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Remote Oxidation of Aliphatic C−H Bonds in Nitrogen-Containing Molecules

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Supporting Information

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, secondary, and primary 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 secondary (2°) and primary (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 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 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, was not effective (entries 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]

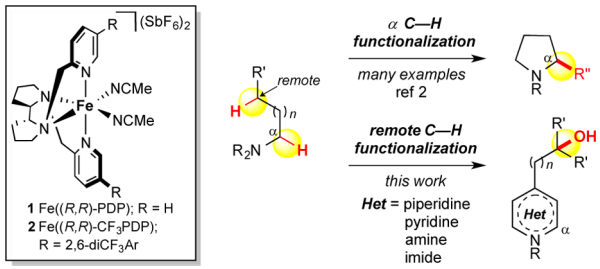

Figure 1. Heterocycle functionalization.

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).

Remote methylene oxidation of piperidine **3g** and pyridine **4c** with Fe(CF_3PDP)[4c] afforded good overall yields but with significantly diminished site-selectivities (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

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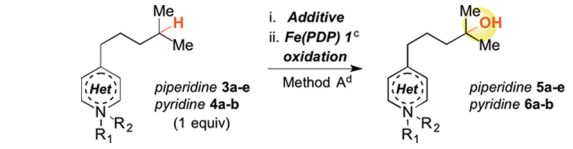
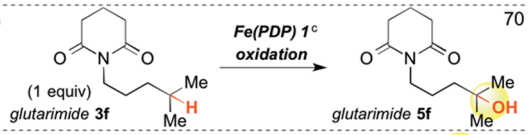
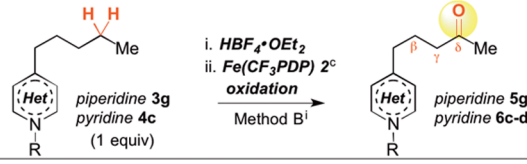
Table 1. Reaction Optimization[a,b]



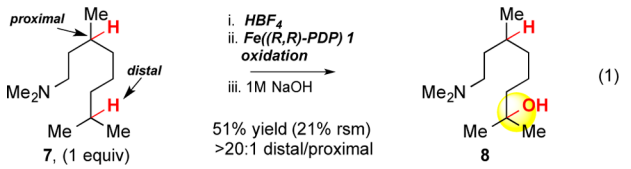
Entry	Heterocycle	R_1	R_2	Additive (equiv)	Yield (%) (rsm)[e]
1	**3a**	Me	-	BF_3•OEt_2 (1.1)	46 (28)
2	**4a**	-	-	BF_3•OEt_2 (1.1)	27 (67)
3	**3a**	Me	-	HBF_4•OEt_2 (1.1)	56 (29)
4	**3a**	Me	-	F_3CCO_2H (1.1)	5 (74)
5[f]	**3a**	Me	-	H_2SO_4 (1.1)	0 (76)
6[g]	**3a**	Me	-	HBF_4•H_2O (1.1)	43 (40)
7	**4a**	-	-	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 (3×): 5 mol% **1**, AcOH (0.5 equiv), H_2O_2 (1.2 equiv), MeCN.[4a] [b]Slow addition: 25 mol% **2**, AcOH (5.0 equiv), H_2O_2 (9.0 equiv), MeCN, syringe pump 6 mL/min.[4b,c] [c]Catalyst enantiomers used interchangeably. [d]Method A: (i) additive (1.1 equiv), CH_2Cl_2, concentrated in vacuo, (ii) iterative addition, (iii) 1 M 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 purifed. Product **5e** isolated/purified as 2° piperidine–BF_3 complex. [i]Method B: (i) HBF_4·OEt_2 (1.1 equiv), CH_2Cl_2, concentrated in vacuo, (ii) slow addition, (iii) 1 M NaOH. [j]Based on isolation.

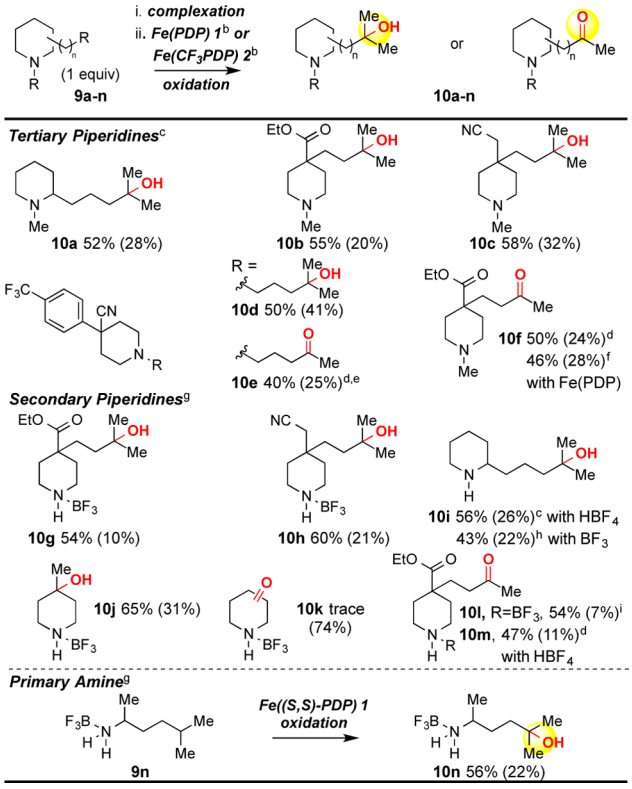
of a linear substrate with competing 3° sites proceeded with excellent selectivity (>20:1 distal/proximal), favoring the site distal from the protonated amine (eq 1). Electron-withdrawing



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, 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_3PDP)-catalyzed remote methylene oxidations were observed in substrates having more electronically differentiating elements (**10e,f** 40% and 50%, respectively).

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 1×. [f]Method B with **1**. [g]Method A with BF_3·Et_2O (1.1 equiv), concentrated 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), concentrated and purified prior to use. Isolated as BF_3 complex, no NaOH workup.

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

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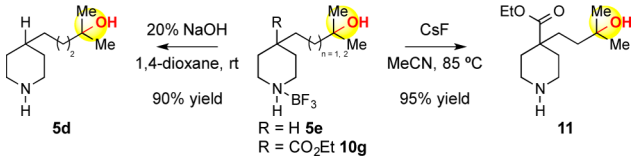
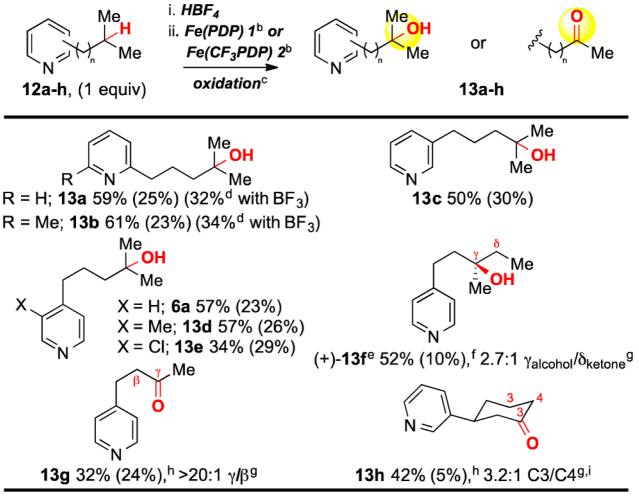
Scheme 1. Amine Deprotection Strategies



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 disubstituted 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

Table 3. Pyridines[a]

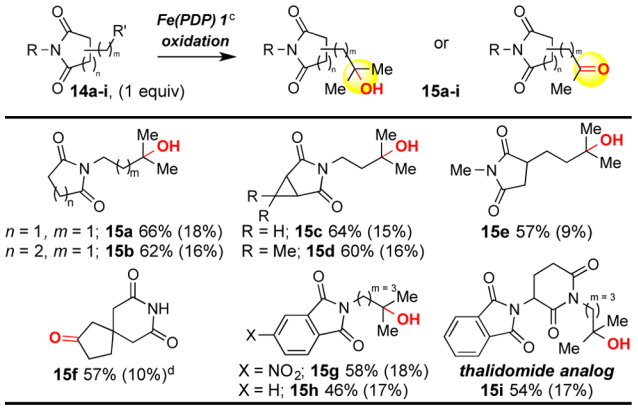


[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4·Et_2O (1.1 equiv). [d]Method B with BF_3·OEt_2 (1.1 equiv), catalyst **1**, and 20% NaOH workup. [e](+)-**13f** refers to pure alcohol. [f]Starting material recycled 1×.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

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 analogue 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

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 1×.

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 analogue **14i** afforded **15i** in good yield (54%). Imides are oxidatively stable and inductively deactivating motifs that promote remote oxidations.

We evaluated the efficacy of the aforementioned nitrogen protection strategies paired with Fe(PDP) or Fe(CF_3PDP) oxidation in the late-stage diversification of medicinally important complex molecules. Dextromethorphan, an antitussive drug of the morphinan class, contains a basic *N*-methylpiperidine 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 diastereomerically pure 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 and diastereoselective remote oxidation at C6 (BDE ≈ 98 kcal/mol) of the steroid core in 42% yield (6:1 alcohol/ketone) (Scheme 2B). 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%

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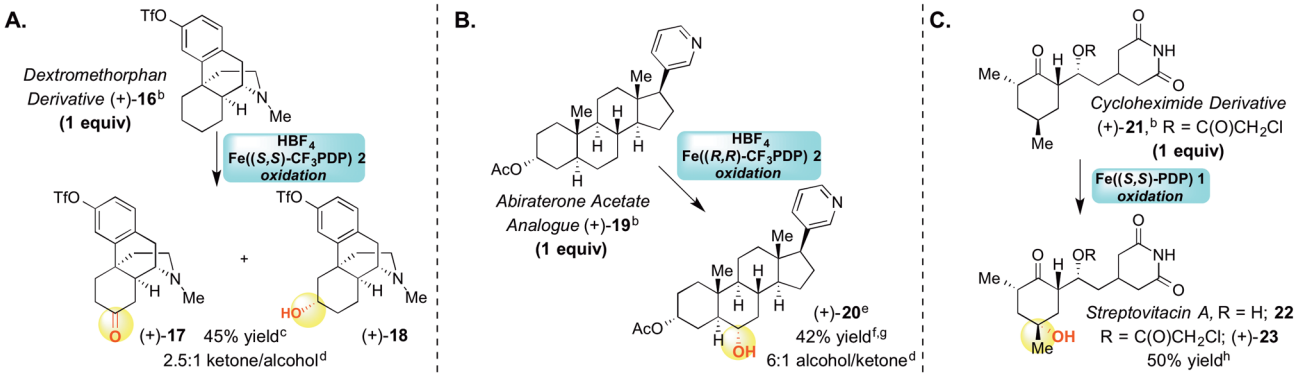
Scheme 2. Late-Stage Functionalization of Nitrogen-Containing Molecules[a]



[a]Isolated yield is average of two runs. [b]Substrates containing chirality demonstrated matched/mismatched reactivity with catalyst enantiomers. [c](i) $HBF_4{\cdot}Et_2O$ (1.1 equiv), CH_2Cl_2, concentrated in vacuo, (ii) slow addition with **2**, (iii) 1 M NaOH. [d]Based on isolation. [e](+)-**20** refers to pure alcohol. [f](i) $HBF_4{\cdot}Et_2O$ (1.1 equiv), CH_2Cl_2, concentrated in vacuo, (ii) iterative addition with **2**, (iii) $NaHCO_3$. [g]Starting material recycled 2×. [h]Iterative addition with **1**.

overall yield.[15] The direct oxidation of cycloheximide derivative **21** with Fe((*S*,*S*)-PDP) affords streptovitacin A derivative **23** in one step and 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10299.

Experimental details and characterization data (PDF)
Spectral data (PDF)
X-ray crystallographic data for **20**-ketone (CIF)

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Notes

The authors declare no competing financial interest.

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