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Remote Oxidation of Aliphatic C—H Bonds in Nitrogen Containing Molecules

Jennifer M. Howell‡, Kaibo Feng‡, Joseph R. Clark, Louis J. Trzepkowski and M. Christina White*

Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois, 61801, United States

Supporting Information Placeholder

ABSTRACT: Nitrogen heterocycles are ubiquitous in natural products and pharmaceuticals. Herein, we disclose a nitrogen complexation strategy that employs a strong Brønsted acid (HBF_4) or an azaphilic Lewis acid (BF_3) to enable remote, non-directed C(sp^3)—H oxidations of tertiary (3°), secondary (2°), and primary (1°) amine- and pyridine-containing molecules with tunable iron catalysts. Imides resist oxidation and promote remote functionalization.

The development of reactions that selectively oxidize inert C(sp^3)—H bonds while tolerating more electron rich nitrogen functionality is a significant, unsolved problem given that nitrogen is ubiquitous in natural products and medicinal agents.[1] Among the challenges for developing such reactions are catalyst deactivation via nitrogen binding and direct oxidation of nitrogen to furnish *N*-oxides. Common electronic deactivation strategies for 2° and 1° amines (e.g. acylation) do not disable hyperconjugative activation leading to functionalization α to the nitrogen (Figure 1).[2] Directing group strategies facilitate oxidation of C(sp^3)—H bonds that are spatially and geometrically accessible from the directing functional group.[3] Remote oxidation of C(sp^3)—H bonds in nitrogen-containing molecules is not currently possible with ligated transition metal catalysis.

Site-selective and -divergent oxidation of tertiary (3°) and secondary (2°) C—H bonds has been demonstrated with small molecule catalysts, Fe(PDP) **1** and Fe(CF_3PDP) **2**, respectively.[4] Discrimination of C—H bonds can be accomplished via catalyst/substrate electronic, steric and stereoelectronic interactions. Inductive effects within a substrate

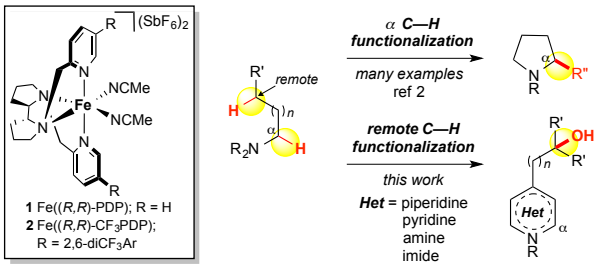
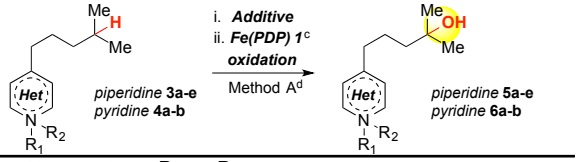
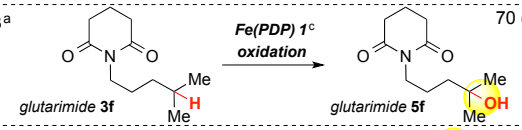
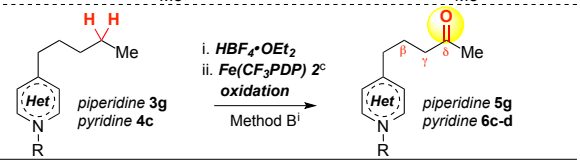


Figure 1. Heterocycle Functionalization

Table 1. Reaction Optimization[a,b]



Entry	Heterocycle	R_1	R_2	Additive (equiv)	Yield (%) (rsm)[e]
1	**3a**	Me	-	BF_3•OEt_2 (1.1)	46 (28)
2	**4a**	-	-	BF_3•OEt_2 (1.1)	27 (67)
3	**3a**	Me	-	HBF_4•OEt_2 (1.1)	56 (29)
4	**3a**	Me	-	F_3CCO_2H (1.1)	5 (74)
5[f]	**3a**	Me	-	H_2SO_4 (1.1)	0 (76)
6[g]	**3a**	Me	-	HBF_4•H_2O (1.1)	43 (40)
7	**4a**	-	-	HBF_4•OEt_2 (1.1)	57 (23)
8[a]	**4b**	O	-	-	0 (65)
9[a]	**3b**	Boc	-	-	n.d. (37)
10[a]	**3c**	TFA	-	-	n.d. (11)
11	**3d**	H	-	HBF_4•OEt_2 (1.1)	40 (26)
12[a,h]	**3e**	H	BF_3	-	44 (22)
13[a]					70 (8)



Entry	Heterocycle	R	Yield (%) (rsm)[e]	Selectivity[j]
14	**3g**	Me	57 (4)	1:1 δ/mixture
15	**4c**	-	53 (10)	2.6:1 δ/γ

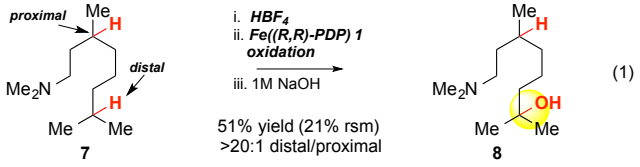
[a]Iterative addition (3x): 5 mol% **1**, AcOH (0.5 equiv), H_2O_2 (1.2 equiv), MeCN (ref 4a). [b]Slow addition: 25 mol% **2**, AcOH (5.0 equiv), H_2O_2 (9.0 equiv), MeCN, syringe pump 6 mL/min (ref 4b,c). [c]Catalyst enantiomers used interchangeably. [d]Method A: (i) Additive (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition, (iii) 1M NaOH. [e]Isolated yields, % recovered starting material (rsm). [f]No product observed with H_2SO_4 (0.55 equiv). [g]In situ addition of HBF_4 (1.1 equiv). [h]2° Piperidine-BF_3 complex **3e** isolated and purified. Product **5e** isolated/purified as 2° piperidine-BF_3 complex. [i]Method B: (i) HBF_4•OEt_2 (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Slow addition, (iii) 1M NaOH. [j]Based on isolation.

strongly influence site-selectivity, as highly electrophilic metal oxidants (e.g. Fe=O) disfavor oxidation of electron-deficient C(sp^3)—H bonds. Functionalities with positive charges, such as ammonium cations, or strongly polarized dative bonds, such as amine-borane adducts, exert a strong inductive effect on adjacent C—H bonds.[5] We hypothesized that Lewis/Brønsted acid complexation of nitrogen would afford nitrogen tolerance and remote site-selectivity in iron-

catalyzed C(sp^3)—H oxidations. Herein, we describe strategies that enable remote, non-directed aliphatic C—H oxidation in substrates containing prevalent nitrogen functional groups: amines (3°, 2°, 1°) and pyridines. Imides tolerate oxidative conditions without complexation and promote remote C(sp^3)—H oxidation.

We evaluated two strategies to effect nitrogen tolerance/remote oxidation: azaphilic, oxidatively stable Lewis acid complexation with boron trifluoride (BF_3) and irreversible protonation with tetrafluoroboric acid (HBF_4), a strong Brønsted acid with a weakly coordinating counterion. Whereas some precedent exists with these strategies for C—H oxidations,[6] olefin oxidations[7a-b] and metathesis,[7c] no examples of remote aliphatic C—H oxidations under ligated transition metal catalysis are known. In metal complexes having basic, dative ligands (e.g. PDP), competitive complexation with acid may lead to catalyst deactivation. Exploration of BF_3 complexation with both 3° piperidine **3a** and pyridine **4a** provided encouraging yields of remotely oxidized products (Table 1, entries 1, 2). HBF_4 protonation afforded remote oxidation products with improved yields for both **3a** and **4a** (entries 3, 7). The same protocol with trifluoroacetic acid or sulfuric acid,[6c] which generate more coordinating counterions, resulted in decreased yield (entry 4, 5). An in situ HBF_4 protocol resulted in diminished yield of **5a**, suggesting excess acid is not beneficial (entry 6). Oxidation of pyridine *N*-oxide **4b** was unproductive (entry 8).[6a]

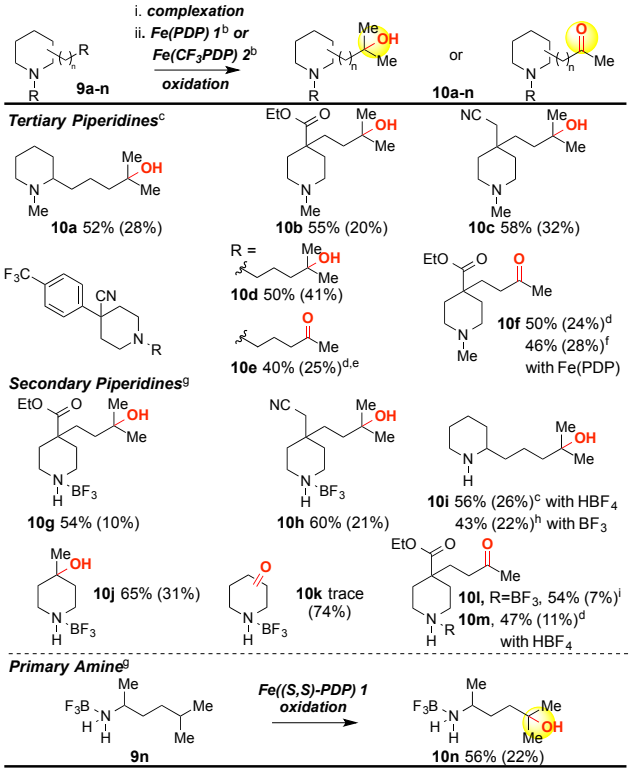
Oxidation of acyl-protected piperidines (**3b-c**, entries 9, 10) resulted in over-oxidized products, likely via *N*-dealkylation pathways. Both HBF_4 protonation and BF_3 complexation are effective with 2° piperidine **3d** (entries 11, 12). The BF_3 complexation strategy is preferable for 2° and 1° amines due to facile purification of oxidized amine-BF_3 complexes. Additionally, these complexes can be stored without precaution to exclude atmosphere.[8] Despite indiscriminate oxidation of carbamates and amides, we found that imides attenuate nitrogen basicity and enable remote oxidation (entry 13).



(1)

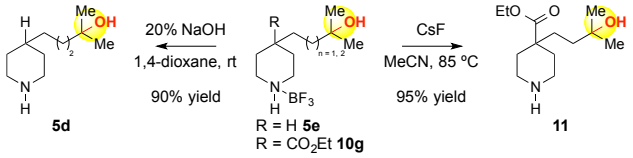
Remote methylene oxidation of piperidine **3g** and pyridine **4c** with Fe(CF$_3$PDP)[4c] afforded good overall yields but with significantly diminished site-selectivities (Table 1, entries 14, 15). In contrast, Fe(PDP) hydroxylation of remote 3° C—H bonds proceeds with high site-selectivity; no benzylic or methylene oxidation products were detected. HBF_4 protonation/oxidation of a linear substrate with competing 3° sites proceeded with excellent selectivity (>20:1 distal/proximal), favoring the site distal from the protonated amine (eq 1). Electron-withdrawing groups (e.g. Br, F, OAc) previously evaluated did not afford such strong inductive deactivation of proximal sites (9:1, 6:1, 5:1 distal/proximal,

Table 2. Basic Amines[a]



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B. [e]Starting material recycled 1x. [f]Method B with **1**. [g]Method A with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. Isolated as BF_3-complex, no NaOH workup. [h]Method A with BF_3•Et_2O (1.1 equiv). [i]Method B with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. Isolated as BF_3-complex, no NaOH workup.

Scheme 1. Amine Deprotection Strategies



respectively).[4a] Collectively, these data suggest that Brønsted/Lewis acid complexation renders basic nitrogen a strong inductive withdrawing moiety, enabling remote C—H oxidations often with high site-selectivities.

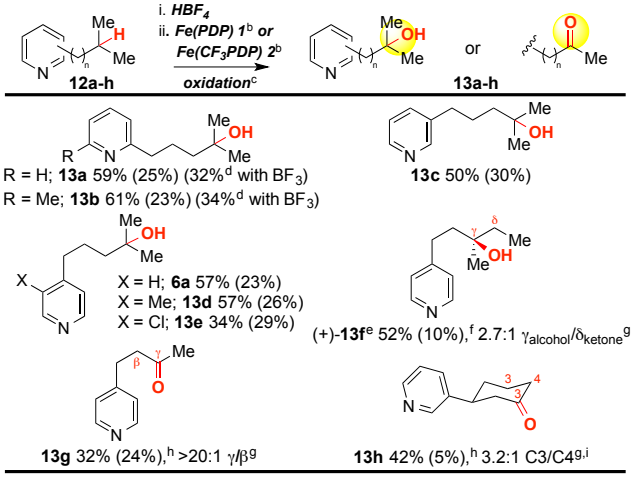
Piperidines substituted at N, C4, and C2 are the most prevalent nitrogen heterocycles in drugs.[1a] Employing HBF_4 protonation, Fe(PDP)-catalyzed tertiary oxidations of *N*-methyl or *N*-alkyl substituted piperidines proceeded uniformly in high yields and with excellent site-selectivities to afford 3° hydroxylated products (Table 2). Notably, piperidine **9a** with C2-alkyl substitution was hydroxylated in 52% yield (**10a**), showcasing the effectiveness of HBF_4 protonation in sterically hindered environments. Piperidines with a variety of functional groups (esters, nitriles, electron deficient aromatics) perform well under conditions where competitive hydrolysis or oxidation may occur (**10b-f**). The 4-phenylpiperidine motif in **10d-e** represents a pharmacophore found in opioids such as ketobemidone and haloperidol.[9] Improved site-selectivities for Fe(CF$_3$PDP)-catalyzed remote methylene oxidations were observed in substrates having more electronic differentiating elements (**10e** and **10f,** 40% and 50%, respectively).

Analogous 2° piperidine-BF_3 complexes worked with equal facility for remote tertiary and secondary oxidations (Table 2). Underscoring the variance in electronics between 3° and 2° C—H bonds, oxidation of **9j** delivered 3° alcohol **10j** in 65% yield, whereas methylene oxidation of **9k** gave trace product. The BF_3 complexation strategy is preferred for oxidation of sterically unencumbered 2° and 1° amines (**10n**), where challenges in product isolation with HBF_4 protonation lead to diminished isolated yields (**10l** vs **10m**). Protonation with HBF_4 is advantageous in cases where steric hindrance at nitrogen retards effective BF_3 coordination (**10i** 56% and 43% yield, respectively). Hydroxylated amine-BF_3 complexes are readily converted to the free amine via base-mediated hydrolysis or exposure to a nucleophilic fluoride source (Scheme 1). The latter protocol is advantageous for substrates containing hydrolytically unstable functional groups, such as **10g**.

Pyridines are the most prevalent heteroaromatic in FDA approved pharmaceuticals.[1a] Fe(PDP)-catalyzed remote hydroxylation of 3° sites in 2-alkylpyridines proceeded smoothly using HBF_4 protonation for both mono- and di-substituted substrates (**13a** 59%, **13b** 61%, Table 3). In these sterically encumbered substrates, complexation with BF_3 affords diminished yields (32% and 34%, respectively). Long-chain 3-alkylpyridines, prevalent in natural products,[10] are efficiently oxidized (**13c** 50%). Remote oxidation proceeds in good yields with electron rich pyridines (**6a, 13d**) whereas yield and mass balance are lower with an electron deficient substrate (**13e** 34% yield, 29% recovered starting material (rsm)). Pyridines having less electronically favored and exposed 3° sites afford modest site-selectivity (**13f** 52%, 2.7:1). The one carbon shortened analog of 4-pentylpyridine (**4c**, Table 1) underwent methylene oxidation with improved site-selectivity (>20:1) but in diminished yield (**13g** 32% yield). In cyclohexanes[4b] having bulky, inductive withdrawing substituents, stereoelectronic preference for oxidation at C3 overrides electronic preference for oxidation at C4 (**13h** 1.6:1 C3/C4 adjusted for number of hydrogens).

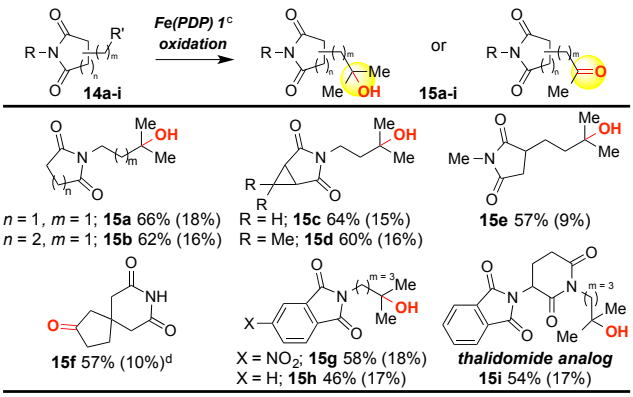
Imides are abundant in biologically active molecules and serve as synthetic precursors to amines.[11] Succinimide **14a** and glutarimide **14b** were oxidized in excellent yield, without requirement for Brønsted/Lewis acid complexation, to afford the corresponding alcohols (Table 4). Cyclopropyl modified succinimides are tolerated in this C—H oxidation reaction (**15c-d**). Spirocyclic glutarimide **14f**, a substructure in anxiolytic agent buspirone,[12] underwent site-selective methylene oxidation in good yield (57%). Analogous to reactivity in enzymatic oxidations,[1b] we have observed Fe(PDP) to effect both oxidative *N*-dealkylation of amines and oxidation of electron neutral or rich aromatics. No *N*-demethylation was observed with imide **14e** (57%) and both 4-nitrophthalimide **14g** and unsubstituted phthalimide **14h** were oxidized in useful yields (**15g** 58%; **15h** 46%).[13] Underscoring the medicinal relevance of this reaction, oxidation of thalidomide analog **14i** afforded **15i** in good yield (54%). Imides are oxidatively stable and inductively deactivating motifs that promote remote oxidations.

Table 3. Pyridines[a]



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B with BF_3•OEt_2 (1.1 equiv), catalyst **1** and 20% NaOH workup. [e](+)-**13f** Refers to pure alcohol. [f]Starting material recycled 1x. [g]Based on isolation. [h]Method B. [i]1.6:1 C3/C4 adjusted for number of hydrogens.

Table 4. Imides[a,b]

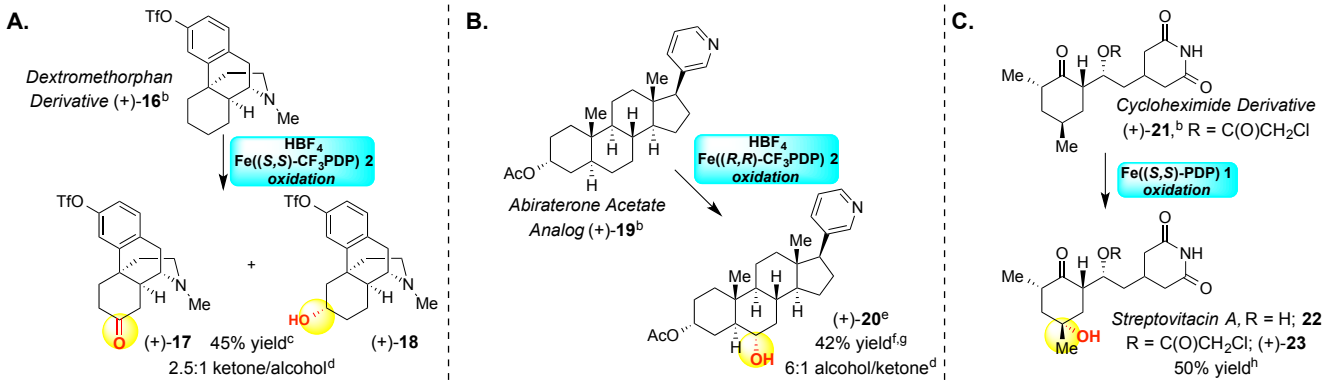


[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Iterative addition. [c]Catalyst enantiomers used interchangeably. [d]Starting material recycled 1x.

We evaluated efficacy of the aforementioned nitrogen protection strategies paired with Fe(PDP) or Fe(CF_3PDP) oxidation in late-stage diversification of medicinally important complex molecules. Dextromethorphan, an antitussive drug of the morphinan class, contains a basic *N*-methyl piperidine moiety, an aromatic ring and a benzylic site, all highly prone to oxidation (Scheme 2A). We hypothesized that benzylic deactivation would result from the proximally fused tertiary piperidine, which as its ammonium BF_4 salt would be rendered a strong inductive withdrawing group. Exposure of **16** to HBF_4 protonation/Fe((*S,S*)-CF_3PDP) oxidation afforded remote, non-benzylic oxidation products, ketone **17** and alcohol **18** in 45% yield with preference for the least sterically hindered methylene site (2.5:1 ketone/alcohol).

Abiraterone acetate, having a C17-(3-pyridyl) motif, is a steroidal antiandrogen used in the treatment of prostate cancer. Despite a strong preference for oxidation at 3° benzylic sites (BDE~83 kcal/mol),[14] exposure of **19** to HBF_4 protonation/Fe((*R,R*)-CF_3PDP) oxidation resulted in a site-selective remote oxidation at C6 (BDE~98 kcal/mol) of the steroid core in 42% yield (6:1 alcohol/ketone) (Scheme 2B).

Scheme 2. Late-Stage Functionalization of Nitrogen Containing Molecules[a]



[a]Isolated yield is average of two runs. [b]Substrates containing chirality demonstrated matched/mis-matched reactivity with catalyst enantiomers. [c](i) HBF_4•Et_2O (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Slow addition with **2**, (iii) 1M NaOH. [d]Based on isolation. [e](+)-**20** Refers to pure alcohol. [f](i) HBF_4•Et_2O (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition with **2**, (iii) $NaHCO_3$. [g]Starting material recycled 2x. [h]Iterative addition with **1**.

These represent the first examples of transition metal catalyzed remote, aliphatic C—H oxidations on a morphinan and nitrogen-containing steroid skeletons.

Cycloheximide, a readily available natural product with broad antimicrobial activity but high toxicity is currently used as a protein synthesis inhibitor. The C4 hydroxylated analogue, streptovitacin A **22**, has shown diminished toxicity and has been obtained via an eight step de novo synthesis proceeding in 7% overall yield.[15] The direct oxidation of cycloheximide derivative **21** with Fe((*S,S*)-PDP) affords streptovitacin A derivative **23** in excellent yield (50%) (Scheme 2C), underscoring the power of remote late stage C—H oxidation to streamline synthesis.

We have demonstrated remote Fe(PDP)-catalyzed oxidation in a range of nitrogen heterocycles by employing Brønsted/Lewis acid complexation strategies. We envision this will be a highly enabling methodology for the generation of medicinal agents via late-stage oxidation and for the evaluation of their metabolites.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

mcwhite7@illinois.edu

Author Contributions

‡These authors contributed equally.

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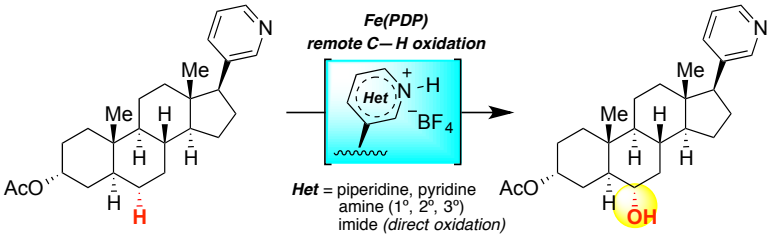

39 examples, avg. 53% yield