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Oxyfunctionalization of the remote C–H bonds of aliphatic amines *via* decatungstate photocatalysis

Danielle M. Schultz,* François Lévesque, Daniel A. DiRocco, Mikhail Reibarkh, Yining Ji, Leo A. Joyce, James F. Dropinski, Huaming Sheng, Benjamin D. Sherry, Ian W. Davies

Abstract: Remotely oxygenated aliphatic amines represent an important class of synthetic building blocks to which there are currently no direct means of access. Reported here is an efficient and scalable solution that relies upon decatungstate photocatalysis under acidic conditions using either H_2O_2 or O_2 as the terminal oxidant. Using these conditions a series of simple and unbiased aliphatic amine starting materials can be oxidized to value added ketone products. Lastly, in situ LED-irradiated NMR spectroscopy was utilized to monitor the kinetics of the reaction, enabling direct translation of the reaction in flow.

Functionalized aliphatic amines represent a common and important class of chemical building blocks for complex molecule synthesis. As a consequence, discovering new approaches for accessing functionalized amine building blocks in a direct and cost-effective manner is of considerable importance. One of the most well-studied approaches for the direct functionalization of aliphatic amines is through sp^3 C–H oxidation.[1] While the most prevalent site of C–H oxidation is α to the nitrogen atom,[2] achieving efficient distal oxidation of unactivated sp^3 C–H bonds has proven to be considerably more challenging. Recently, effective remote sp^3 C–H hydroxylation of unprotected amines was found to be accessible through the deactivation of the amine C_α–H bonds via protonation,[3] allowing the less activated and remote C–H bonds to undergo oxidation.[4] Despite the great strides in amine C–H hydroxylation, the ability to convert simple and unprotected aliphatic amines to ketone products via 4 e- oxidation of a methylene remains an unsolved problem.[5] The value of such a transformation is most apparent in the case of remotely oxygenated pyrrolidine, piperidine and azepane. This important class of simple building blocks has a substitution pattern prevalent in biologically relevant molecules[6] with the ketone functional group serving as an excellent handle to introduce diversity (Figure 1). We hypothesized that the unique H-atom transfer (HAT) properties of decatungstate anion (DT, $[W_{10}O_{32}]^{-4}$),[7] a polyoxometalate photocatalyst,[8] could provide a potential solution to this long standing problem.

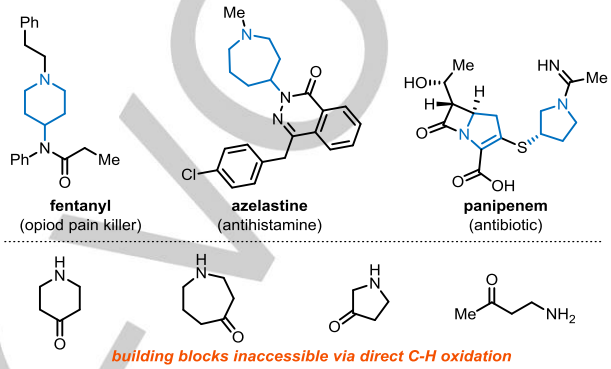

Figure 1. Pharmaceuticals that contain aliphatic amines with distal functionality.

As pioneered by Hill and coworkers, decatungstate anion has a long history of performing oxidation reactions on unbiased aliphatic alkanes,[9] with the preliminary studies focusing on the autoxidation of cyclohexane to cyclohexanol and cyclohexanone (Figure 2).[10] Consequently, we wondered if distal oxygenation of aliphatic amines could be accomplished by merging the concept of remote C–H activation via amine protonation [3,11] with decatungstate photocatalysis.[12-13] Moreover, we envisioned that this catalyst system would be less likely to yield a mixture of alcohol and ketone products, as hydroxylated intermediates would serve as better substrates for HAT than the starting material. Lastly, this method would be amenable to continuous flow photochemistry, overall making decatungstate photooxidation a scalable solution for remote amine oxygenation.

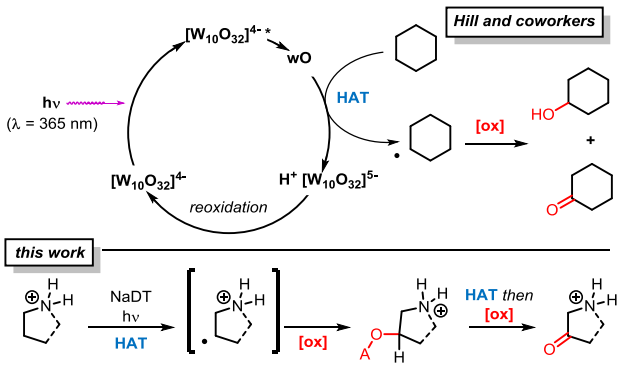

Figure 2. Application of decatungstate photocatalysis toward remote oxygenation of simple and unbiased amines

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Pyrrolidine (**1**) was selected as the model system to study, as oxidation would yield pyrrolidin-3-one (**2**), an important building block present in numerous pharmaceuticals.[6b] The described reaction represents a 4 e- oxidation of pyrrolidine (to yield the kinetic product) without the formation of 2-pyrrolidone[14] – a transformation that, to the best of our knowledge, has not been reported to date. Initial efforts to determine suitable reaction conditions were carried out via high-throughput experimentation (HTE) in which tetrabutylammonium decatungstate (TBADT) was screened with different oxidants, acids, and solvents using our photochemical screening platform[15] and HPLC with single ion monitoring (SIM) MS for analysis (Figure 3).[16] Under certain conditions HCl tended to generate chlorinated products and other acids such as TFA, H_3PO_4, and MSA were found to be less effective. Gratifyingly, after several rounds of HTE, proof of concept for remote C–H oxygenation was demonstrated with H_2SO_4/H_2O_2 in acetonitrile, yielding exclusively **2** in 59% yield with no oxidation at C-2 observed.

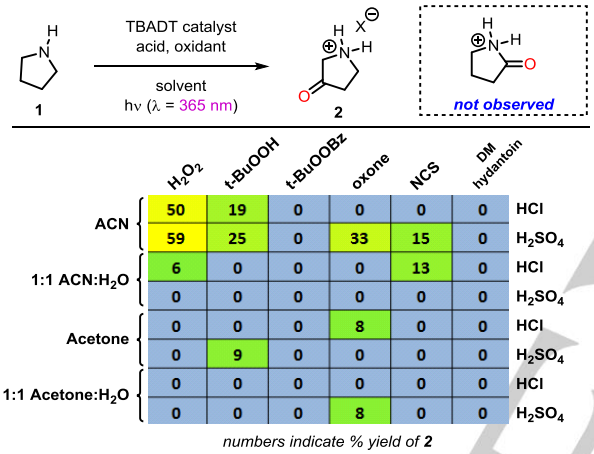
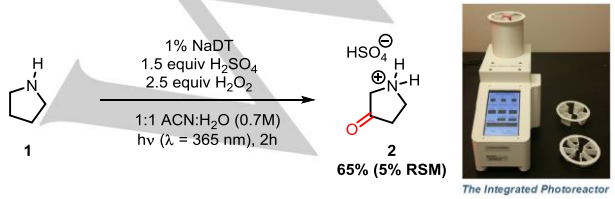


Figure 3. Use of HTE to screen conditions for remote oxidation of pyrrolidine.

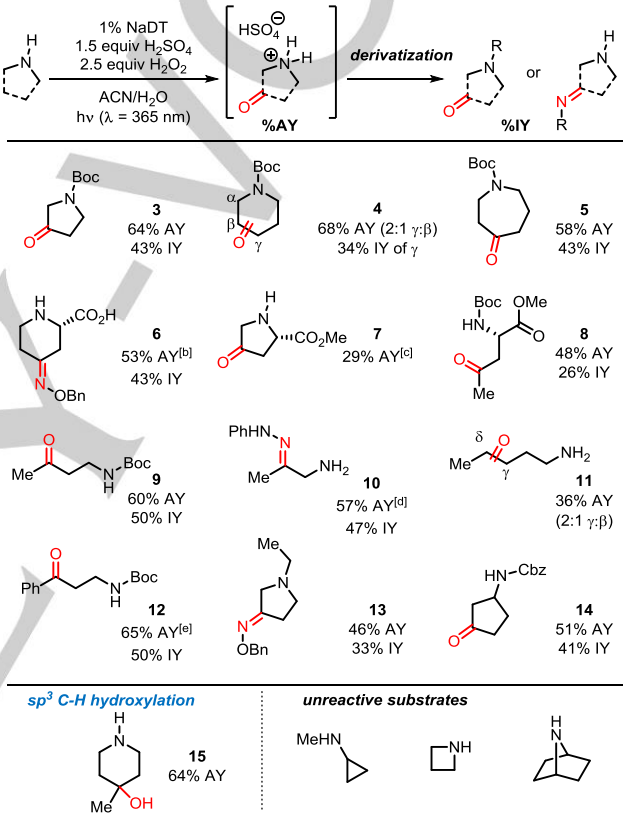
From this initial proof of concept, we established a standard set of reactions conditions (Scheme 1) using sodium decatungstate (NaDT) in place of TBADT for solubility purposes.[16] All reactions were performed in the recently reported small-scale integrated photoreactor that enabled enhanced photon efficiency in a standardized environment.[17] Omission of light, H_2O_2, or NaDT from the reaction led to trace formation of **2**; however, the exclusion of acid led to clean formation of *N*-hydroxypyrrolidine. Increasing or decreasing the equivalents of H_2O_2 failed to promote higher yields or efficiency. Little to no conversion was observed upon the bathochromic shift of the light source to 420 and 450 nm, further supporting that the decatungstate anion is the active catalyst mediating HAT.



Scheme 1. Optimized reaction conditions performed in photoreactor.

With optimized conditions in hand we began to study the scope of the transformation, with all reactions conducted on a >5 mmol scale (Table 1). Amine salts were shown to be viable substrates, precluding the need for additional acid; for example, norvaline and proline methyl ester were purchased and oxidized as their HCl and H_2SO_4 salts, respectively. While the cationic keto amine products were stable in solution, isolations were achieved through several derivatization methods from the crude reaction mixtures allowing Boc, Cbz, benzyloxime and phenylhydrazone products to be isolated. To determine the efficiency of the photooxidation, assay yields (AY) were determined prior to derivatization.[18]

Table 1. Decatungstate photocatalyzed oxidation of aliphatic amines[a]



[a] Reactions were performed with 1 equiv of amine on a >5 mmol scale. Assay yields (AY) were determined at end of reaction by ^{1}H NMR analysis with an internal standard. Isolated yields (IY) reported for derivatized products. [b] H_2O as solvent. [c] 23% AY of RSM. [d] 3-aminopropanoic acid formed in 22% AY. [e] 2 mol% NaDT, 4 equiv of H_2O_2 and ACN as solvent.

At the outset, we were curious if larger cyclic amines would yield single oxidation products similar to pyrrolidine. Oxidation of piperidine proceeded with similar efficiency as pyrrolidine, yielding a 68% AY (34% IY of **4**); however, a 2:1 mixture of γ:β keto products was observed. In contrast, the oxidation of azepane led exclusively to oxidation at the most remote C–H bond in 58% AY, to give **5**. This interesting result suggest that a catalyst controlled HAT event might be operating via an ion pair of the substrate with the catalyst. Amino acids were also amenable to oxygenation as was observed in the oxidation of L-pipecolic acid, (S)-proline methyl ester, and L-norvaline. Oxidation occurred exclusively at C-4 when L-pipecolic acid and (S)-proline methyl ester were subjected to the decatungstate photooxidation, affording **6** and **7**, respectively. C-4 variants of pipecolic acid and proline represent two large families of pharmacologically active compounds, and their preparation has

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been the subject of several reviews.[19] Next, we turned our attention towards the oxidation of linear aliphatic amines that have 1° sp^3 C–H bonds available for oxidation. Expecting a mixture of oxidation products we were instead surprised to find that the oxidation of L-norvaline and butylamine yielded **8** and **9**, respectively, as single regioisomers. This observed regioselectivity for oxygenation of distal 2° C–H bonds made us question if oxidation of 1° sp^3 C–H bonds were likewise feasible. Thus, subjection of propylamine, whose 2° C–H bonds are in closer proximity to the protonated nitrogen yielded 22% of 1° oxidation product 3-aminopropanoic acid; however, 2° C–H oxygenation was still favored by the formation of **10** in 57% AY. In turn, oxidation of amylamine, a substrate with δ 2° C–H bonds, gave a 2:1 mixture of δ:γ ketone products **11** in 36% AY.

Long reaction times (17 hours) were required for the benzylic oxidation of 3-phenylpropylamine to afford **12**, potentially due to the disfavorable approach of the arene ring to the anionic catalyst for HAT.[20] *N*-ethylpyrrolidine, a 3° amine with both linear and cyclic C–H bonds, afforded cyclic oxidation product **13** with no oxidation products derived from oxidation of the ethyl group detected. Carbocyclic ring oxidation can also be accessed with these conditions, with cyclopentanone **14** being formed in 51% AY (41% IY) from cyclopentylamine. Attempts to oxidize bridging and smaller carbocyclic/heterocyclic amines have proven unsuccessful to date and the presence of remote 3° C–H bonds leads to hydroxylation (see **15**). Lastly, unless otherwise mentioned, no other products were observed during reaction optimization (see SI) and in Table 1, overall suggesting that light-mediated decomposition accounts for the remaining mass balance.

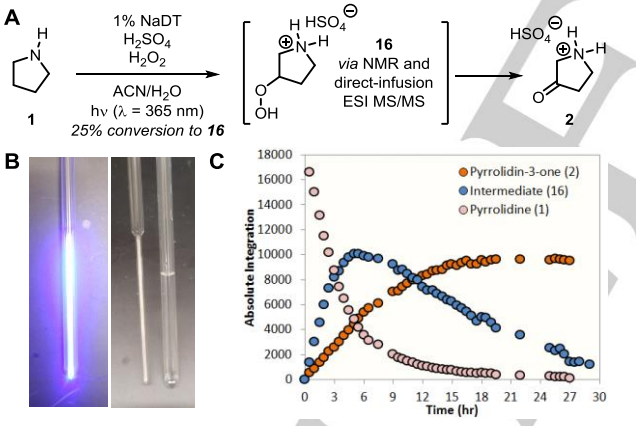

Figure 4. A. Identification of intermediate **16**. **B**. Picture of the NMR tube setup both assembled and unassembled. **C**. Kinetics of pyrrolidine photooxidation using *in situ* LED-irradiated NMR.

Throughout the course of our studies we did not observe hydroxylated products at the end of our reactions; however halting the oxidation of **1** at 25% conversion revealed an intermediate by ^{1}H NMR spectroscopy that was present in a 1:4 ratio with **1**. Detailed *in situ* NMR analysis coupled with direct-infusion ESI MS/MS allowed for identification of the intermediate as 3-hydroperoxypyrrolidine **16** (Figure 4A and SI). With this information in hand, we studied the mechanism of the photochemical oxidation by observing the growth and decay of intermediate **16**. Our studies were carried out utilizing a modified setup to the recently reported in situ LED-irradiated NMR,[21] with the LED filament being placed inside the coaxial capillary tube to isolate it from the reaction mixture (Figure 4B). The sample was irradiated at 365 nm throughout the reaction course and a series of ^{1}H NMR spectra were used to determine the kinetics of the reaction (Figure 4C). While several different mechanistic scenarios are likely operable, over the course of 30 h no additional intermediates were detected, suggesting that **16** plays a significant role in the formation of **2**.

Organic hydroperoxides are common intermediates that have been observed in the decatungstate photocatalyzed oxidation of 3° sp^3 C–H bonds with oxygen,[10, 22] as a result the identification of **16** made us question if oxygen could be used as our terminal oxidant. To investigate aerobic conditions, and avoid the problems associated with scale in batch photochemistry,[23] we decided to perform the reaction in a commercially available continuous flow reactor setup.[16] The generation of a plug flow regime (utilizing a T-mixer) maximizes the specific surface area between the liquid/gas phases,[24] thus overcoming mass transfer limitation associated with batch processes. To our delight, oxygen served as an effective oxidant for pyrrolidine; however, >1h residence time was required which forced us to recycle the reaction mixture through the reactor. Two light sources were investigated, a medium pressure mercury lamp (150 W) and a 365 nm LED lamp (62 W input, 16 W radiant power); however, the LED lamp provided a faster rates and less decomposition. As shown in Figure 5A, performing the reaction in a pressurized vessel improved conversion and a small oxidation scale-up (5 g of pyrrolidine) resulted in a space time yield of 15 mmol/h/mL, similar to that observed in batch (Figure 5B).

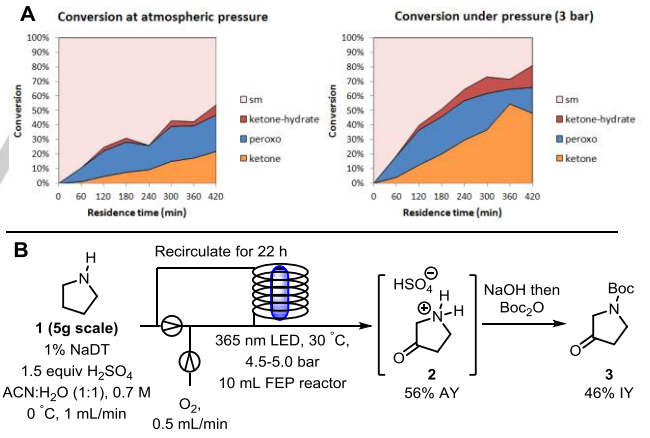

Figure 5. A. Effect of oxygen pressure on the oxygenation of **1** in flow. **B.** 5 g pyrrolidine oxidation demonstration in flow.

In conclusion, through the use of decatungstate photocatalysis in an acidic environment, we were able to effect the direct conversion of unbiased aliphatic amines to remotely oxidized products using either H_2O_2 or O_2 as the terminal oxidant. More importantly, these conditions provide a scalable solution for transforming simple and inexpensive aliphatic amines to value added ketone products that are not readily available and average >$100/g. Current efforts are underway to further expand upon this amine oxidation methodology with the hope of impacting other substrate classes that have eluded direct oxidation.

Acknowledgements

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Keywords: oxidation • photocatalysis • decatungstate • flow • radical

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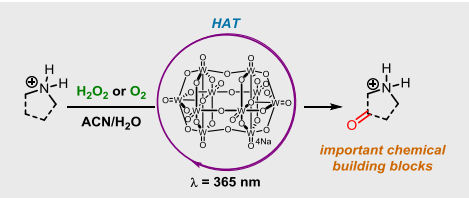

Decatungstate anion, a UV absorbing photocatalyst, was utilized in the conversion of unprotected aliphatic amines to remotely oxidized ketone building blocks using H_2O_2 or O_2 as the terminal oxidant. LED-irradiated NMR studies aided in the identification of a key reaction intermediate that ultimately allowed the transformation to be translated into flow.

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