HHS Public Access

Author manuscript

Org Lett. Author manuscript; available in PMC 2019 April 06.

Published in final edited form as:

Org Lett. 2018 April 06; 20(7): 2011–2014. doi:10.1021/acs.orglett.8b00558.

Selective Heteroaryl N-Oxidation of Amine-Containing Molecules

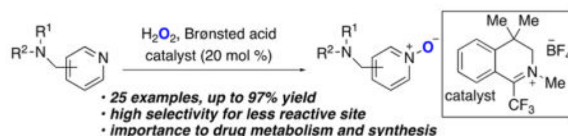
Robert M. B. Dyer, **Philip L. Hahn**, and **Michael K. Hilinski**[*]

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, United States

Abstract

The first examples of nonenzymatic N-oxidation of heteroarenes in the presence of amines are reported. Pyridine, quinoline, and isoquinoline *N*-oxides are selectively formed in the presence of more reactive aliphatic and alicyclic amines by use of an in situ protonation strategy and an iminium salt organocatalyst. Application to late-stage functionalization that mimics phase 1 metabolism of small-molecule drugs is also demonstrated.

Graphical Abstract



Achieving enzymatic levels of selectivity in oxidation reactions without resorting to biocatalysis is a significant unsolved problem in synthetic methods development.[1,2] In particular, the selective late-stage oxidation of natural products and designed bioactive molecules in order to modulate biological activity and physicochemical properties is regarded as an enabling application.[3] One of the biggest unsolved challenges in this area is the development of nonenzymatic methods that directly mimic oxidative metabolism.[4] This is of critical importance to the pharmaceutical industry, given the need for rapid identification, preparation, and characterization of the biological activity of drug metabolites.[5] Due to the relative structural complexity of drug candidates, which frequently include multiple functional groups that are prone to oxidation, the desired selectivity can be difficult to attain.

One class of transformations for which this is the case are metabolic oxidations of nitrogen-containing heteroaromatic rings (Scheme 1a). These generally fall into two categories: N-oxidation catalyzed most often by the cytochrome p450 (CYP)[6,7] or flavin-containing

[*]Corresponding Author: hilinski@virginia.edu.

ORCID

Michael K. Hilinski: 0000-0003-2861-7099

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00558.

Experimental details as well as spectroscopic and analytic data for all new compounds and oxidation products (PDF)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

monooxygenase (FMO)[8] families of enzymes and C(sp^2)–H hydroxylation adjacent to nitrogen catalyzed most often by aldehyde oxidase (AO).[9] In regards to the former transformation, nonenzymatic site-selective hetero-aryl N-oxidation is complicated by the fact that pharmaceuticals often contain aliphatic amines, which are generally more nucleophilic and thus are preferred sites of oxidation. At present, this complication can only be dealt with indirectly. For example, the state of the art for achieving selective synthesis of heteroaryl *N*-oxides in tertiary amine-containing compounds is exhaustive N-oxidation followed by selective reduction (Scheme 1b).[10,11] This approach, first illustrated in the 1940s, has not been demonstrated to be widely applicable. Given that more than two potential N-oxidation sites in a substrate or functionality sensitive to reducing conditions would greatly complicate this process, a one-step site-selective solution would be the preferred contemporary strategy. However, no examples of such a transformation have been reported. In addition to metabolite synthesis, methods for predictably site-selective N-oxidation would have other potential applications in drug discovery, given the increasing attention paid in recent years to heteroaromatic *N*-oxides as potential drug candidates.[12] As such, the lack of any nonenzymatic site-selective solutions creates a barrier to the development of new therapeutics. Herein, we describe unprecedented site-selective N-oxidations of heteroarenes in the presence of aliphatic amines. We also demonstrate the application of this method to late-stage oxidation that mimics xenobiotic metabolism.

Our strategy for site-selective N-oxidation takes advantage of the fact that, in general, the reactivity of amines and heteroarenes toward electrophilic oxidants has a positive correlation with basicity. In the presence of a suitable oxidant, in situ protection of a more nucleophilic amine by use of a Brønsted acid would in principle lead to selective formation of the heteroaromatic *N*-oxide.[13] For typical drug substrates containing an amine and a heteroarene, such as nicotine (**1**, Table 1), the difference in acidity between the protonated amine and protonated heteroarene is on the order of 5 pK_a units, which would correspond to a 10^5-fold difference in concentration between the two protonated forms when 1 equiv of a strong acid is used. Thus, identification of oxidation conditions compatible with use of a stoichiometric acid additive and that demonstrate a sufficient rate of heteroarene oxidation would in principle lead to the desired selectivity.

Initial evaluation of this strategy using the isolated mono-HBF_4 salt of nicotine as a substrate revealed that peracids, historically oxidants of choice for pyridine N-oxidation,[11,14] provided only the undesired pyrrolidine *N*-oxide when employed under typical conditions (Table 1, entries 1 and 2). Alternatively, the use of dimethyldioxirane (DMDO)[15] provided the first indication of the desired selectivity, resulting in exclusive formation of pyridine *N*-oxide **3**, albeit at low conversion (11:1 ratio of starting material to desired product) when 1 equiv was employed (entry 3). To avoid using a large excess of reagent, we explored the use of organocatalytic conditions known to approximate the reactivity of DMDO.[16] Specifically, using a trifluoromethyl iminium salt developed previously in our laboratory for use in catalytic oxaziridinium-mediated oxidations[17] the desired conversion and selectivity were attained, providing 77% isolated yield of free base **3** following basic workup and purification (entry 4). The use of 10–20 mol % of **4** allowed for minimization of the amount of hydrogen peroxide employed (2 equiv). No pyrrolidine *N*-oxide was observed under these

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

conditions, highlighting the considerable site selectivity enabled by the protonation strategy. Encouraged by these results, we evaluated whether the prior preparation of the amine salt could be avoided, enabling the desired one-step site-selective transformation. Addition of 1 equiv of HBF_4 to the iminium salt-catalyzed oxidation conditions enabled selective oxidation of the nicotine free base, with isolated yield identical to that achieved using the pre-prepared salt (entry 5). Control reactions indicate that catalyst **4** is required (entry 6) and that the use of HFIP, which we have previously shown is required as a cosolvent for best results when using catalyst **4**[17] and which is separately known to modulate oxidation selectivity through hydrogen bonding effects,[18] is not sufficient to provide the desired selectivity in the absence of an appropriate oxidant (entry 7) or HBF_4 (entry 8). Strong acids other than HBF_4 (e.g., H_2SO_4) can be used with comparable results (entry 9). Finally, under the optimized conditions the use of an organocatalytic strategy offers superior results to the use of isolated DMDO (entry 10).

Pyridines are the most abundant nitrogen-containing aromatic heterocycles in approved drugs[19] and are frequent targets for metabolic N-oxidation.[6,8] We evaluated the substrate scope of site-selective N-oxidation by employing a number of differentially substituted pyridine-containing substrates, which in each case also contained at least one aliphatic amine (Table 2). In all but one case, site-selective pyridine N-oxidation was observed, and in many cases, synthetically useful yields were achieved. In all cases, yields were limited primarily by conversion rather than substantial formation of the undesired *N*-oxide. Alicyclic, tertiary, and secondary amines were tolerated; however, attempts to oxidize a substrate bearing a primary amine (**11**) resulted in trace amounts of oxidation of the primary amine and no conversion to the desired pyridine *N*-oxide. Substitution of the pyridine ring at the 2-position proved detrimental compared to substitution at the 3- or 4-position (substrate **27** vs **25** or **5**), which could arise from steric effects or decreased nucleophilicity of the pyridine nitrogen due to inductive withdrawing effects of the protonated amine. Oxidation of a substrate containing a piperazine ring (**19**) gave selectively the product of pyridine oxidation, demonstrating that site selectivity is also achievable in the presence of more than one tertiary amine nitrogen (entry 6). In this case 1 equiv of HBF_4 was sufficient to prevent more than trace oxidation of either piperazine nitrogen.

Experiments were also performed to probe the effect of additional substitution on the pyridine ring, which revealed additional functional group compatibility and the influence of substituent effects on reaction outcome (Table 3). Pyridines substituted with halogens in the 3-position gave the highest yields observed for any substrates (entry 1). In contrast, strongly σ-withdrawing substituents at the 2-position (F, CF_3) resulted in no observed product formation.[20] Other 2-substituted pyridines (OMe, CH_3) were oxidized in good yields (entry 2). Site-selective N-oxidation was also observed for substrates bearing quinoline and isoquinoline rings (entries 3–6), expanding the range of pharmaceutically relevant heteroaromatic scaffolds shown to be amenable to this chemistry.

For complex, drug-like, or natural product substrates, the products of site-selective N-oxidation can in principle be subjected to further known transformations of *N*-oxides,[21] enhancing the impact of this single transformation by providing access to additional diverse products of late-stage functionalization. As one application of this strategy, we envisioned

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

that formal site-selective C(sp^2)–H hydroxylation might be achieved by a two-step sequence of selective N-oxidation followed by subsequent transformation to the desired formal C–H hydroxylation product. We specifically selected this transformation for its potential ability to mimic metabolic oxidation of bioactive compounds by aldehyde oxidase (AO),[22] for which there is no analogous nonenzymatic method. The importance of AO metabolism and its impact on drug discovery have become increasingly recognized in recent years,[9] with several clinical drug failures resulting from metabolism by AO in humans that had not been observed in preclinical animal studies.[23] Quinine (**51**), a known substrate of AO,[24] was subjected to this two-step C–H hydroxylation strategy. First, the desired quinoline *N*-oxide was formed selectively in 54% yield (Scheme 2). This reaction highlights the functional group tolerance of the catalytic N-oxidation, given that the desired product is selectively formed in the presence of other easily oxidized functional groups, such as an olefin and a secondary benzylic alcohol, in addition to a tertiary amine. The *N*-oxide **52** can be converted in one step to the observed product of AO oxidation as shown by Cook and co-workers.[25] Overall, this oxidation/transposition sequence demonstrates both the selectivity and valuable application of this method to metabolite synthesis.

In summary, we report the first demonstration of a method for heteroarene N-oxidation that is both predictably site selective and suitable for late-stage functionalization. The method reverses the inherent N-oxidation selectivity for all substrates evaluated, favoring heteroarene oxidation over the oxidation of aliphatic amines. As such, it is expected to provide a platform for selective modification of complex bioactive compounds that is complementary to other approaches. Furthermore, the demonstrated application of this method to metabolite synthesis could facilitate drug discovery in cases where the rapid preparation of relevant metabolites is unattainable through other means.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding from the American Chemical Society Petroleum Research Fund Doctoral New Investigator Program (PRF#56158-DNI), the National Institutes of Health (R01 GM124092), and the University of Virginia is gratefully acknowledged.

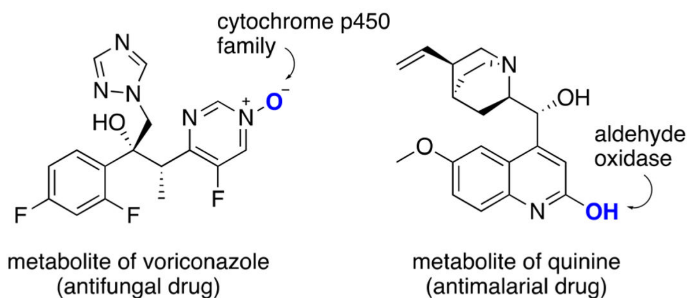
References

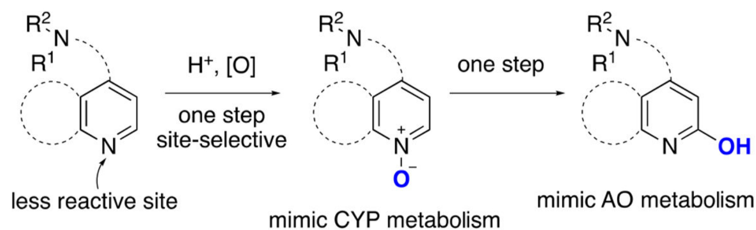
1. Newhouse T, Baran PS. Angew Chem, Int Ed. 2011; 50:3362–3374.
2. White MC. Science. 2012; 335:807–809. [PubMed: 22344434]
3. Michaudel Q, Journot G, Regueiro-Ren A, Goswami A, Guo Z, Tully TP, Zou L, Ramabhadran RO, Houk KN, Baran PS. Angew Chem, Int Ed. 2014; 53(45):12091–12096.
4. Genovino J, Sames D, Hamann LG, Touré BB. Angew Chem, Int Ed. 2016; 55:14218–14238.
5. Obach RS. Pharmacol Rev. 2013; 65:578–640. [PubMed: 23406671]
6. Lewis DFV. Curr Med Chem. 2003; 10:1955–1972. [PubMed: 12871098]
7. Vitaku E, Smith DT, Njardarson JT. J Med Chem. 2014; 57:10257–10274. [PubMed: 25255204]
8. Krueger SK, Williams DE. Pharmacol Ther. 2005; 106:357–387. [PubMed: 15922018]
9. Pryde DC, Dalvie D, Hu Q, Jones P, Obach RS, Tran TD. J Med Chem. 2010; 53:8441–8460. [PubMed: 20853847]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

10. Ochiai E, Okamoto T, Kobayashi Y. Yakugaku Zasshi. 1948; 68:109–111.
11. Taylor E, Boyer N. J Org Chem. 1959; 24:275–277.
12. Mfuh AM, Larionov OV. Curr Med Chem. 2015; 22:2819–2857. [PubMed: 26087764]
13. For selected examples of this strategy as applied to other selective oxidations of amine substrates see: Asensio G, Gonzalez-Nunez ME, Bernardini CB, Mello R, Adam W. J Am Chem Soc. 1993; 115:7250–7253.Ferrer M, Sánchez-Baeza F, Messeguer A, Diez A, Rubiralta M. J Chem Soc, Chem Commun. 1995; 50:293–294.Lee M, Sanford MS. J Am Chem Soc. 2015; 137:12796–12799. [PubMed: 26439251] Howell JM, Feng K, Clark JR, Trzepkowski LJ, White MC. J Am Chem Soc. 2015; 137:14590–14593. [PubMed: 26536374] Mbofana CT, Chong R, Lawniczak J, Sanford MS. Org Lett. 2016; 18:4258–4261. [PubMed: 27529646] Lee M, Sanford MS. Org Lett. 2017; 19:572–575. [PubMed: 28094967] Mack JBC, Gipson JD, Du Bois J, Sigman MS. J Am Chem Soc. 2017; 139:9503–9506. [PubMed: 28660763]
14. Cymerman CJ, Purushothaman KK. J Org Chem. 1970; 35:1721–1722. [PubMed: 5440349]
15. Curci R, Dinoi A, Rubino MF. Pure Appl Chem. 1995; 67:811–822.
16. Typical dioxirane-mediated catalytic conditions require basic pH which would be incompatible with the protonation strategy. See the following and references therein: Shuler WG, Johnson SL, Hilinski MK. Org Lett. 2017; 19:4790–4793. [PubMed: 28841323]
17. Wang D, Shuler WG, Pierce CJ, Hilinski MK. Org Lett. 2016; 18:3826–3829. [PubMed: 27391543]
18. Dantignana V, Milan M, Cussó O, Company A, Bietti M, Costas M. ACS Cent Sci. 2017; 3:1350–1358. [PubMed: 29296677]
19. Vitaku E, Smith DT, Njardarson JT. J Med Chem. 2014; 57:10257–10274. [PubMed: 25255204]
20. Evidence suggests that pyridine N-oxides bearing strongly electron-withdrawing groups at the 2-position are unstable. See: Sarantakis D, Sutherland JK, Tortorella C, Tortorella V. J Chem Soc C. 1968:72–73.
21. Bull JA, Mousseau JJ, Pelletier G, Charette AB. Chem Rev. 2012; 112:2642–2713. [PubMed: 22352938]
22. Garattini E, Terao M. Expert Opin Drug Metab Toxicol. 2012; 8:487–503. [PubMed: 22335465]
23. Zhang X, Liu HH, Weller P, Zheng M, Tao W, Wang J, Liao G, Monshouwer M, Peltz G. Pharmacogenomics J. 2011; 11:15–24. [PubMed: 20177421]
24. Lepri S, Ceccarelli M, Milani N, Tortorella S, Cucco A, Valeri A, Goracci L, Brink A, Cruciani G. Proc Natl Acad Sci U S A. 2017; 114:E3178–E3187. [PubMed: 28373537]
25. Díaz-Arauzo H, Cook JM, Christie DJ. J Nat Prod. 1990; 53:112–124. [PubMed: 2348197]

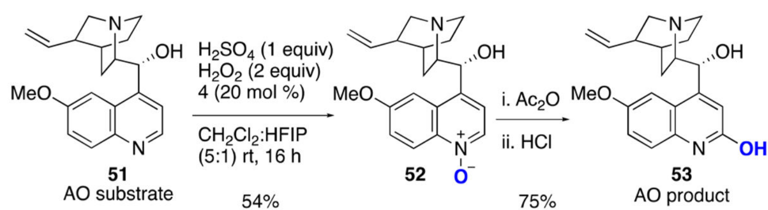
Author Manuscript Author Manuscript Author Manuscript Author Manuscript





Scheme 1.
Site-Selective Oxidation of *N*-Heteroarenes

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript



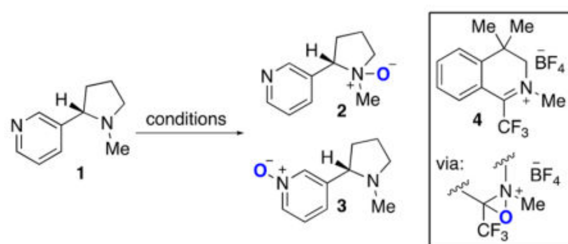
Scheme 2.

Two-Step Strategy to Mimic Metabolic C(sp^3)–H Hydroxylation by Aldehyde Oxidase

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Table 1

Optimization of the Reaction Conditions[a]



entry	substrate	conditions[a]	ratio of 1:2:3[b]	yield of 3 (%)[c]
1	1·HBF_4	*m*-CPBA, CH_2Cl_2, rt	1:5:0	—
2	1·HBF_4	H_2O_2, AcOH, 80 °C	0:1:0	—
3	1·HBF_4	DMDO, CH_2Cl_2, rt	11:0:1	—
4	1·HBF_4	H_2O_2, **4** (20 mol %)	1:0:5	77%
5	1	HBF_4·OEt_2, H_2O_2, **4** (20 mol %)	1:0:4	77%
6	1	HBF_4·OEt_2, H_2O_2	1:0:0	—
7	1	HBF_4·OEt_2, *m*-CPBA	2:5:0	—
8	1	H_2O_2, **4** (20 mol %)	0:1:0	—
9	1	H_2SO_4, H_2O_2, **4** (20 mol %)	—	66%
10	1	HBF_4·OEt_2, DMDO	—	15%

[a]One equivalent of oxidant was used for entries 1, 3, 7, and 10. Two equivalents were used for entries 4–6, 8, and 9. Four equivalents were used for entry 2. For entries 4–10, a 5:1 mixture of CH_2Cl_2:HFIP was used as the solvent, and the reactions were run at room temperature.

[b]Ratios determined by integration of HPLC chromatograms.

[c]Isolated yield.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Table 2

Scope of the Amine Component[a]

HBF_4 or H_2SO_4 (1 equiv)
50% aq. H_2O_2 (2 equiv)
catalyst **4** (20 mol %)
CH_2Cl_2:HFIP (5:1), rt, 16 h

entry	substrate	product	yield[b]
1	**1**	**3**	77[c]
2	**5** $R^1 = R^2 = Et$	**6** $R^1 = R^2 = Et$	77
	7 $R^1 = R^2 = i\text{-Pr}$	**8** $R^1 = R^2 = i\text{-Pr}$	61
	9 $R^1 = H$, $R^2 = Et$	**10** $R^1 = H$, $R^2 = Et$	80
	11 $R^1 = R^2 = H$	**12** $R^1 = R^2 = H$	0
3	**13**	**14**	62
4	**15**	**16**	54
5	**17**	**18**	34
6	**19**	**20**	50
7	**21**	**22**	30
8	**23**	**24**	40
9	**25**	**26**	66
10	**27**	**28**	41

[a]Reaction conditions: substrate (0.5 mmol), **4**, (0.1 mmol), H_2SO_4 (0.5 mmol), and 50% aq. H_2O_2 (1.0 mmol) in a mixture of CH_2Cl_2 (2.5 mL) and HFIP (0.5 mL) under air atmosphere.

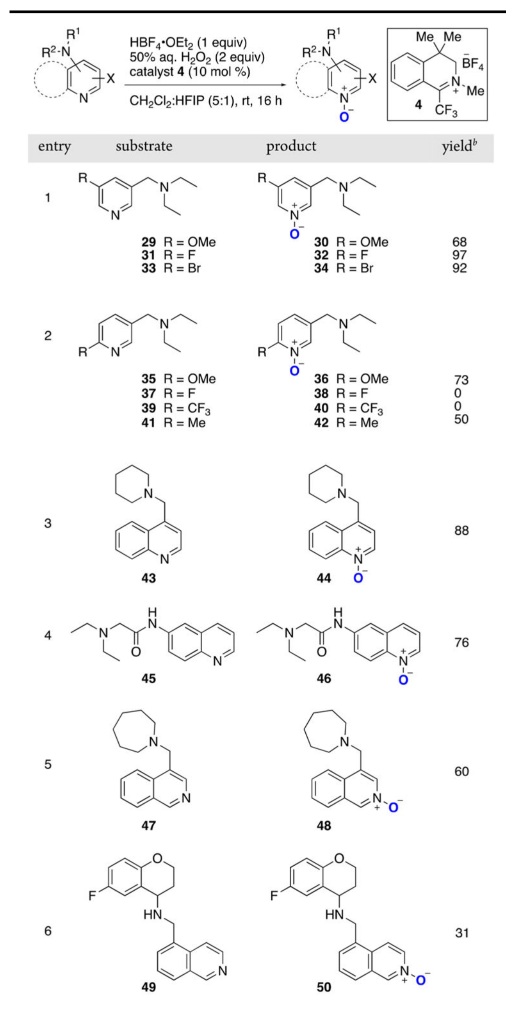
[b]Isolated yield.

[c]$HBF_4 \cdot OEt_2$ (0.5 mmol) was used in place of H_2SO_4.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Scope of the Heteroarene Component[a]



[a]Reaction conditions: substrate (0.5 mmol), **4**, (0.05 mmol), $HBF_4 \cdot OEt_2$ (0.5 mmol), and 50% aq. H_2O_2 (1.0 mmol) in a mixture of CH_2Cl_2 (2.5 mL) and HFIP (0.5 mL) under air atmosphere. Entry 6: H_2SO_4 (0.5 mmol) was used in place of $HBF_4 \cdot OEt_2$. Entry 4: Reaction performed on 1.5 mmol scale.

[b]Isolated yield.