Site-Selective Benzylic C–H Hydroxylation in Electron-Deficient Azaheterocycles

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Abstract

Benzylic C–H bonds can be converted into numerous functional groups, often by mechanisms that involve hydrogen atom transfer at the key bond breaking step. The abstracting species is most often an electrophilic radical, which makes these reactions best suited to electron-rich C–H bonds to achieve appropriate polarity matching. Thus, electron deficient systems such as pyridine and pyrimidine are relatively unreactive, and relatively underrpresented in substrate scopes. In this report, we describe a new method for benzylic hydroxylation—essentially an unknown reaction in the case of pyrimidines—that makes use of an iodine(III) reagent to affords very high selectivity towards electron-deficient azaheterocycles in substrates with more than one reactive position and prevents over-oxidation to carbonyl products. The identification of key reaction byproducts supports a mechanism that involves radical coupling in the bond forming step.

Benzylic sp^3 C–H bonds are often the weakest C–H bond in organic molecules. For that reason, their conversion into other functional groups has been a mainstay of organic chemistry for nearly 150 years.[1] Recently, the ability to convert these bonds into benzylic radicals has led to a wealth of new reactions, which often work in highly complex settings and rapidly build molecular complexity.[2–6] When the desired position for functionalization is adjacent to an electron-deficient heterocycle such as pyridine, however, reaction development is often challenging. Specifically, in cases where the key C–H bond is broken by hydrogen atom transfer (HAT), that reaction step is sensitive to polarity matching between the hydrogen atom donor and acceptor.[7] In most cases, the hydrogen atom acceptor (*e.g.* Br•) is electrophilic,[8] and is best matched with electron-rich benzylic positions. If there is a more electron-rich C–H bond present in the molecule, the heterobenzylic position may not be the most reactive site.

This polarity matching effect can be very clearly seen from the work of the White group,[9] for example, where coordination of an alkylpyridine to either Brønsted or Lewis acids resulted in C–H hydroxylation occurring at a simple alkyl C–H bond to produce tertiary alcohol 1 (Fig. 1). When other reactive positions are present—such as benzylic C–H bonds adjacent to an all-carbon aromatic—no pyridine coordination is necessary to see very high site-selectivity *away* from the heterocycle as shown by Stahl (for 2)[10] and by Xie and Zhu (for 3),[11] for example. This challenge becomes particularly pronounced when considering an even more electron-deficient heterocycle such as pyrimidine (4). A CAS SciFinder® search for the direct C–H hydroxylation (5) or esterification (6) of pyrimidine returned only a small handful of results (details of the search strings are in the Supporting Information). In the case of hydroxylation, 11 of the 12 published examples used either very strong bases to induce benzylic deprotonation,[12–16] or were actually multi-step telescoped reactions that involved conversion of the pyrimidine to an intermediate N-oxide,[17] benzylic bromide,[18] or aldehyde.[19] One authentic direct hydroxylation was found, wherein $KMnO_4$ delivered the desired product in 8% yield.[20] For direct esterification, there were only two examples published that features a primary or

secondary C–H bond in a pyrimidine derivative, one for a single-ring pyrimidine (7)[21] and one for a quinazoline (8).[22] The core of the challenge here can be directly described: essentially any HAT conditions that can overcome poor polarity matching to yield the first C–O bond will be highly reactive towards the remaining benzylic C–H bond(s) in the product: those bonds are now significantly weakened by the adjacent oxygen lone pairs, and are also rendered much more nucleophilic.[23,24]

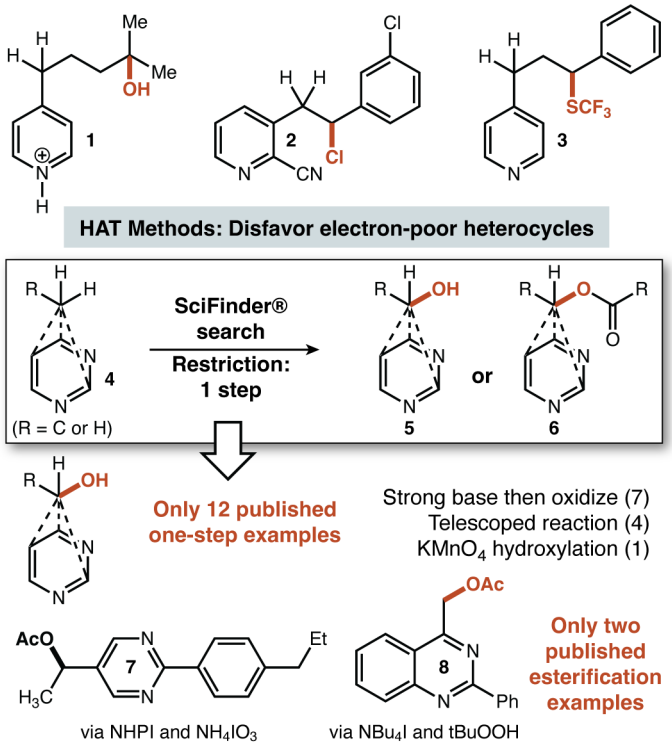

Figure 1. Literature context for the specific challenge of benzylic hydroxylation adjacent to electron-deficient heterocycles such as pyridine and pyrimidine.

Given the widespread presence of azaheterocycles in medicines and materials,[25–30] there have been many efforts to develop benzylic C–H functionalization reactions that favour positions adjacent to heterocycles such as pyridine.[31] Recent examples of these efforts have resulted in the selective formation of C–N,[32] C–F,[33–37] C–S,[11,34,38] C–Cl,[39] C–C,[40–44] and C=O[45,46] bonds adjacent to electron-deficient heterocycles in the presence of more electron-rich benzylic C–H bonds. To our eyes, notably absent from this list was the direct formation of C–O bonds at position where overoxidation was possible. Recently, there have been significant advanced made for related reactions that provide important context for our new system (*vide infra*). First, Ritter and Maruoka reported net benzylic hydroxylation reactions using peroxide and hypervalent iodine reagents, respectively—with mesyloxy (**9**) and trifluoroacetoxy (**10**/**11**) function groups as the initial products (Fig. 2a).[47,48] The reactive H-atom acceptors used should strongly favor electron rich C–H bonds, which is supported by the yields reported by Maruoka (c.f. **10** vs. **11**). Importantly, in both of these cases, the initially formed products were resistant for further C–H oxidation.

We were very interested to see the recent report of Dutton and co-workers, who reported the formation of a coordination complex **12** between pyridine and $PhICl_2$, supported by x-ray crystallography (Fig. 2b).[49] There seemed to be a potential parallel between this species and some of the initially proposed intermediates from our own work on site-selective pyridine fluorination.[33,50] More recent experimental and computational studies by Dudding and Lectka have strongly suggested that hydrogen bonding between Selectfluor® and basic heterocycles such as pyridine is the dominant mode of interaction (Fig. 2c).[51–

[54] Such pre-coordination of a strong oxidant to the heterocycle allows for C–H activation by proton-coupled electron transfer (PCET). We wondered whether coordination complexes analogous to **12** might also allow for site-selective C–H activation by proton-coupled electron transfer in contexts beyond fluorination. As is well established, single electron reduction of iodine(III) reagents results in fragmentation that can provide heteroatom radicals, which often leads to new C–X bonds.[55]

A potential alternative approach could be based off of the work of Guo, who reported the use hypervalent iodine for the production of aldehydes from methylquinolines, proposed to occur through a dearomatization mechanism.[56] In the case of secondary carbons, acetoxylation was observed instead (Fig. 2d). We were able to successfully reproduce this system in our laboratory, but found pyridine to be completely inert to the conditions—perhaps unsurprising, given that pyridine is be more difficult to dearomatize than quinoline. While the potential for this approach to be adapted to simple pyridines and pyrimidines certainly exists, the fact that PCET fluorination conditions are compatible with these species convinced us that attempting to develop an analogous strategy for hydroxylation was an appropriate starting point.

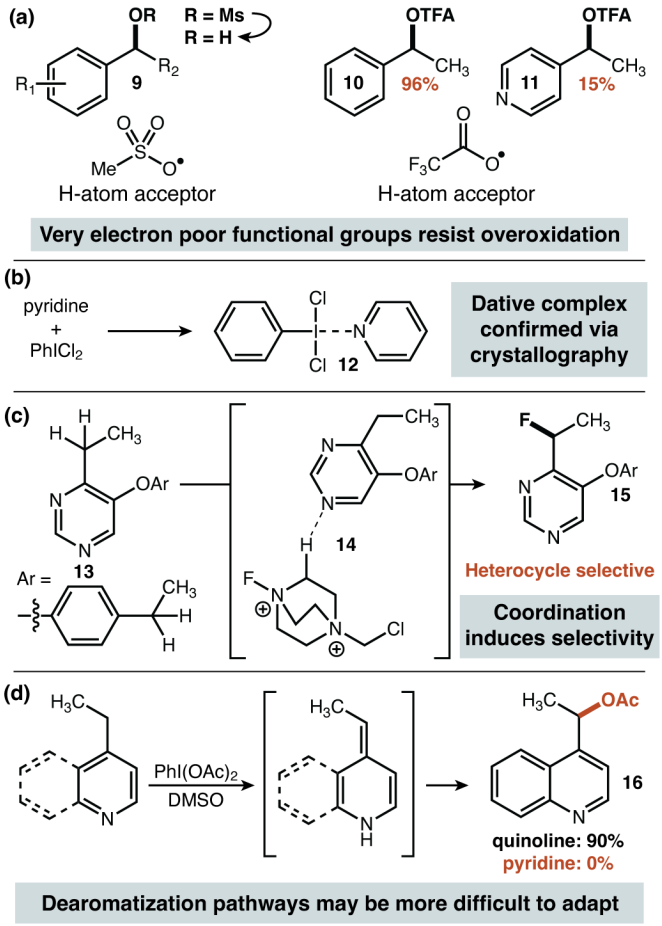

Figure 2. (a) Benzylic oxidations reported by Ritter and Maruoka are resistant to over-oxidation. (b) Experimental support for the formation of a coordination complex between pyridine and hypervalent iodine(III) reagents. (c) Previous example of coordination-induced selectivity that resulted from the interaction of the target heterocycle and a chemical oxidant. (d) A dearomatization strategy published by Guo is effective for extended aromatic systems but not single-ring substrates.

Our investigations used 4-heptylpyridine **17** as a model substrate (to produce **18**), with initial screening in three NMR solvents using commercially available PIFA immediately generating a starting point for development. A series of iodine(III) reagents

with simple modifications made to the carboxylate component (**19**) demonstrated the critical nature of the trifluoroacetate component (Fig. 3). The electronic nature of the aromatic ring was varied next (**20**), with no other reagents demonstrating an improvement compared to commercially available choices. Investigation of a range of simple acidic and basic additives along with optimization of standard reaction parameters resulted in an increase of the NMR yield of oxidation product to 70%. The intermediate trifluoroacetate ester was found to be very labile to either aqueous work-up or silica gel chromatography, with free alcohols being the only products obtained after purification (*vide infra*).

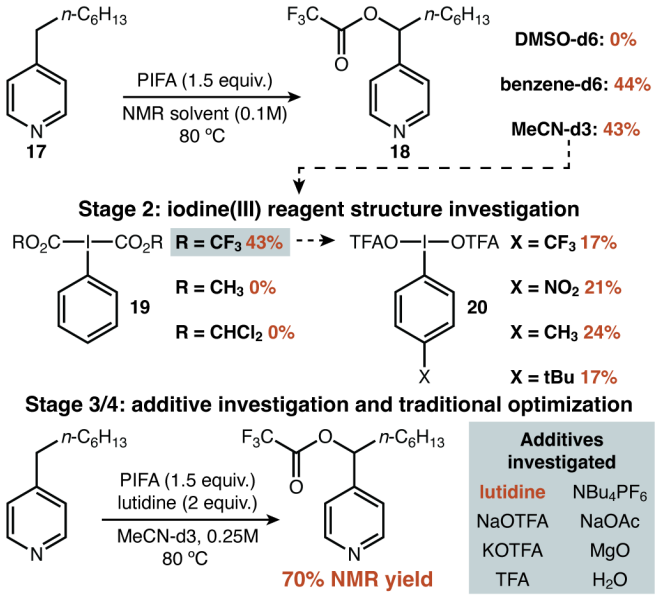

Figure 3. Summary of optimization studies for this heterobenzylic oxidation system.

We were most interested to see if these reaction conditions could deliver site-selective C–O bond formation when more reactive electron-rich benzylic C–H bonds were also present. As shown in Figure 4, allylic, propargylic and other benzylic positions are not reactive under these conditions. Notably, **23**, **26**, and **29** feature doubly-benyzlic C–H bonds at the 3-position of the pyridine ring, but the reaction conditions developed here can successfully activate the 4-position in preference. Pyridine, quinoline, pyrimidine, and quinazoline substrates yield alcohol products from 27-72% NMR yield, with a handful of the substrates shown suffering from minor difficulties with isolation. Two additional substrates provide important information about the limitations of reaction scope. Very electron rich fragments, such as that in diaryl ether **33** are sensitive to the strong oxidant PIFA, and this substrate did not result in productive reaction even with complete consumption of the starting material. Interesting, the directly C-C linked biaryl **34**, resulted in apparent hydroxylation at both benzylic positions, in approximately equivalent yield. Given that no hydroxylation was detected at the doubly-benzylic position in **23**, it seems unlikely that this is a result of direct HAT. Rather, we suspect that this substrate has the flexibility required to directly undergo an intramolecular 1,6–radical transfer. We used 2,4-DNP stain—which had proven able to detect ~1% aryl ketones in our prior work—to probe for overoxidation products in the crude reaction mixture.[46] Any TLC spots that resulted in a 2,4-DNP colour change were isolated and investigated by ^{1}H NMR, and in none of these cases were measurable amounts of ketones obtained. We investigated the analogous oxidations of 4-methyl and 4-isopropylpyridine, with ^{1}H NMR of the crude reaction mixture providing two important observations to help explain the lack of ketone products. In the case of 4-methylpyridine, we *do* observe carbonyl products – in this case, the aldehyde ^{1}H signal is as intense than the desired product in the crude reaction mixture. 4-isopropylpyridine is much

less reactive than 4-heptylpyridine. These observations taken together suggest that steric access to the benzylic C–H bond is what prevents overoxidation in the substrates shown.

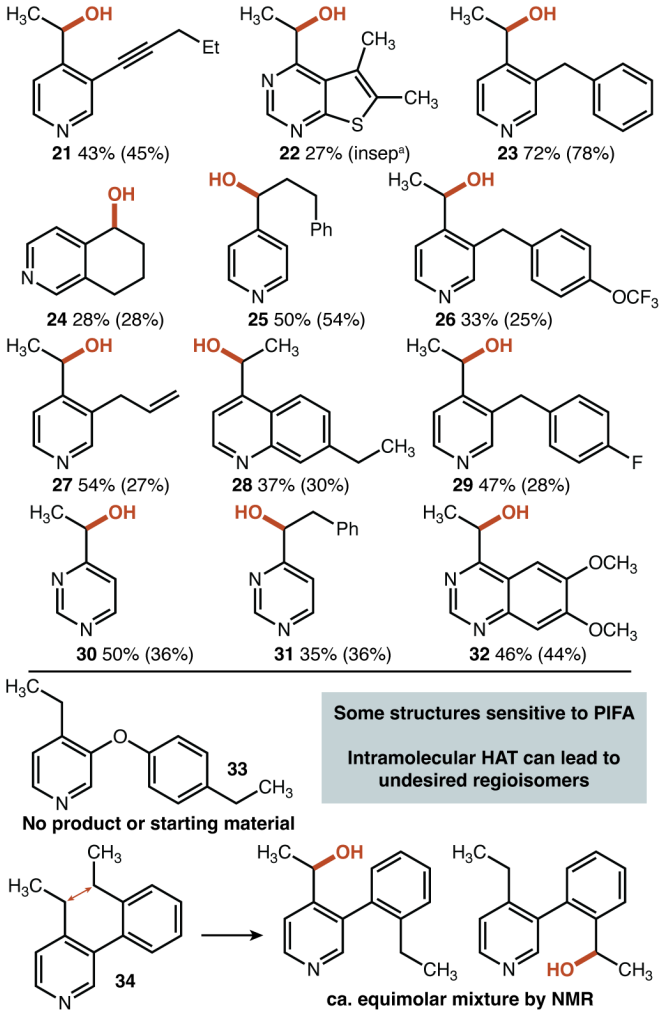

Figure 4. Substrate scope and important unsuccessful reactions. ^{1}H NMR yields and isolated yields are reported (isolated yields in parentheses). NMR yields are of the intermediate trifluoroacetate ester relative to internal standard; silica gel purification hydrolyses the ester and free alcohols were the product isolated in all cases. [a]Product was isolated as an inseparable mixture with some residual starting material.

We have gathered evidence that is consistent with the design principles outlined above (Fig. 5). First, UV/Vis analysis of each individual reaction component (*i.e.* 4-ethylpyridine, 2,6-lutidine, PIFA) was compared to the spectrum obtained from a diluted reaction mixture aliquot taken at 30 minutes. A significant absorbance between 250-300 nm that does not appear to be the simple addition of the reaction components can be observed. While this observation could not distinguish between coordination between the pyridine lone pair and iodine atom of PIFA (*i.e.* **35**) versus a different mode of interaction, the fact that some charge-transfer complex is formed between these species is a necessary precondition for proton-coupled electron transfer to be a reasonable mechanism for radical formation. Next, the isolation of two specific reaction by-products provided further support for a radical mechanism involving PCET—generating **36** and **37**—for this reaction. First, when 4-benzylpyridine **38** was exposed to the reaction conditions, significant amounts of the substrate dimer **40** could be observed. Our previous work on

pyridine fluorination supported the proposal that this dimer could result from initial radical dimerization (via **39**) and unsaturation.[33] Second, 19F NMR analysis of the crude reaction mixture when 4-propylpyridine was used as a substrate contained a signal that matched the literature value for the product resulting from C–CF_3 bond formation at the benzylic position (**42**).[44] With no source of CF_3 available in the reaction other than the trifluoroacetoxy groups of the oxidant, we believe this supports the formation of CF_3CO_2• radicals (**41**) as a reaction intermediate. Based on this evidence for the existence of both the benzylic and trifluoroacetoxy radicals, we believe the C–O bond in this reaction is forged by radical combination. C–H kinetic isotope effect measurements (see Supporting Information) show a primary isotope effect at the benzylic position (K_H/K_D = 6.1), which is consistent with the proposed mechanism if coordination complex formation is reversible, but PCET is not.[57]

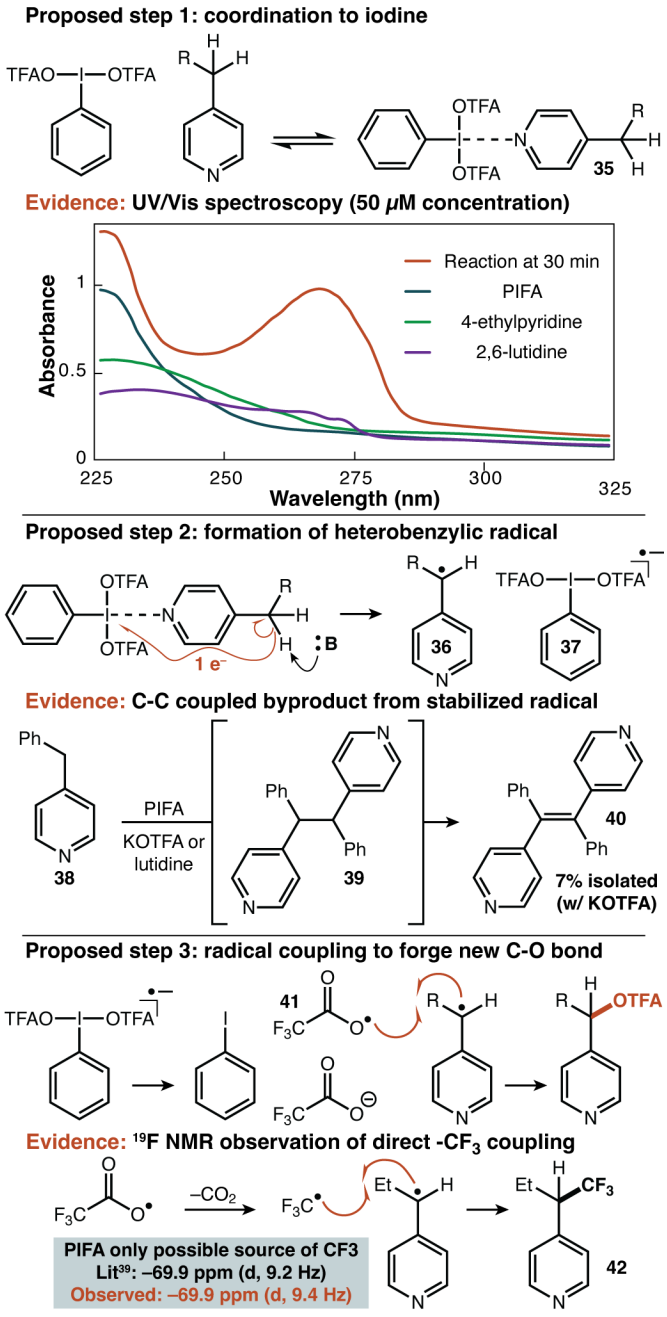

Figure 5. Summary of important observations to support a proposed PCET mechanism.

Given the strong preference of hydrogen atom transfer methods for electron-rich benzylic C–H bonds, the development of site-selective reactions that prefer electron-deficient positions adjacent to heterocycles such as pyridine and pyrimidine demands alternative mechanistic strategies. In this report, we have detailed the development of a direct method for C–O bond formation in these systems that avoids over-oxidation. The sum of our observations, paired with several important reports in the recent literature, are consistent with a mechanism that involves proton-coupled electron transfer to break the heterobenzylic C–H bond, and radical coupling to yield the new C–O bond.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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