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β-Functionalization of Saturated Aza-Heterocycles Enabled by Organic Photoredox Catalysis

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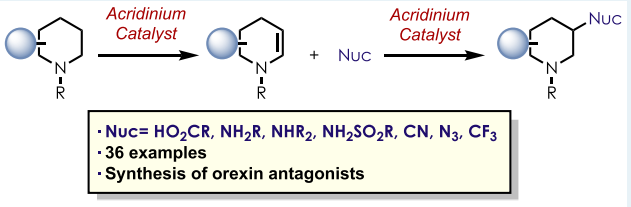
ABSTRACT: The direct β-functionalization of saturated aza-heterocycles has remained a synthetic challenge because of the remote and unactivated nature of β-C−H bonds in these motifs. Herein, we demonstrate the β-functionalization of saturated aza-heterocycles enabled by a two-step organic photoredox catalysis approach. Initially, a photoredox-catalyzed copper-mediated dehydrogenation of saturated aza-heterocycles produces ene-carbamates. This is followed by an anti-Markovnikov hydrofunctionalization of the ene-carbamates with a range of heteroatom-containing nucleophiles furnishing an array of C−C, C−O, and C−N aza-heterocycles at the β-position.



KEYWORDS: *photoredox, organic, catalysis, heterocycle, dehydrogenation, anti-Markovnikov*

Saturated heterocycles adorn many small-molecule therapeutics and agrochemicals. In particular, piperidine and pyrrolidine are ranked as the first and fifth most common heterocycles in FDA-approved pharmaceuticals, respectively (Scheme 1).[1] As such, C−H functionalization of these and other saturated aza-heterocycles would present an attractive strategy to rapidly synthesize and modify these motifs. Numerous methods have been developed for the α-functionalization of aza-heterocycles,[2−6] with some strategies relying on α-lithiation[7] or catalytic methods involving transition metal[8,9] or photoredox catalysis.[10−13] Direct C−H functionalization of piperidines at C-4 remains limited, but some recent work employing transition metal and photoredox strategies have been communicated for the activation of these typically unreactive C−H bonds.[14−17] Remote functionalization of unactivated sp^3 C−H bonds, particularly the C-3, or β-position, in saturated aza-heterocycles, remains a significant challenge.

A conventional approach to the synthesis of β-functionalized piperidines typically relies on nucleophilic substitution of the sulfonate ester from the corresponding 3-hydroxypiperidine. However, this strategy is severely limited by the minimal commercial availability of prefunctionalized 3-hydroxypiperidines, which are required for the synthesis of more complex piperidine scaffolds. To circumvent this limitation, it is common to install the functionality through S_NAr reactions of more decorated pyridiniums followed by exhaustive hydrogenation to afford the desired saturated heterocycle.[18−26]

More recently, catalytic approaches to β-substituted aza-heterocycles commonly rely on transition metal catalysis.[15,27−32] For example, β-alkylation of piperidines was accomplished via ruthenium/NHC catalysis to couple piperidines with aldehyde or alcohol partners via dehydrogenation and hydrogen atom transfer processes (Scheme 1a).[33−36] Recently, MacMillan and co-workers developed a C−H trifluoromethylation of aza-heterocycles via dual hydrogen atom transfer and copper catalysis, which affords β-trifluoromethylated pyrrolidines or γ-trifluoromethylated piperidines.[16] During the preparation of this manuscript, β-alkylation of piperidines was demonstrated via a three-step sequence with bromoacetates via ene-carbamate intermediates (Scheme 1b).[37] Despite these advances, approaches to the direct installation of heteroatoms are far less developed.

To our knowledge, the only example of direct β-functionalization to form a heterosubstituted aza-heterocycle is the oxidative β-sulfonylation using *N*-iodosuccinimide (NIS) and sulfinite salts to produce enaminyl sulfones.[38] While this is a versatile synthetic intermediate, this methodology is still limited by the types of coupling partners in this transformation. Herein, we report one of the only examples of β-heterofunctionalization of aza-heterocycles. This approach relies on two key steps enabled by organic photoredox catalysis: (1) a copper-mediated dehydrogenation followed by (2) an anti-Markovnikov alkene hydrofunctionalization.[39,40] Each step utilizes an acridinium catalyst as a multipurpose oxidizing agent via photoinduced electron transfer (Scheme 1c).

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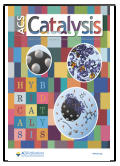

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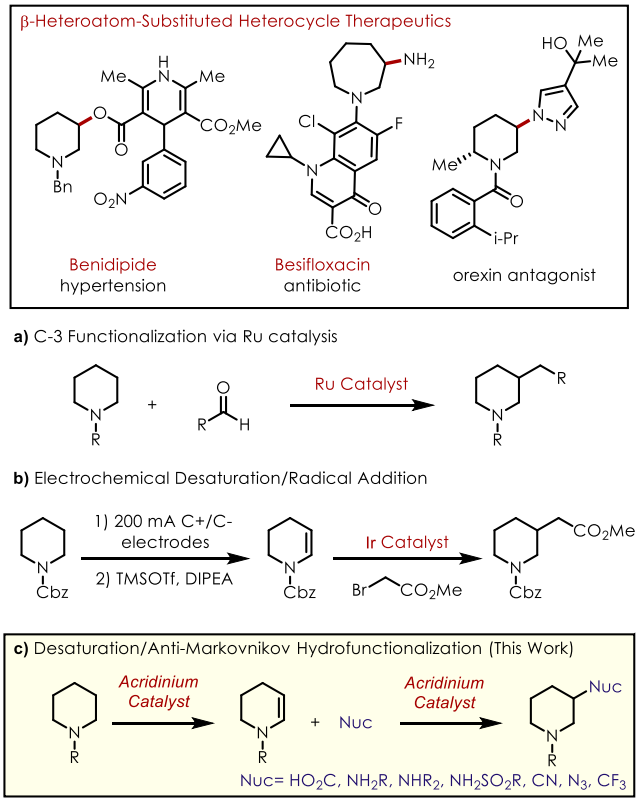
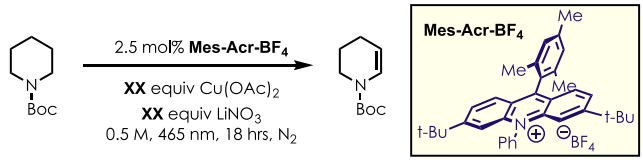
Scheme 1. Examples of Bioactive C-3-Substituted Aza-Heterocycles and Methods for C−H Functionalization at C-3 through (a) Ruthenium Catalysis,[34−36] (b) Electrochemical Methods,[37] or (c) Organic Photoredox Catalysis



We first sought to develop a robust photoredox-catalyzed dehydrogenation of piperidines to afford the unsaturated 2,3-ene carbamate starting materials required for the β-functionalization procedure. The synthesis of enamides and enecarbamates has been accomplished through an anodic methoxylation and elimination sequence of the corresponding amine by Shono and co-workers.[41,42] Recently, Marsden utilized an analogous approach for the synthesis of 2,3-unsaturated aza-heterocycles,[37] but despite these advances, the synthesis of enecarbamates has remained relatively unexplored.[43] Our lab has previously established that α-carbamyl radicals of pyrrolidines, piperidines, and piperazines can be produced by photoxidation and deprotonation of the parent saturated heterocycle. Thus, we sought to develop a method to intercept these radicals with a terminal oxidant to effect unsaturation.[11,12] Our initial aim was to accomplish the dehydrogenation through hydrogen evolution with cobaloxime catalysis;[44] however, the alkene was only observed in low yield. We then turned to copper(II) salts, which have been shown to function as single electron oxidants[45,46] that can oxidize α-amino radicals formed via a Kochi decarboxylation of amino acids to produce 2,3-unsaturated enamides.[47]

Reaction optimization was initiated using conditions resembling Tunge's conditions with copper(II) acetate as a terminal oxidant with *N*-Boc piperidine as a model substrate.[47] Lithium nitrate was found to be crucial as an additive in order to help facilitate the formation of the α-amino radical by hydrogen atom transfer, which successfully produced the desired product in 45% yield (Table 1, entry 2).[48] Additional

Table 1. Optimization of Piperidine Dehydrogenation



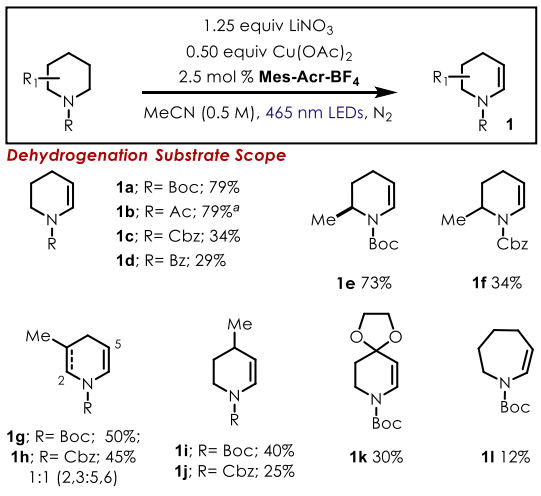
entry	Cu (equiv)	$LiNO_3$ (equiv)	yield
1[a]	1.5	n/a	n/a
2[a]	1.5	1.50	45%
3[a,b]	1.5	1.50	n/a
4	1.5	1.50	62%
5	1.0	1.50	80%
6	0.50	1.50	84%
7	0.25	1.50	48%
8	0.50	1.25	86%
9[c]	0.25	1.25	81%

[a]0.2 M. [b]DCE, TFE, or DCM as the solvent. [c]*t*-BuOOH (1.0 equiv) as an additive.

solvent screening was undertaken, but reactivity was only observed in acetonitrile with a lithium nitrate additive (entry 3). Increasing the reaction concentration from 0.2 to 0.5 M increased yields up to 62%, and decreasing copper loading to 0.50 equiv improved the yields up to 84% (entries 4−6). Decreased copper loading to 0.25 equiv was found to maintain high yields in combination with a terminal oxidant (*tert*-butyl peroxide) to facilitate copper(I) reoxidation but failed to improve the reaction yields beyond 81% (entry 9). The optimal conditions were found to be 0.50 equiv of Cu(II) with 1.25 equiv of lithium nitrate as a hydrogen-atom-abstracting reagent in acetonitrile (entry 8).

Having identified the optimal conditions, we explored the scope of the photoredox-catalyzed dehydrogenation with various piperidines (Chart 1). Boc- and acyl-protected piperidines produced the desired unsaturated products **1a** and **1b** in good yields. Other piperidine protecting groups, including Cbz and benzoyl (Bz), produced the desaturated products **1c** and **1d**, respectively, albeit in lower yields. Alkyl substitution at various positions was tolerated, yielding the

Chart 1. Dehydrogenation Scope‡



‡Average isolated yields are reported (0.200 mmol, n = 2). [a]Yield determined by ^{1}H NMR using $(Me_3Si)_2O$ as an internal standard.

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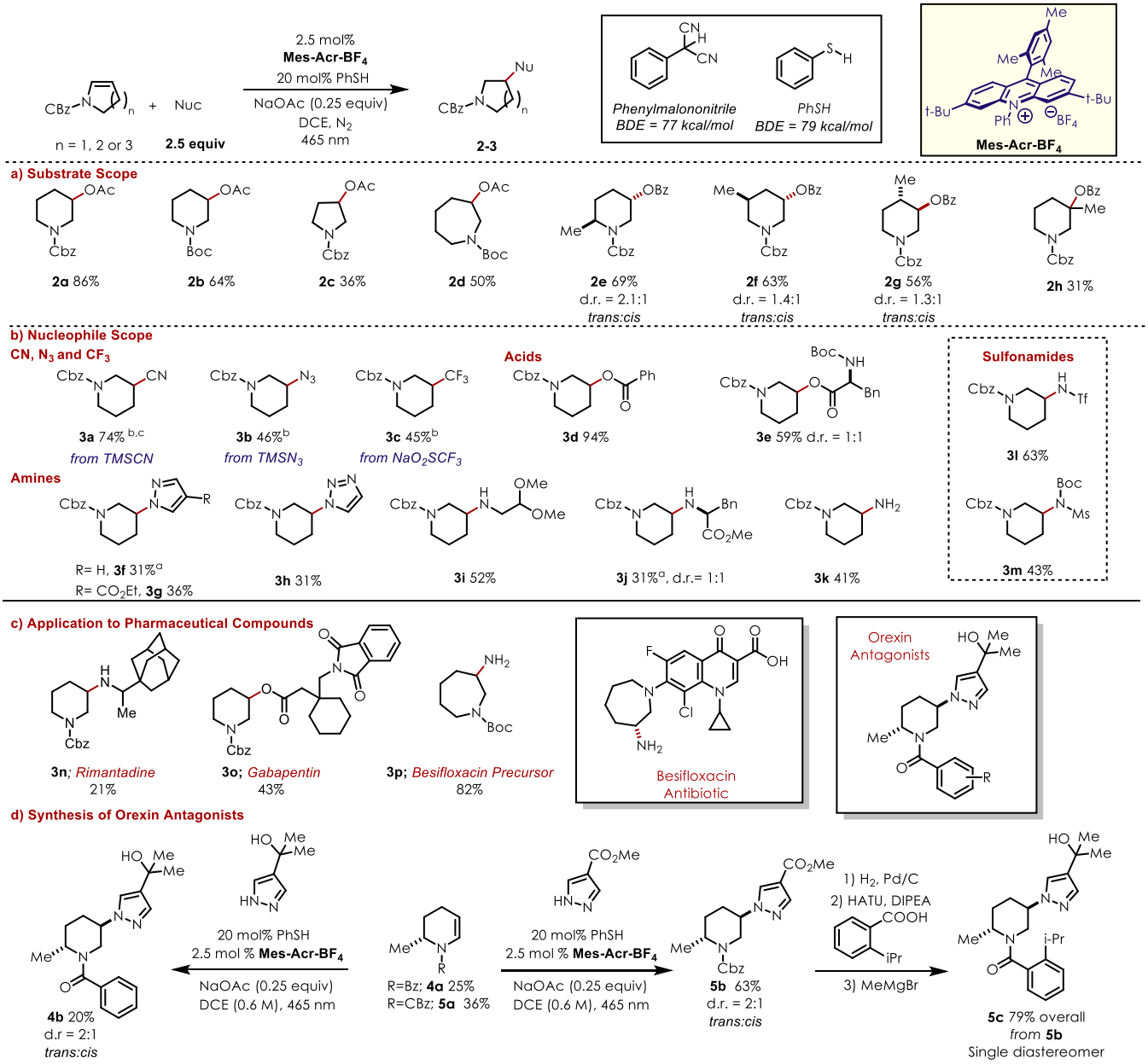
Chart 2. Aza-Heterocycle β-Functionalization via anti-Markovnikov Hydrofunctionalization: (a) Substrate Scope, (b) Nucleophile Scope, (c) Application to Pharmaceuticals and (d) Synthesis of Orexin Antagonists



[a]Phenylmalononitrile instead of thiophenol. [b]Without NaOAc. [c]5.0 equiv of nucleophile. [d]Average isolated yields are reported (0.200 mmol, n = 2).

desaturated ene-carbamates **1e**−**1k** in good to moderate yield. Selective desaturation of 2-methyl piperidines afforded the products **1e** and **1f** from oxidation at the less-hindered carbon center with no loss of stereochemistry with the enantiopure (*S*)-2-methylpiperidine. By contrast, 3-methyl piperidines **1g** and **1h** afforded a 1:1 mixture of regioisomeric ene-carbamate products, likely because of unselective 2- vs 6-hydrogen atom abstraction. Azepane, **1l**, undergoes desaturation, albeit in poor yield (12%), while piperazines and the more strained 5-membered pyrrolidine were unfortunately unreactive under these conditions.

With a route to access 2,3-unsaturated ene-carbamates, we turned our attention to developing a β-functionalization method that would produce a range of 3-substituted piperidines, a synthetic sequence which we anticipated could be valuable to medicinal chemists.

Our laboratory has established a program for anti-Markovnikov addition of a range of nucleophiles to simple olefins via the intermediacy of alkene cation radicals.[49] By comparison, ene-carbamates have been relatively understudied as potential substrates for this hydrofunctionalization manifold, with the exception of a single example from our lab,[40] but would accomplish our goal of 3-selective functionalization of aza-heterocycles. Reaction optimization was started with the Cbz-piperidinyl ene-carbamate **1c** as a model substrate, which has been shown to undergo β-functionalization with acetic acid as a nucleophile.[40] The optimal conditions were determined to be with 2.5 equiv of nucleophile with 2.5 mol % **Mes-Acr-BF$_4$**

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and 20 mol % thiophenol as a hydrogen atom donor in DCE, furnishing the desired addition product in good yields (see S9 for full optimization details).

Examining the scope of this transformation, we observed that both *N*-Cbz and *N*-Boc ene-carbamates yielded the acetylated products **2a** and **2b** in moderate to good yields (Chart 2). In addition to piperidine, the corresponding pyrrolidine and azepine ene-carbamates produced the desired acetylated products **2c** and **2d**, respectively. Alkylated piperidines substituted at positions 2−4 yielded the benzoylated products **2e**−**2h** as a mixture of diastereomers with little relative stereocontrol. Interestingly, 5-methyl-3,4-dihydropyridine afforded the quaternary β-functionalized piperidine **2h**, despite this being the more substituted position of the alkene, albeit in lower yield.

A variety of oxygen, nitrogen, and carbon nucleophiles were also assessed in this reaction (Chart 2). Cyanide and azide nucleophiles (TMSCN and $TMSN_3$, respectively) produced the desired β-cyano or azido aza-heterocycles **3a** and **3b** in good and moderate yields, respectively. The β-trifluormethylated adduct, **3c**, was isolated in 45% yield using the Langlois reagent; however, some α-functionalization was also observed (22% yield). Carboxylic acids such as benzoic acid and *N*-Boc phenylalanine were also found to be suitable nucleophilic partners, affording **3d**−**3e** in good yields. Azole-derived nucleophiles gave the heterocyclic products **3f**−**3h** in 31−36% yields. Primary amines were effective reaction partners, producing the β-aminated products, **3i** and **3j**, in modest yields. Amino acids such as phenylalanine can add either via *N*- or *O*- simply by selection of the protecting groups, furnishing either the aminated or acetylated products, **3j** and **3e**, but unfortunately, the resident amino acid chirality does not control stereoselectivity in the addition step. The direct β-amine product, **3k**, can be synthesized using ammonium carbamate as the source of amine. Trifluoromethyl and methyl sulfonamide derivatives were also competent nucleophiles giving the desired products **3l** and **3m** in moderate yields. Finally, pharmaceutical-derived nucleophiles successfully underwent the β-amination and acetylation with Rimantidine and Gabapentin derivatives **3n** and **3o**, respectively. With this methodology, a besifloxacin precursor, **3p**, was formed from the azepine with ammonium carbamate in good yield.

With a two-step procedure for the β-functionalization of saturated aza-heterocycles defined, we sought to demonstrate the utility of this sequence for the synthesis of active pharmaceutical intermediates. A 2016 patent from Merck examined orexin antagonists synthesized via nucleophilic substitution of 3-hydroxypiperidines which gave access to β-pyrazole substituted benzoyl piperidine derivatives.[50,51] The synthesis of these derivatives would be greatly simplified using the two-step dehydrogenation and β-functionalization sequence, which would begin with the simple methyl substituted piperidine rather than the prefunctionalized 2-methyl-3-hydroxypiperidine. Subjecting (*R*)-(2-methylpiperidin-1-yl)-(phenyl)methanone to the copper mediated dehydrogenation gave the desired ene-carbamate, **4a**, in 25% yield. The photoredox-catalyzed hydrofunctionalization of the ene-carbamate with 2-(1*H*-pyrazol-4-yl)propan-2-ol as the nucleophile gave the desired product, **4b**, as a mixture of 2:1 *trans:cis* diastereomers in two steps. A related orexin antagonist, **5c**, was prepared in five steps through hydrofunctionalization of **5a** with methyl 1*H*-pyrazole-4-carboxylate which gave a 2:1 mixture of *trans:cis* diastereomers of **5b** in 63% yield. The *trans* diastereomer was isolated and carried through a three-step sequence to give the final orexin antagonist, **5c**.

Though preliminary, we propose that the mechanism for dehydrogenation commences with a photoinduced electron transfer event (PET) between nitrate anion (E_{ox}= +1.97 V vs SCE)[48,52] and **Mes-Acr-BF$_4$*** (+ 2.10 V vs SCE), leading to the formation of nitryl radical.[53] The radical then abstracts a hydrogen atom from the α-piperidinyl C−H position. Either an inner sphere or outer sphere oxidation of the α-amino radical by Cu(II) affords the desired ene-carbamate. The reduced catalyst, **Mes-Acr$^{\bullet}$**, is oxidized by an additional equivalent of Cu(II) acetate to turn over the catalytic cycle and produce Cu(I). Substoichiometric use of copper acetate was found to be optimal in these reactions. Disproportionation of Cu(I) to Cu(0) and Cu(II) or by oxidation of Cu(I) by **Mes-Acr-BF$_4$*** could be the mechanism whereby the required Cu(II) species is regenerated.[54] The hydrofunctionalization begins by an oxidation of the ene-carbamate from **Mes-Acr-BF$_4$***. We have studied the mechanism of alkene anti-Markovnikov hydrofunctionalization and invoke a similar mechanism in this instance.[39,55] Since both transformations utilize the same photooxidation catalyst, we attempted a one-pot direct C−H functionalization; however, only α-substituted adducts were observed. We believe this is likely attributed to a copper-mediated coupling of the nucleophile with the α-radical that is formed. Studies to achieve this one-pot transformation are ongoing.

In conclusion, we have developed a two-step protocol for the synthesis of β-functionalized aza-heterocycles using an acridinium salt as the photooxidant. First, a copper-mediated photoredox-catalyzed dehydrogenation of saturated aza-heterocycles provides access to an array of ene-carbamates. A subsequent photoredox-catalyzed hydrofunctionalization of the ene-carbamates produces a range of C−O, C−C, and C−N β-substituted aza-heterocycles. We anticipate this route will greatly simplify the synthesis of hetero β-substituted aza-heterocycles, which we hope will find utility for the rapid synthesis of bioactive molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00099.

Experimental procedures and supporting ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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