, forming 13% of amide **1** (Table 1, entry 8; see SI for other temperatures tested). In addition, optimizing the water content of the reaction mixture at this temperature (Table 1, entry 9) resulted in an even higher, synthetically useful 58% yield of **1**. No product formation (Table 1, entry 10) was observed in the absence of oxidant as well as in the absence of Fe under a N_2 atmosphere (Table 1, entries 9 and 12). However, reactions in the absence of $FeCl_3$ in air showed a background reaction (15%; Table 1, entry 11), which could be suppressed with 50 mol% TEMPO as radical scavenger (see SI).

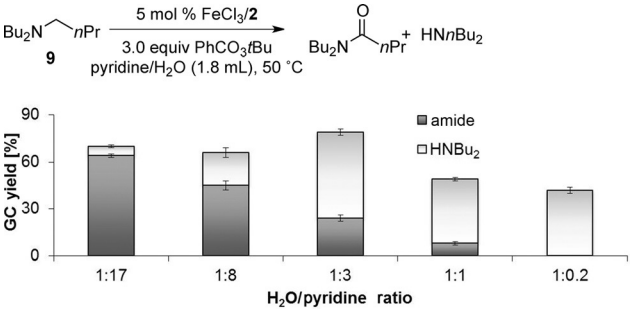
A more detailed study of the influence of water on product formation is shown in Scheme 2. Interestingly, very low and very high water loadings do not promote amide formation (Scheme 2A). Observation of a strong dependence of product formation on the water content suggests that H_2O is inherently involved in the mechanism of the reaction and possibly the source of the O atom incorporated into the amide product. In order to trace the source of incorporated oxygen, we oxidized N*n*Bu_3 under a N_2 atmosphere, using 11 equiv of $H_2{}^{18}O$ (97% ^{18}O; Scheme 2B); notably, 89% incorporation of ^{18}O into product **9** was observed. In contrast, subjecting the product to the reaction conditions did not result in more than 3% ^{18}O incorporation (Scheme 2C), which makes ^{18}O exchange in the product after amide formation unlikely. Overall, these data suggest that ^{18}O is introduced into the product in an intermediate. Potential pathways are nucleophilic attack of $H_2{}^{18}O$ at a possible iminium intermediate or direct amine hydroxylation by a ^{18}O-labeled Fe–oxo species.



Scheme 2. a) Water addition, b) $H_2{}^{18}O$ incorporation, and c) background studies.

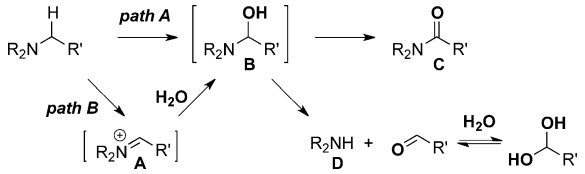
Furthermore, the reaction time (see SI) also has a distinct influence on the yield, indicating that the optimal yield is achieved after 8 h. Lower yields thereafter indicate that the amide products are slowly decomposing under the reaction conditions.

The significant dependence of amide formation on the H_2O concentration in the reaction medium further suggests that amide formation—just as in biological systems—is only one possible outcome of the C_α–H oxidation of amines and depends on the concentration of water and oxidation equivalents present at the catalytically active site. Thus, we analyzed a crude reaction mixture after 24 h by GCMS to gain a better understanding of potential side products. Interestingly, both double oxidation products and dealkylation products were observed (for details see the SI). Based on this observation, we postulated that the selectivity for amide formation versus dealkylation should be determined by the relative rates of dealkylation versus oxidation of a common hemiaminal intermediate. To test this hypothesis, we performed a series of experiments in which the H_2O/pyridine ratio was systematically changed from 1:17 to 1:0.2 (Scheme 3).



Scheme 3. Selectivity of product formation versus H_2O loading.

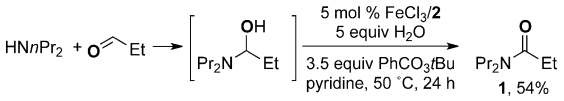
Interestingly, a clear dependence of product selectivity on the H_2O concentration was observed, with higher amounts of water favoring the formation of dealkylation product. Further optimizations (see SI, Table S8) afforded the dealkylation product *N*,*N*-dibutylamine in 64% yield; other substrates also undergo oxidative dealkylation under these conditions (see SI, Table S9). Overall, these studies suggest a reaction mechanism similar to the mechanism postulated for CYP-catalyzed oxidations of amines (Scheme 4).[28] This mechanism accounts for the formation of both amide (**C**) and oxidative dealkylation product (**D**) through a common hemiaminal intermediate (**B**). Accessing **B** from the amine



Scheme 4. Mechanistic hypothesis. Path A represents a direct hydroxylation pathway; path B would be a stepwise electron and proton abstraction.

substrate can proceed through two different pathways: Path A suggests a radical rebound mechanism, while path B proceeds through sequential electron and proton transfers.

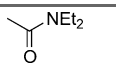
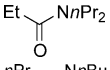
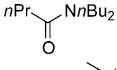
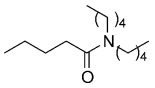
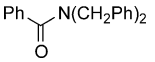
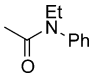
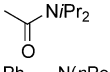
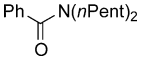
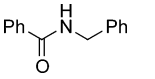
The presence of a hemiaminal intermediate in our reactions is further supported by in-situ FTIR detection of a reaction intermediate with characteristic hemiaminal bands[29] at $\tilde{\nu} = 1400$, 1450, and 1600 cm^{-1}. Based on these data, we reasoned that amide synthesis should also proceed under the established conditions when a hemiaminal is accessible through a different pathway. To this end, a mixture of di(*n*-propyl)amine and propionaldehyde (Scheme 5) was subjected to the reaction conditions. After minor optimizations, amide **1** was obtained in 54% yield, suggesting that hemiaminals are likely intermediates of oxidative amide formation.



Scheme 5. Amide formation from propionaldehyde and HN*n*Pr$_2$.

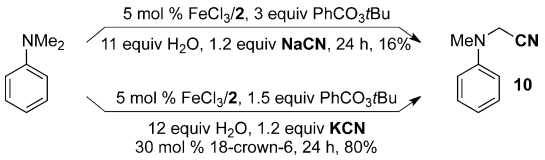
To explore the scope of the developed catalytic system, several tertiary amine substrates were tested under the reaction conditions. The yields shown in Table 2 are optimized for each substrate with respect to reaction time, H_2O and oxidant loading, and reaction temperature. For aliphatic, tertiary amines, the obtained yields increased with the alkyl chain length and the highest yield was observed for tri(*n*-pentyl)amine (71%; Table 2, entry 4). Tribenzylamine was also successfully employed (59%; Table 2, entry 5), suggesting that the protocol is generally applicable for aliphatic and benzylic amine substrates. The unsymmetrical amines EtN*i*Pr$_2$, PhNEt$_2$, and BnN(^{n}Pent)$_2$ all provided lower yields (21–41%; Table 2, entries 6–8). However, no starting materials or dealkylation products were observed in these reactions, suggesting that other side reactions are rapid with these substrates (see SI). One secondary amine (Bn$_2$NH; Table 2, entry 9) was also oxidized using the protocol (54% GC yield and 46% yield of isolated product). Unfortunately, other secondary aliphatic amines (such as HN(*n*Pent)$_2$ or HN*n*Bu$_2$) showed exclusively dealkylation products or amides PhCONR$_2$, which are likely derived from nucleophilic attack of the amines at the oxidant. As the only tested aniline substrate showed only low yields, we decided to test if other C_α–H functionalizations would proceed more readily with this type of substrate. We reasoned that modifications of the

Table 2: Substrate scope of amide formation with simple amines.[a]

Entry	Substrate	Product	Conditions	GC Yield (isolated)
1[b]	NEt_3		24 equiv H_2O, 2 h	52%
2	N(*n*Pr)$_3$		11 equiv H_2O, 6 h	63%
3	N(*n*Bu)$_3$		11 equiv H_2O, 24 h	64% (57%)
4	N[(CH$_2$)$_4$CH$_3$]$_3$		15 equiv H_2O, 48 h	71% (63%)
5	N(CH$_2$Ph)$_3$		1 equiv H_2O, 24 h	59% (58%)
6[c]	Et_2NPh		30 equiv H_2O, 6 h	41%
7	*i*Pr$_2$NEt		6 equiv H_2O, 24 h	21%
8	PhCH$_2$N(*n*Pent)$_2$		9 equiv H_2O, 24 h	29%
9	HN(CH$_2$Ph)$_2$		5 equiv H_2O, 24 h	54% (46%)

[a] Conditions: 2-picolinic acid (3.1 mg, 0.025 mmol, 5.0 mol%), $FeCl_3 \cdot 6H_2O$ (0.025 mmol, 5.0 mol%), $PhCO_3tBu$ (280 μL, 291 mg, 1.50 mmol, 3.00 equiv), H_2O (1 to 30 equiv), amine (0.50 mmol, 1.0 equiv), 50 °C, sealed vial. [b] 3.5 equiv $PhCO_3tBu$. [c] 4 equiv $PhCO_3tBu$, 70 °C.

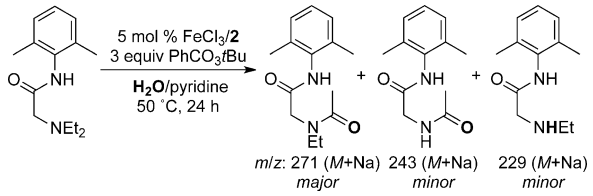
developed amine oxidation protocol might give access to other C_α–H functionalizations beyond amide formations. Thus, we added NaCN as nucleophile to a reaction mixture with Me_2NPh as substrate and obtained 16% unoptimized yield of the α-aminonitrile **10** (Scheme 6). Further optimizations of H_2O and oxidant loading as well as switching to KCN as CN^- source in combination with 30 mol% of 18-crown-6 to solubilize KCN afforded 80% yield of **10**, suggesting that iminium intermediates (**A**; Scheme 4) are readily accessible with the developed catalyst system.



Scheme 6. C_α–H cyanation with an analogous catalytic system.

Finally, one goal for the C_α–H functionalization of amines is to mimic CYP activity to access putative metabolites. Generally, establishing the identity of amine metabolites is important, since such compounds can have altered biological activities compared to the original amines.[30] Both amides and dealkylation products are common metabolites.[31,32] In order to demonstrate the feasibility of using the developed amine oxidation protocols for the direct synthesis of metabolites, we subjected the active pharmaceutical ingredient Lidocaine to

the optimized reaction conditions for the oxidation of N*n*Pr$_3$. LCMS analysis of the reaction mixture showed the corresponding amide product as major product (Scheme 7), while only minor amounts of dealkylated products were obtained.



Scheme 7. Oxidation of Lidocaine, the pharmaceutically active ingredient in Lidoderm.

The dealkylation product has previously been identified as metabolite;[33] conversely, the biological relevance of the amide product has not been reported. However, the change in addition of 14 mass units by C_α–H oxidation would be analogous to the mass change caused by methylation, another common metabolic reaction.[30] We thus conclude that the developed amine oxidation protocol provides not only a protocol for the unprecedented synthesis of amides from tertiary aliphatic amines, but also a method to distinguish between the two metabolic pathways of methylation and amine to amide oxidation, as the mild conditions enable the use of more complex substrates than simple tertiary amines.

Overall, the studies detailed above show that PhCO$_3$*t*Bu can be successfully employed in amine C_α–H functionalizations and that the resulting Fe-catalyzed protocols show promise for novel C–H bond functionalizations of aliphatic, benzylic, and aromatic amine substructures, which are common in biologically active molecules. Thus, the protocol can be expected to expedite the synthesis of oxidative metabolites relevant for toxicity studies of pharmaceutically active compounds under mild conditions.

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Keywords: C–H functionalization · iron catalysis · metabolite synthesis · oxidation · reaction mechanism

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