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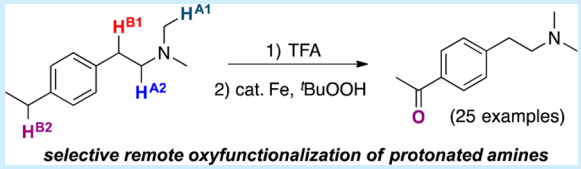
Iron-Catalyzed Oxyfunctionalization of Aliphatic Amines at Remote Benzylic C−H Sites

Curren T. Mbofana, Eugene Chong, James Lawniczak, and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 North University Ave, Ann Arbor, Michigan 48109, United States

Supporting Information

ABSTRACT: We report the development of an iron-catalyzed method for the selective oxyfunctionalization of benzylic C(sp^3)−H bonds in aliphatic amine substrates. This transformation is selective for benzylic C−H bonds that are remote (i.e., at least three carbons) from the amine functional group. High site selectivity is achieved by in situ protonation of the amine with trifluoroacetic acid, which deactivates more traditionally reactive C−H sites that are α to nitrogen. The scope and synthetic utility of this method are demonstrated via the synthesis and derivatization of a variety of amine-containing, biologically active molecules.



C−H bond functionalization reactions serve as powerful methods for streamlining the synthesis and late-stage modification of complex organic molecules. Aliphatic amines are particularly common functional groups in natural products and pharmaceuticals, comprising more than 33% of the top 100 selling pharmaceuticals in 2013.[1] As such, aliphatic amine-containing substrates represent important targets for selective C−H functionalization methods.[2] The transition-metal-catalyzed C(sp^3)−H oxygenation of aliphatic amines has been particularly well-studied, as these transformations mimic cytochrome P450 metabolism.[3] The electron rich C−H bonds that are α to nitrogen are typically the most reactive sites in these molecules. Thus, the treatment of unprotected aliphatic amines (e.g., **1** in Figure 1) with metal catalysts/oxidants most commonly results in α-oxidation to afford mixtures of amide, imine, and enamine products (e.g., **A**, **B**, and **D**).[4] These can then undergo further transformations such as hydrolysis and/or oxidation to generate secondary products such as **C**, **E**, and **F**.[5]

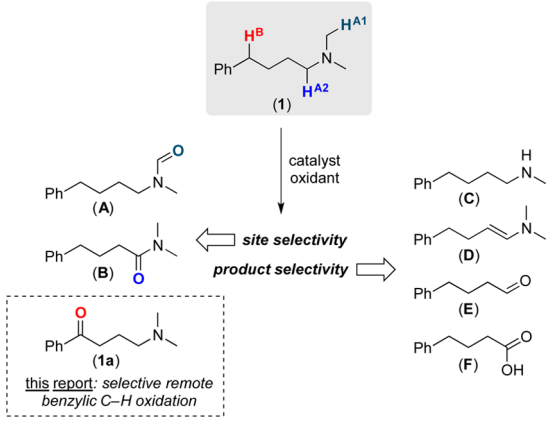


Figure 1. Treatment of amines such as **1** with catalysts/oxidants leads to complex mixtures of C−H oxidation products.

Due to the high reactivity of the α-C−H bonds of aliphatic amines, it can be challenging to functionalize selectively at C−H sites that are remote to nitrogen (e.g., H^B in **1**).[6] Traditionally, remote C−H oxidation has required either (i) the use of a directing group to deliver the catalyst to a remote C−H site[7] or (ii) the use of a protecting group on nitrogen to attenuate the reactivity of the α-C−H bonds.[8] We hypothesized that the strong preference for α-oxidation could be overridden using a much simpler approach, namely in situ protonation of the amine nitrogen.[9] Protonation converts the electron-donating amine into an inductively electron-withdrawing ammonium salt.[10] This should deactivate proximal C−H sites, thereby enabling selective oxidation at C−H sites that are remote to nitrogen.[11,12]

Early precedent for this approach was disclosed by Asensio, who demonstrated the remote C(sp^3)−H oxyfunctionalization of a small set of protonated aliphatic amines with TFDO.[13] More recently, we and others have leveraged this protonation strategy to achieve transition-metal-catalyzed remote oxyfunctionalization of a more diverse variety of nitrogen-containing substrates, using K_2PtCl_6,[9] Fe(PDP),[14] and Mn/Ru-based catalysts.[15] However, all of these reactions exhibit limitations with respect to substrate scope and/or selectivity. Furthermore, most require catalysts derived from noble transition metals and/or relatively expensive supporting ligands. Herein, we demonstrate the use of simple Fe salts in combination with picolinic acid to catalyze the remote C(sp^3)−H oxidation of protonated amines. This method is particularly effective for the selective oxygenation of remote benzylic C−H bonds in aliphatic amines, a substrate class that has not been addressed with previous catalysts/methods. This paper describes the development, optimization, scope, and applications of this method in a variety of aliphatic amine-containing substrates.

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Our test substrate for this transformation (**1**) contains both 1°- and 2°-C−H bonds α-to nitrogen (H^{A1} and H^{A2}) as well as benzylic C−H bonds remote to nitrogen (H^{B}). Furthermore, it is a 3° amine and, thus, is not amenable to many of the protecting group/directing group strategies for remote oxidation that have been reported in the literature.[7,8] We first explored Gif-type[16,17] C−H oxidation conditions using $FeCl_3$/picolinic acid as the catalyst and ^{t}BuOOH as the oxidant.[18] When the unprotonated amine **1** was treated with 10 mol % of $FeCl_3$, 25 mol % of picolinic acid, and 3 equiv of ^{t}BuOOH (TBHP) in a solvent mixture of pyridine/acetonitrile, a complex mixture of oxidation products was obtained (Figure 2a). These include multiple

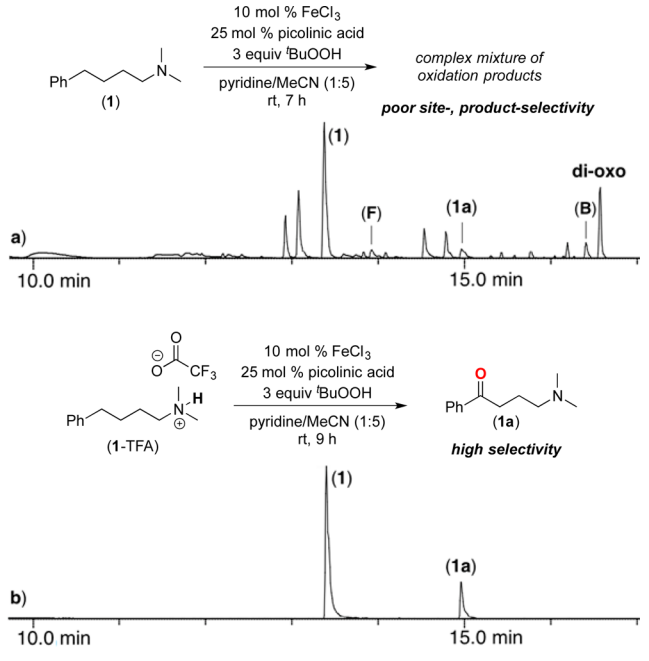

Figure 2. GCMS trace of the oxidation of **1** conducted: (a) without an acid additive and (b) after protonation with CF_3CO_2H.

products of oxidation α to nitrogen (e.g., **B**, **F**, and dioxo products related to **A** and **B**) along with traces of the desired benzylic oxidation product **1a**. However, the protonation of **1** with CF_3CO_2H prior to treatment under otherwise analogous conditions resulted in the clean formation of **1a** as the sole detectable oxidation product in 24% yield (Figure 2b). The high selectivity of this transformation is exemplified by the GCMS trace of the crude reaction mixture (compare parts a and b of Figure 2).

We next optimized this reaction with respect to Fe salt, solvent, acid additive, catalyst loading, oxidant loading, and oxidant addition procedure. Full details of this optimization can be found in Table S1, and only highlights of these studies are discussed below. The reaction proceeds in similar yield with a variety of simple Fe salts [e.g., $FeCl_3$, $FeCl_2$, $Fe(OTf)_3$, $Fe(OAc)_2$, $Fe(BF_4)_2$]. However, without picolinic acid, minimal conversion is observed. The MeCN solvent can be substituted with H_2O, but the pyridine additive is crucial for reactivity. A variety of strong acids can be used for protonation of the amine (e.g., CF_3CO_2H, HBF_4, HCl, H_2SO_4), and the choice of acid has a relatively minor impact on the reaction yield. Finally, the slow addition of ^{t}BuOOH improves conversion significantly and also represents best practice from a safety perspective.[19,20] Overall, our optimal conditions involve use of the amine substrate as the limiting reagent in conjunction with 1.1 equiv of CF_3CO_2H, 5 mol % of $FeCl_3$, 12.5 mol % of picolinic acid in a pyridine/MeCN (1:5) solvent mixture with slow addition of ^{t}BuOOH (70 wt % in H_2O, 18 equiv), resulting in 65% yield of **1a** and <5% of other oxidation products, along with 14% remaining starting material (see Figure S1 for a ^{1}H NMR spectrum of the crude reaction mixture).[21] Product **1a** was obtained in 60% isolated yield under these conditions. Notably, attempts to apply the recently reported Fe(PDP)/H_2O_2 system[14] to substrate **1** resulted mainly in decomposition, and none of product **1a** was detected (Figure S2). This result highlights the complementarity of the current transformation to existing methods.

We next examined the impact of chain length on reactivity and selectivity (Table 1). For substrates bearing three-, four-, or five-

Table 1. Catalytic Oxidation of Alkylphenylamines

substrate	product	isolated yield[a]
Ph NMe2 (1)	Ph NMe2 O (1a)	60%
Ph NMe2 (2)	Ph NMe2 O (2a)	56%
Ph NMe2 (3)	Ph NMe2 O (3a)	20 (38%)[b]
Ph NMe2 (4)	no reaction	-
Ph NMe2 (5)	no reaction	-
NMe2 (6)	NMe2 O (6a)	63%[c]
NMe2 (7)	NMe2 O (7a)	60%[c]

[a]Reactions run under standard conditions [CF_3CO_2H (1.1 equiv), $FeCl_3$ (5 mol %), picolinic acid (12.5 mol %), ^{t}BuOOH (70 wt % in H_2O (18 equiv) in pyridine/MeCN (1:5) at rt, 48 h]. [b]Yield in parentheses determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [c]Run with 12 equiv of ^{t}BuOOH.

carbon chains between the protonated amine and the aromatic ring (**3**, **1**, and **2**, respectively), the benzylic C−H oxidation product was obtained in isolated yields ranging from 20 to 60%. The lowest yield was observed with product **3a**. In this case, the major side product was phenyl vinyl ketone (14% yield), which is believed to derive from a retro-Michael reaction of the initial product **3a**.[22] In contrast, amine substrates **4** and **5**, which contain shorter two- and one-carbon chains between the protonated amine and the aromatic ring, were unreactive. This is likely because the benzylic sites in these systems are highly deactivated due to their proximity to the electron-withdrawing protonated amine. We also examined analogues of **4** and **5** that contain benzylic sites at the remote 4-position of the aromatic ring (substrates **6** and **7**). In both cases, C−H oxidation occurs selectively at the benzylic site remote to the nitrogen to afford **6a** and **7a** in 63% and 60% yield, respectively.

Piperidine derivatives are substrates of particular interest since piperidine is the most common nitrogen heterocycle in drug molecules (Figure 3).[23] Based on the results in Table 1, we anticipated that C−H sites on the piperidine ring would be relatively unreactive toward C−H oxygenation due to their

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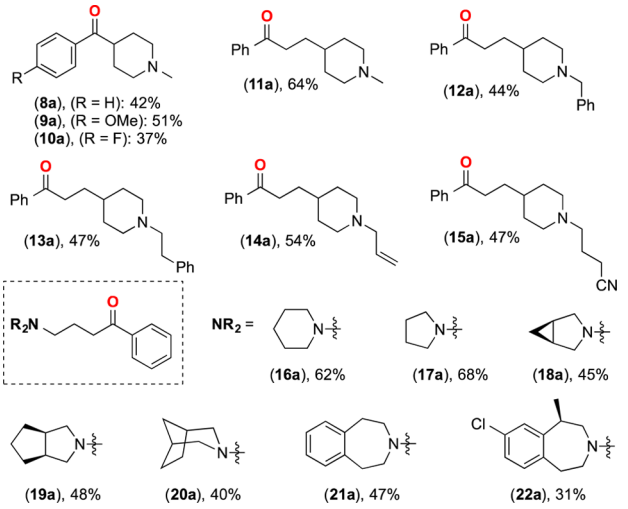

Figure 3. Substrate scope for catalytic oxidation of benzylic C−H bonds. Reactions were all run under standard conditions.

proximity to the electron-withdrawing protonated amine. Indeed, minimal reactivity was observed when 1-methylpiperidine or 1,4-dimethylpiperidine were subjected to our standard conditions (≤11% yield of the corresponding C−H oxygenation products).[24] However, piperidine substrates bearing remote benzylic sites underwent clean oxidation to form **8a**−**15a** in modest to good isolated yield and high site selectivity (Figure 3). In the series of substrates with substituted aromatic rings, a higher yield was obtained with an electron-donating substituent (*p*-OMe, **9a**) than the relatively electron neutral (*p*-H, **8a**) and (*p*-F, **10a**) substituents.[25] Increasing the chain length between the piperidine ring and the benzylic site furnished **11a** in 64% yield. A variety of substituents were tolerated on the piperidine nitrogen, including *N*-benzyl (**12a**), *N*-homobenzyl (**13a**), and *N*-allyl (**14a**). In all three of these examples, oxidation occurred selectively at the remote benzylic site rather than at benzylic or allylic C−H bonds proximal to nitrogen. An *N*-butyronitrile-containing substituent was also compatible and reacted to form **15a** in 47% isolated yield. No evidence for nitrile hydrolysis was observed under these conditions.

We surveyed a series of other alicyclic amine substrates that are common motifs in pharmaceuticals and/or natural products. The nitrogen of each was alkylated with a side chain containing a potential site for remote benzylic oxidation. As shown in Figure 3, C−H oxygenation proceeded in moderate to good yield for substrates containing piperidine (**16a**, 62%), pyrrolidine (**17a**, 68%), 3-azabicyclo[3.1.0]hexane (**18a**, 45%), *cis*-octahydrocyclopenta[*c*]pyrrole (**19a**, 48%), 3-azabicyclo[3.2.1]-octane (**20a**, 40%), and 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**21a**, 47%). This latter result motivated us to examine a derivative of the weight loss drug lorcaserin,[26] which contains both 2° and 3° benzylic C−H bonds in the nitrogen heterocycle. However, here again, the remote benzylic oxidation product **22a** was obtained selectively in 31% isolated yield. The majority of the mass balance in this system was unreacted starting material.

A final set of studies focused on the application of this transformation to the synthesis and derivatization of amine-containing bioactive molecules (Figure 4). The oxidation of readily available precursor **23** afforded the piperidine alkaloid (±)-sedaminone (**23a**) in 48% isolated yield. A related transformation was used to prepare several pharmaceuticals from the butyrophenone family, a class of antipsychotic drugs for

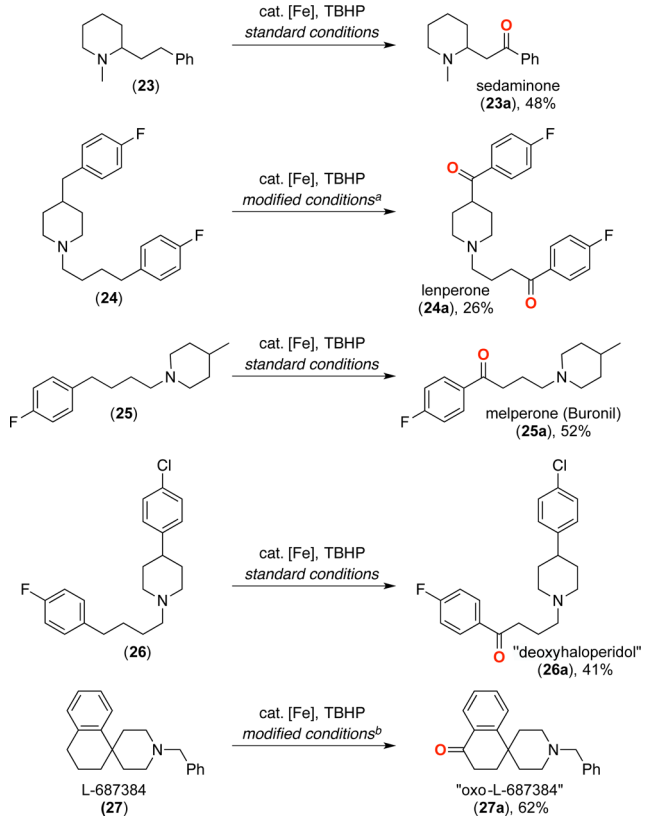

Figure 4. Applications toward synthesis and derivatization of bioactive molecules. Reactions were run under standard conditions unless otherwise indicated. Reaction run with (a) 10 mol % of $FeCl_3$ and 54 equiv of ^{t}BuOOH over 5 d; (b) 6 equiv of ^{t}BuOOH over 24 h.

the treatment of schizophrenia. For example, double benzylic oxidation of **24** delivered lenperone (Elanone V) (**24a**) in modest 26% yield.[27] Melperone (Buronil) (**25a**) was obtained in 52% yield from precursor **25**. Similarly, "deoxyhaloperidol" (**26a**) was formed in 41% yield from precursor **26**.[28] Finally, the late-stage oxidation of protonated L-687384 (**27**), a sigma receptor agonist,[29] afforded "oxo-L-687384" (**27a**) in 62% yield.

In summary, this paper describes the development of an Fe-catalyzed method for selective oxidation of remote benzylic C−H bonds in aliphatic amine substrates. Our approach takes advantage of amine protonation, a strategy that electronically deactivates proximal C−H bonds, and thereby renders remote oxidation feasible and selective. Notably, even C−H bonds that are doubly activated (i.e., those that are benzylic/allylic and also α to the amine nitrogen) are sufficiently deactivated by amine protonation such that oxidation occurs selectively at remote benzylic sites. Applications to the synthesis and late-stage modification of amine-containing bioactive molecules were successfully demonstrated. Ongoing work in our laboratory is focused on further expanding the scope and applications of this approach to amine C−H functionalization as well as on exploring the mechanism of this transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02003.

Optimization data, experimental data, and complete characterization data for all new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: mssanfor@umich.edu.

Notes

The authors declare no competing financial interest.

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(18) Similar conditions have been used previously for the benzylic C−H oxygenation of other substrate classes. See ref 17b.

(19) Caution: Reactions of peroxides and metal-based catalysts can be highly exothermic and can result in rapid in gas evolution. As such, reaction vessels should be properly vented to avoid pressure build up. Furthermore, the ^{t}BuOOH should be only added by slow addition as outlined in the Supporting Information.

(20) During reaction optimization, we observed that the effect of adding additional Fe catalyst and peroxide was the same as just adding additional peroxide. Hence, we chose to only add additional peroxide via slow addition.

(21) The incomplete mass balance of this reaction is likely due to instability of the product under the reaction conditions. For example, when a pure sample of product **1a** was subjected to the optimal reaction conditions in place of substrate **1**, only 35% was recovered at the end of the reaction.

(22) This was confirmed by independently subjecting oxidation product **3a** to CF_3CO_2H and $FeCl_3$ in pyridine/MeCN (1:5).

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(24) The low reactivity of 1,4-dimethylpiperidine further highlights the complementarity of the current system to the Fe(PDP)/H_2O_2 method, which affords good yields with a closely related substrate (ref 14).

(25) Electron-rich heterocycles are prone to side reactions under these highly oxidizing conditions. We have tested one substrate containing a pyridine functional group (*N*,*N*-dimethyl-3-(pyridin-4-yl)propan-1-amine). Under our standard conditions, we recovered 60% of the starting material along with a complex mixture of minor products. More detailed studies will be needed to assess whether this low reactivity is due to the pyridine functional group (we deem this unlikely based on the compatibility with pyridine solvent) or the fact that the 4-pyridyl group is electron withdrawing (especially if it becomes protonated) and hence deactivates the benzylic site in this substrate.

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(27) The crude reaction mixture showed quantitative conversion of **24** to a mixture of the dioxo and two mono-oxo products in a 15:7:1 ratio as determined by GCMS.

(28) In these two cases, only the mono-oxidation product was isolated, and GCMS analysis of the crude reaction mixtures showed a single C−H oxygenation product.

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