Communication

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A Combined Iron/Hydroxytriazole Dual Catalytic System for Site Selective Oxidation Adjacent to Azaheterocycles

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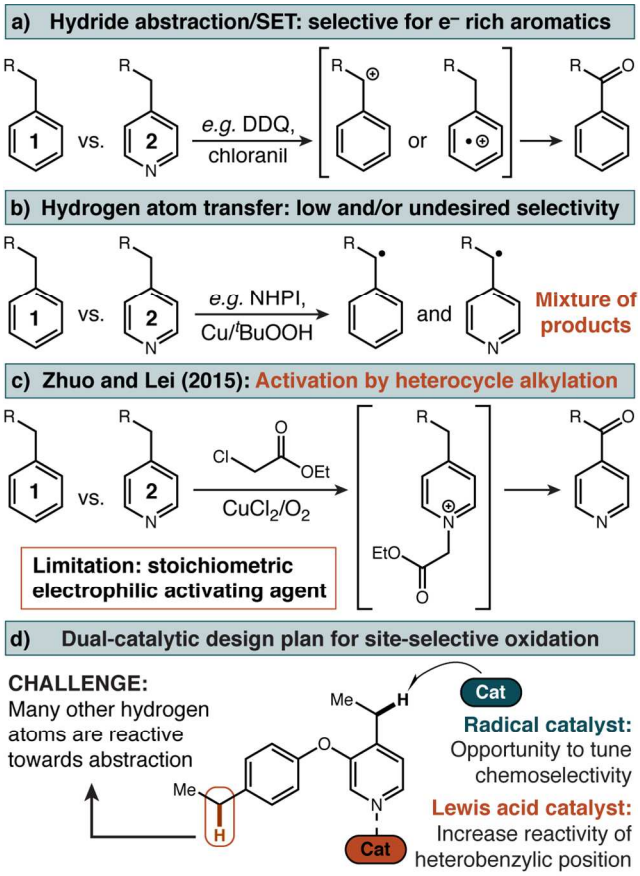
Supporting Information Placeholder

ABSTRACT: This report details a new method for site-selective methylene oxidation adjacent to azaheterocycles.A dual catalysis approach, utilizing both an iron Lewis acid and an organic hydroxylamine catalyst proved highly effective.We demonstrate thatthis method provides complementary selectivity to other known catalytic approaches and represents an improvement over current heterocycle-selective reactions that rely on stoichiometric activation.

Nitrogen-containing heterocyclesare key motifs found in an array of pharmaceuticals, agrochemicals and natural products.[1]Specifically, over 250 FDA-approved drugs include *aromatic* azaheterocycles.[1b] New techniquesthatpredictably diversify these substructures in complex settingswill enablefurther discovery.[2]For example, systems that could oxidize heterobenzylic sp^3C-H bonds in the presence of other reactive positions would circumvent more common methods for the synthesis ofcomplex heterobenzylic ketones, whichoftenrequire multi-step sequences.[3]Such technology would also allow for late-stage synthesis of potential metabolites.[4]

The overwhelming majority of known benzylic oxidation methods cannot be used to *site-selectively* oxidize adjacent to azaheterocycles.[5] A comparison of the reactivity of an alkylbenzene (**1**) and alkylpyridine (**2**)shows why(Scheme 1), and we experimentally confirm these following statements:We expected hydride abstraction or single electron transfer (Scheme 1a) to be selective for electron rich positions.[6] A number of hydrogen atom transfer (HAT) oxidations are known (Scheme 1b),[7] but most HAT mediating agents typically display modest to good selectivity for nucleophilic positions.[8] Heterobenzylic deprotonation is potentially viable, but has only been demonstrated withactivated positions where the pK_a of the benzylic C-H issignificantlylowered.[9] Several methods have been shown to allow for selective oxidation at positions *away* from the azaheterocycle.[10] An important advance was realized by Leiand Zhuo in 2015 (Scheme 1c),[11] where they demonstratedthat azaheterocycles could be activatedby



Scheme 1. Knownsite selectivity of oxidation by different mechanistic pathways (a–c) and our proposed strategy (d).

alkylation. Whilethis represented a significant improvement, the use of a stoichiometricelectrophilic activator may limit applications in

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complex settings. A fully catalytic system for heterocycle-selective oxidation remains absent and is highly desirable.

We envisioned a dual-catalytic approach to address this need (Scheme 1d). Thermodynamic and kinetic studies have demonstrated that metal coordination can modulate homolytic C-H, C-C, and X-H bond strength and reactivity, and we aimed to use these effects to enforce site-selectivity.[12] We further aimed to fine tune selectivity by optimizing thestructure of a second organic catalyst, inspired by the known HAT ability of *N*-hydroxyphthalimide (NHPI).[13] Herein, we describe the successful execution of this design plan.

Wefirst investigated known oxidation methods (Table 1). DDQ is completely selective for ethylbenzene (**1**) over ethylpyridine (**2**) (entry 1). A number of reports have described the non-competitive oxidation of alkylheterocycles.They displayed either low reactivity (entry 2) or favored benzylic oxidation (entries 3-5) in this competitive setting.[14]Thestoichiometric alkylation strategy of Zhuo and Lei (entry 6, 87:1) served as a benchmark for our own investigations.

We were drawn to copper and iron for their benign nature. $Cu(OTf)_2$ and $Fe(BF_4)_2{\bullet}6H_2O$ proved to be the most effective of each element from several simple salts tested (see Supporting Information). A selection of multi-dentate ligands andpotential HAT catalysts were investigated (Table 2) in a competition experiment featuring ethylpyridine (**1**) and ethylbenzene (**2**). $Cu(OTf)_2$ performed poorly independent of ligand (entries 1-3), while$Fe(BF_4)_2$-based systems showeda strikingdependence (entries 4-9). Tris(pyrazole)borate (**11**) is uniquely effective (entry 7, 74%, 44:1 selectivity):the closelyrelated tris(pyrazole)methane (**12**) only delivered trace product (entry 8, 2.4%). Not all iron sources showed such dependence: $FeCl_2$ can deliver modest yield (38%) even in the absence of ligand, and only delivers slightly higher yield (44%) with ligand **11** included (TableS1, Supporting Information). Yield andselectivityimprovedfurther with $Fe(BF_4)_2$ by tuning HAT catalyst structure(entries 7, 10-12). 1-Hydroxy-7-azabenzotriazole (HOAt, **8**) delivered optimal chemical yield and siteselectivity (entry 12, 86%, 95:1 selectivity). Reactions lacking a HAT catalyst still showed

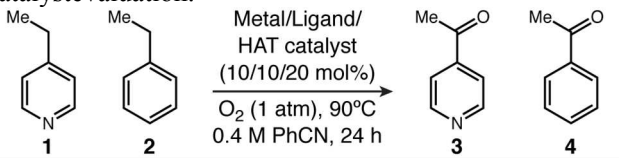
Table 1. An evaluation of current oxidation methodology.

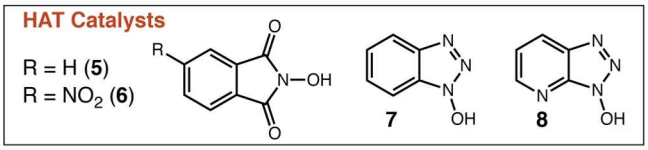
Entry	Reaction system	Literature	3:4 selectivity[a]
1	DDQ	Usual conditions	<1:99
2	CuI/AcOH/DMSO	ref. 9b	No reaction
3	NHPI/$Co(OAc)_2$/AcOH	ref. 14c	1:43
4	NHPI/$Co(OAc)_2$/BuOAc	ref. 14a	1:2.2
5	CuI/^{t}BuOOH/neocuproine	ref. 14b	1:5.0
6	$ClCH_2CO_2Et/CuCl_2$	ref. 11	87:1

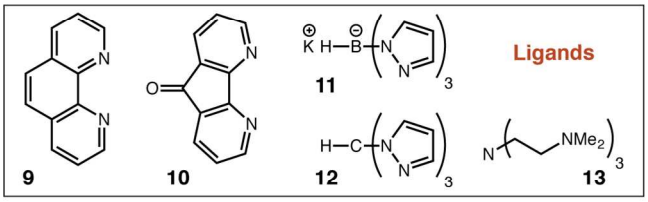
Standard for sucess of fully catalytic system: ≥87:1 selectivity

[a]Measured by direct GC analysis of crude reaction mixture

Table 2. Metal, ligand, and organic HAT catalystevaluation.







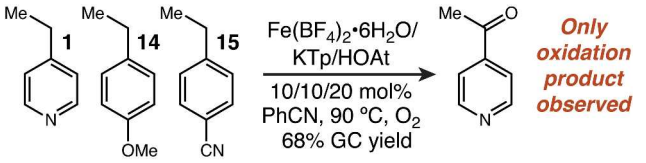
Entry	Metal	HAT	Ligand	Yield **3**[a]	Yield **4**[a]	**3**:**4** ratio[a]
1	$Cu(OTf)_2$	**5**	None	31%	19%	1.6:1
2	$Cu(OTf)_2$	**5**	**9**	33%	36%	1:1.1
3	$Cu(OTf)_2$	**5**	**11**	7.1%	29%	1:4.1
4	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	None	4.4%	1.1%	4.0:1
5	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	**9**	7.1%	2.9%	2.4:1
6	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	**10**	2.0%	0.6%	3.3:1
7	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	**11**	74%	4.1%	44:1
8	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	**12**	2.4%	0.9%	2.7:1
9	$Fe(BF_4)_2{\bullet}6H_2O$	**5**	**13**	<0.5%	<0.5%	N/A
10[b]	$Fe(BF_4)_2{\bullet}6H_2O$	**6**	**11**	72%	0.9%	80:1
11[b]	$Fe(BF_4)_2{\bullet}6H_2O$	**7**	**11**	80%	1.9%	42:1
12[b]	$Fe(BF_4)_2{\bullet}6H_2O$	**8**	**11**	86%	0.9%	95:1
13[b]	$Fe(BF_4)_2{\bullet}6H_2O$	None	**11**	37%	0.9%	41:1

[a]Yields and selectivities determined by direct GC analysis. [b]16 h reaction time.

modest conversion (37%, entry 13), which may reflect these iron(II) complexes' ability to directly activate dioxygen.[15]Still, the full system composed of $Fe(BF_4)_2$/**11**/**8** clearly delivered the best performance.A three-substratecompetition also showed that heterocycleselectivity was high in the presence of electron-rich and poor positions (Scheme 2, **1** vs. **14** vs. **15**).These conditions typically result in full conversion when secondary C-H bonds are present at the reactive position. Primary or tertiary bonds return significant

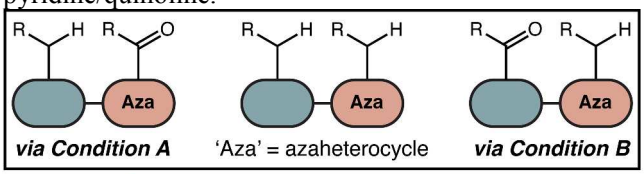
starting materials (25-40%, see Supporting Information).

We applied our newly designed C-H oxidation method to pyridines with multiple benzylic positions.Avariant of Ishii'sconditions,[14c, 16] was used for comparison, as a representativesystem that favors electron-rich benzylic positions (Table 3). With our conditions, we do not observe single oxidation at theundesired aromatic position (site 'O'). In cases where smallamounts of byproduct could be isolated, the structures



Scheme 2. Aromatic electronic effects on site selectivity.

Table 3. Selective oxidation adjacent to pyridine/quinoline.



Condition A: $Fe(BF_4)_2•6H_2O$/**11/6** (10/10/20 mol%), PhCN, 90 °C

Condition B: $Co(OAc)_2•4H_2O$/**5** (2.5/20 mol%), AcOH, 90 °C

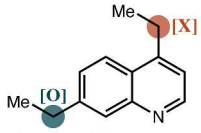
Entry 1^a

Condition **A**: 67% yield, >20:1 X:O
Condition **B**: 56% yield, <1:20 X:O[b]

Entry 2^a

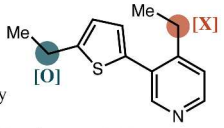
Condition **A**: 73% yield, >20:1 X:O
Condition **B**: No reaction

Entry $3^{a,c,d}$



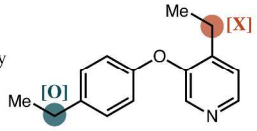
Condition **A**: 90% yield, 21:1 X:X+O
Condition **B**: ~40% yield, ~1:3 X:All others

Entry 4^a



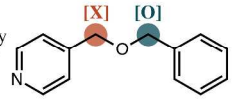
Condition **A**: 42% yield, >20:1 X:O
Condition **B**: 48% yield, <1:20 X:O

Entry 5^a



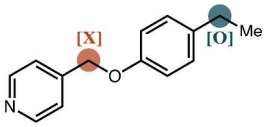
Condition **A**: 62% yield, >20:1 X:O
Condition **B**: 50% yield, <1:20 X:O

Entry $6^{a,d}$



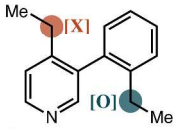
Condition **A**: 75% yield, 28:1 X:X+O
Condition **B**: <5% yield

Entry $7^{a,d}$



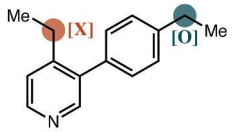
Condition **A**: 60% yield, 19:1 X:X+O
Condition **B**: <5% yield

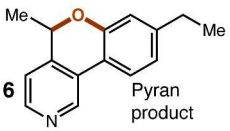
Entry $8^{a,d}$



Condition **A**: 29% yield, 3:1 X:X+O
Condition **B**: No reaction

Entry 9^a



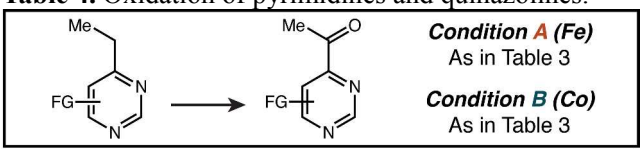


Condition **A**: 47% yield, >20:1 X:O —with an additional 24% of pyran product **16**
Condition **B**: 62% yield, <1:20 X:O

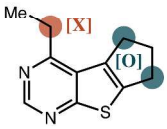
[a]Yields reported are isolated yields after purification by chromatography. >20:1 or <1:20 selectivity refers to cases where the minor regioisomer was not isolated.
[b]In addition to 56% C=O, 2% -CHOH and 4% -CHOAc at site 'O' were observed.
[c]Condition 'B' delivered a mixture of byproducts with one or both sites oxidized.
[d]"X+O" refers to byproducts that had undergone oxidation at both reactive positions.

appeared to have undergone oxidation at both reactive position (entries 3, 6, 7, and 8 "X+O"). With the exception of substitution at both biaryl ortho positions (entry 8), useful results were obtained throughout (42-90% yield, 19:1 or better selectivity). This was trueboth when the benzylicpositionswere adjacent to separaterings (entries 1, 4-9) or located on the same ring system (entries 2 and 3). These conditions are also compatible with benzylic heteroatoms. A direct ether-to-ester conversion is possible(entries 6 and 7), as well as the conversion of anamide to an imide (*vide infra*).3-ethylpyridine is entirely unreactive, while 2-ethylpyridine is modestly reactive (25%, see SupportingInformation).Ishii'sconditions give theopposite selectivityin every case where reaction was observed(entries 1, 3-5, 9).One othernoteworthybyproductwas observed in entry 9. Cyclization to form a pyran (**16**)likely occurs during breakdown of an intermediate hydroperoxide. Measurable amounts (~3%) of an analogous byproduct could also be observed in entry 8.

Table 4. Oxidation of pyrimidines and quinazolines.

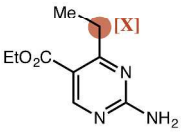


Entry 1^a



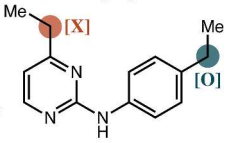
Condition **A**: 51% yield, >20:1 X:O
Condition **B**: Multiple products

Entry 2^a



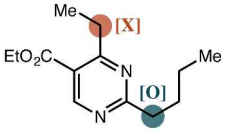
Condition **A**: 67% yield
Condition **B**: 7% yield

Entry 3^a



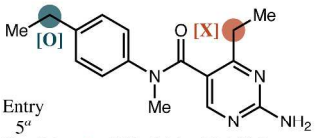
Condition **A**: 57% yield, >20:1 X:O
Condition **B**: No reaction

Entry 4^a



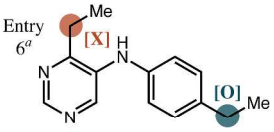
Condition **A**: 54% yield, >20:1 X:O
Condition **B**: 8% yield, >20:1 X:O

Entry 5^a



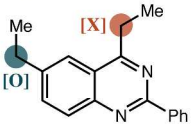
Condition **A**: 47% yield, >20:1 X:O
Condition **B**: No desired products

Entry 6^a



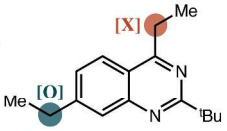
Condition **A**: 41% yield, >20:1 X:O
Condition **B**: 36% yield, >20:1 X:O

Entry $7^{a,b}$



Condition **A**: 68% yield, 27:1 X:X+O
Condition **B**: 45% yield, >20:1 X:O

Entry $8^{a,b}$



Condition **A**: 51% yield, 18:1 X:X+O
Condition **B**: 59% yield, 5.6:1 X:O

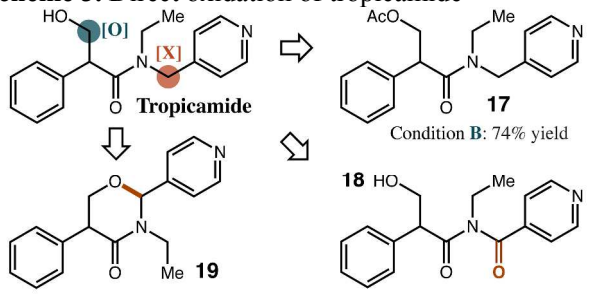
[a]Yields reported are isolated yields after purification by chromatography. >20:1 or <1:20 selectivity refers to cases where the minor regioisomer was not isolated.
[b]"X+O" refers to byproducts that had undergone oxidation at both reactive positions.

We next investigated pyrimidines and quinazolines (Table 4). Again, our conditions completely distinguish

between reactive positions adjacent to separate rings (entries 3, 5-6) or on the same ring (entries 1, 4, 7-8). While cobalt-catalyzed conditions were selective for the heterobenzylic position in many cases, across the range of substrates shown, iron-based conditions were either higher yielding or more selective—or both—in all cases. As the heterocycle–iron interaction is disfavored by steric congestion the oxidation systemsbegin to converge, as would be expected (*c.f.* entry 2vs. 7 and8). We have encountered two noteworthylimitations: As with many dioxygen-based systems, *N*-dealkylation of alkylamines is observed.[17] Strongly chelating substituents (*e.g.* 2-acetamido) are not currently tolerated.

Finally, we were pleasedto see our conditions wereamenableto direct modificationof a pharmaceuticalagent: the anti-muscarinic agent tropicamide could be directly oxidized at the heterobenzylic position (Scheme 3). Inaddition to the carbonyl product (**18**, 55% yield), trapping ofan initial oxidation product by cyclization also produces aninteresting cyclized derivative (**19**, 11% yield). Cobalt-catalyzed conditions only resulted in substrate acetylation.

Scheme 3. Direct oxidation of tropicamide



Condition **A**: 66% total yield: 55% **18** and 11% **19** (as a single racemic diastereomer)
Yields reported are isolated yields after purification by chromatography.

Given the reaction response to both catalyst structures, we believe that C-H cleavage occurs by HAT from a metal-coordinated[12] heterocycle. The resulting radical then delivers carbonyl products through an autoxidation mechanism.[18] We have initiated mechanistic studies to either support of oppose this speculation, with the aim to increase reactivity toward primary and tertiary positions, and understand factors controlling chemoselectivity (*i.e.* production of aldehydes vs. acids or tertiary alcohols vs. C-C bond fragmentation). These results will be reported in due course.

ASSOCIATED CONTENT

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

Experimental procedures, optimization tables,GC traces, and characterization data for new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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