Photoredox/Pyridine *N*-oxide Catalyzed Carbohydroxylation and Aminohydroxylation of *α*-Olefins.

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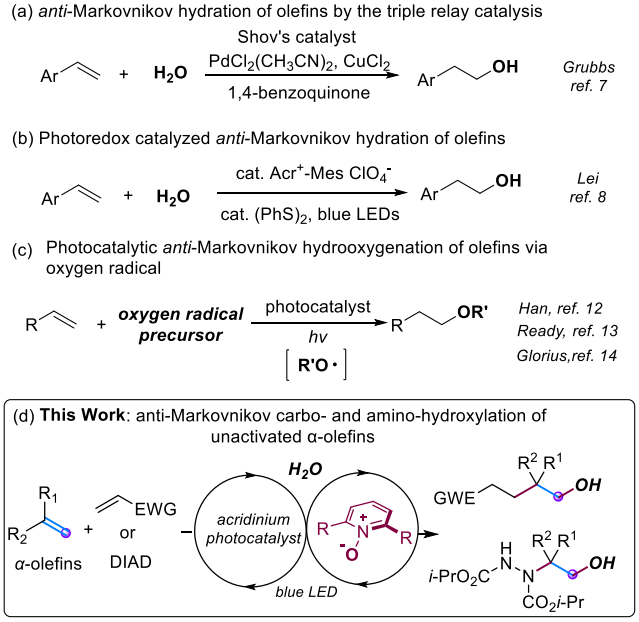
ABSTRACT: Anti-Markovnikov carbohydroxylation and aminohydroxylation of α-olefins were developed in this research by photoredox catalyst and pyridine *N*-oxide. This approach offers the catalytic and direct conversion of unactivated alkenes to a series of primary alcohols including the ones bearing *β*-quaternary carbon centers and *β*-amino alcohols. The anti-Markovnikov selective transformation is enabled by the radical addition of α-olefin from pyridine *N*-oxy radical, which is generated from readily available pyridine *N*-oxide via photoredox catalyzed single-electron oxidation. Mechanistic studies reveal that the reaction might occur with an *N*-alkoxypyridinium intermediate and following nucleophilic substitution. The implications of this method for anti-Markovnikov addition of α-olefins were further demonstrated by the examples of carboetherification, carboesterification, and lactone formation.

Primary alcohols are one of the fundamental substrates in organic chemistry, and they have broad usefulness in pharmaceutical, agrochemical, and bulk/fine chemical industries.[1] Their synthesis from terminal alkenes *via* anti-Markovnikov hydration represents a direct and compelling synthetic route using abundantly available substrates.[2] Most commonly, primary aliphatic alcohols can be accessed through a two-step redox process. For instance, the two-step hydroboration-oxidation sequence is a robust and widely applied approach to achieve anti-Markovnikov hydration of alkenes.[3] In industry, the Ziegler process and hydroformylation/hydrogenation prevail in the production of primary alcohols.[4] In addition, the synthesis of primary alcohols can be achieved by transition metal catalyzed regioselective hydrogenation of epoxides.[5] However, these transformations generally require stoichiometric oxidation/reduction and multi-step operations. To address these challenges, tremendous efforts have been made in the development of direct and catalytic anti-Markovnikov hydration of olefins by transition metal catalysis and photoredox catalysis.[6] For example, a triple relay catalysis system has been developed by the Grubbs group for the formal anti-Markovnikov hydration of styrenes (Scheme 1a).[7] A photoredox approach was reported by the Lei group using acridinium photoredox catalyst that enables the single-electron oxidation of styrenes and multi-substituted alkenes to achieve anti-Markovnikov hydration (Scheme 1b).[8] Despite these significant achievements, the reported catalytic approaches to primary alcohols through the anti-Markovnikov addition share the common limitations to styrenes or multi-substituted olefin substrates. For example, *α*-olefins are beyond the scope of anti-Markovnikov hydration in modern photoredox chemistry due to their

Scheme 1. Catalytic Anti-Markovnikov Hydration and Hydrooxygenation of Olefins and This Work.

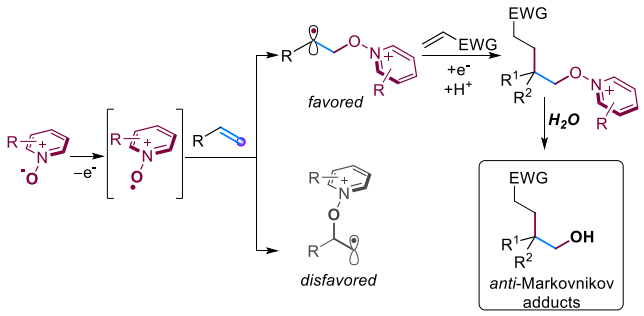


challenging single-electron oxidation.[6b] In this regard, we report an organophotoredox/pyridine *N*-oxide catalyzed anti-Markovnikov carbohydroxylation and aminohydroxylation of α-olefins (Scheme 1d). The anti-Markovnikov carbohydroxylation successfully delivered a series of primary alcohols including the ones bearing β-quaternary carbon centers and medicinally relevant pyridine cores. Additionally, the examples of aminohydroxyla-

tion provided a new method for the production of *β*-amino alcohols.

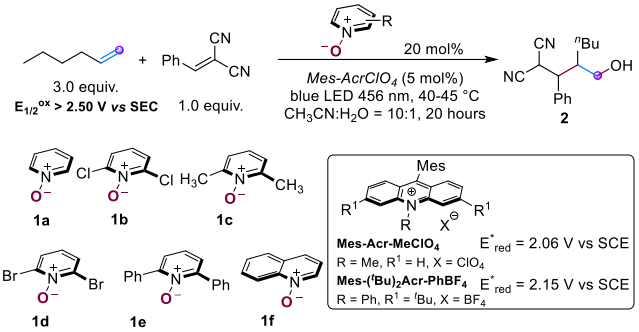
The radical addition of olefins has long been recognized as a powerful tool to achieve anti-Markovnikov process. Impressive nitrogen-,[9] sulfur-,[10] and halide-centered[11] radical mediated catalytic anti-Markovnikov addition reactions of unactivated olefins were reported, however, the corresponding oxygen-centered radical mediated reactions remain elusive. Pioneering reports from the Han group and the Ready group respectively achieved anti-Markovnikov hydrooxygenation and hydroesterification of unactivated olefins by using oxime carbamates and *N*-(acyloxy)phthalimides as oxygen radical precursors (Scheme 1c).[12,13] The Glorius group later reported photoinduced anti-Markovnikov hydrooxygenation of unactivated alkenes applying alkoxycarbonyloxylpyridinium salts as alkoxycarbonyloxyl radical precursors.[14] These strategies rely on the use of stoichiometric oxygen radical precursors. Recently, our group and others reported the photoredox catalyzed pyridine *N*-oxy radical generation through single-election oxidation of pyridine *N*-oxides for the development of C-H functionalizations and radical cascade reactions.[15] We postulated that the photocatalytically generated pyridine *N*-oxy radicals may initiate the regioselective anti-Markovnikov addition of α-olefins in accordance with persistent radical effect and favored polarity matching (Scheme 2). The resulting nucleophilic carbon radial intermediate can react with an electro-deficient alkene followed by single election transfer and protonation to generate the *N*-alkoxypyridinium intermediate. Subsequently, the *N*-alkoxypyridinium intermediate reacts with water through substitution to furnish the primary alcohol product achieving the anti-Markovnikov carbohydroxylation.

Scheme 2. Anti-Markovnikov Addition by Pyridine *N*-oxy Radical.



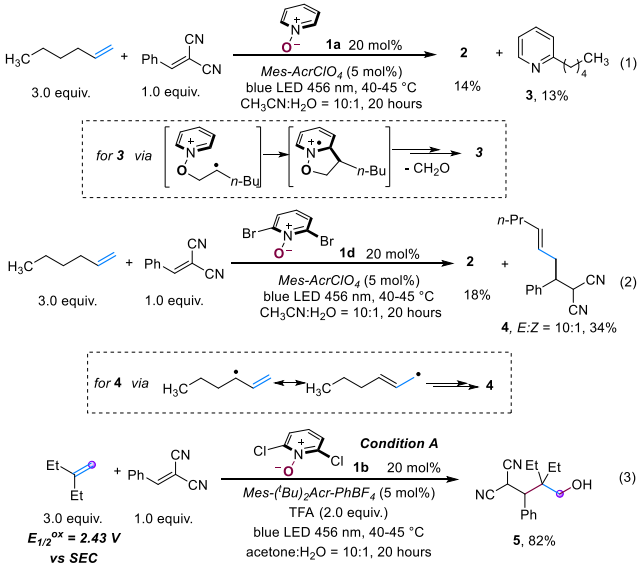
To test the principle, the carbohydroxylation of 1-hexene with benzalmalononitrile and water was chosen as the modern reaction. Based on our and others' previous studies, 9-mesityl-10-methylacridinium ($E_{1/2}^{red*}$ = +2.06 V vs SCE) was chosen as the photoredox catalyst to initiate the photoinduced single-electron oxidation of pyridine *N*-oxides for the generation of pyridine *N*-oxy radicals;[6b,15] meanwhile 1-hexene ($E_{1/2}^{ox}$ > +2.50 V vs SCE)[16] is outside of the oxidation range of the acridinium excited state. We started our investigation with a survey of pyridine *N*-oxides in the modern reaction with Mes-Acr-MeClO$_4$ under irradiation with blue light (456 nm Kessil). In line with our

Table 1. Reaction Optimization[a]



entry	conditions	conversion (%)[c]	**2** (%)[b]
1	**1a** (eq. 1)	20	14
2	**1b**	34	29
3	**1c**	10	6
4	**1d** (eq. 2)	61	18
5	**1e**	25	20
6	**1f**	<5	<5
7	**1a,** Mes-(^{t}Bu)$_2$Acr-PhBF$_4$	45	38
8	**1a,** Mes-(^{t}Bu)$_2$Acr-PhBF$_4$, acetone/H$_2$O = 10/1, TFA (2.0 equiv.) (*Condition A*)	68	50
9	**1a** (50 mol%), Mes-(^{t}Bu)$_2$Acr-PhBF$_4$, acetone/H$_2$O = 10/1, TFA (2.0 equiv.) (*Condition B*)	>95	74

[a] Reaction conditions: alkene (0.6 mmol, 3.0 equiv.), benzalmalononitrile (0.2 mmol, 1.0 equiv.), 20 mol% of *N*-oxide, and 5 mol% of photocatalyst in CH$_3$CN/H$_2$O = 10:1 (2.0 ml) under blue LED light (λ_{max} = 456 nm, 34 W) for 20 h. [b] Yields were determined by analysis of the ^{1}H NMR spectra of reaction mixture using dibromomethane as an internal standard, regioselectivity was determined by crude ^{1}H NMR analysis. [c] Conversion of benzalmalononitrile were determined by analysis of the ^{1}H NMR spectra of reaction mixture.



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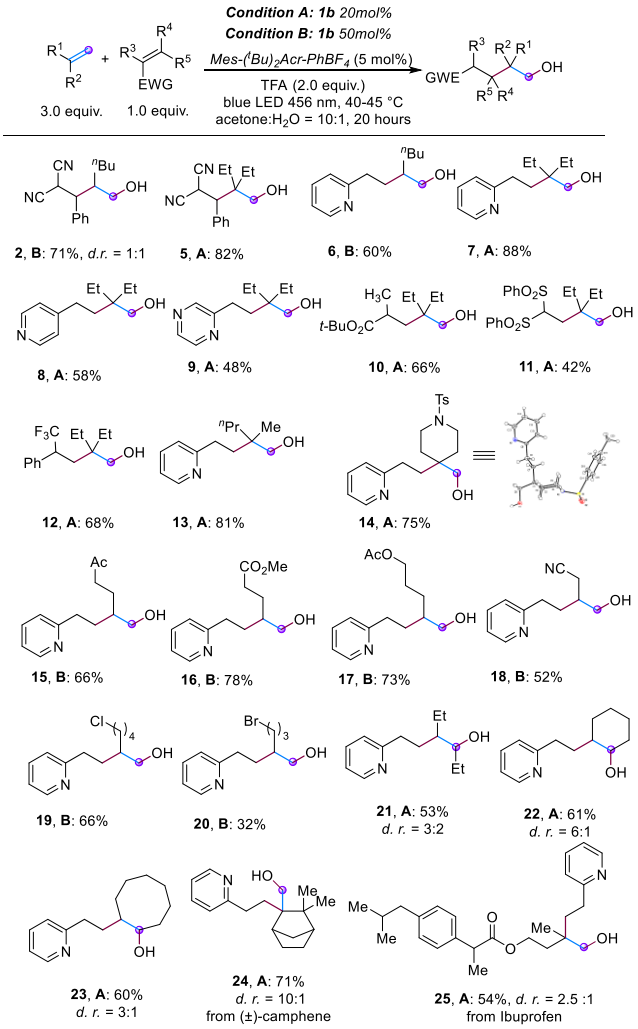
hypothesis, when 20 mol% pyridine *N*-oxide (**1a**) was applied, the desired carbohydroxylation product **2** (*d.r.* = 1:1) was obtained in 14% yield with exclusive anti-Markovnikov regioselectivity and unreacted radical acceptor was recovered (Table 1, entry 1). Noteworthy, the use of **1a** (eq 1) gave an *ortho*-alkylation product **3** (13%), whose generation is rationalized based on the previous report *via* an intramolecular radical *ortho*-addition followed by *β*-N-O and *β*-C-C bonds scissions with losing formaldehyde fragment.[17] *ortho*-Substituted *N*-oxides **1b**-**1e** (entries 2-6) delivered **2** without *ortho*-acylation, 2,6-dichloropyridine *N*-oxide **1b** was the most efficient for carbohydroxylation. It is worth mentioning that, when **1d** was applied, the allylic alkylation product **4** of 1-hexene with benzalmalononitrile was obtained in 34% (**4**, eq 2). Compound **4** is formed through allylic C–H functionalization with **1d** as H-atom abstraction agent, while the alkylation product was not detected when **1b** was examined. We postulated that the more electrophilic oxy radical from **1b** may exhibit a faster alkene addition rate than the one from **1d**. These results reveal that the competing radical addition and hydrogen abstraction of olefin could be controlled by the structural modulation of pyridine *N*-oxides, and further exploration is being undertaken in our laboratory. Following the promising results, extensive condition optimizations including surveys of photocatalysts, solvents, and additives were performed (see Table S1-S4 in the Supporting Information (SI)). Mes-(^{t}Bu)$_2$Acr-PhBF$_4$ ($E_{1/2}^{red*}$ = +2.15 V vs SCE)[6b, Fga18] proved to be the most efficient photocatalyst (entry 7). The addition of trichloroacetic acid (TFA) and the use of acetone as solvent further improved the reaction efficiency (entry 8). Encouragingly, as shown in eq. 3, when the reaction of 2-ethyl-1-butene ($E_{1/2}^{ox}$ = +2.43 V vs SCE) was subjected with 20 mol% **1b** in the presence of Mes-(^{t}Bu)$_2$Acr-PhBF$_4$ and TFA in acetone/water under blue light irradiation (*Condition A*), desired product **5** was received in high isolated yield (82%, eq 3) with exclusive *anti*-Markovnikov selectivity and completed conversion of benzalmalononitrile. Considering the ready availability of pyridine *N*-oxides, the loading of **1b** was increased to 50 mol% in the reaction of 1-hexene, and **2** can be produced in satisfactory yield (74%, entry 9, *Condition B*). Control experiments revealed the necessity of light, pyridine *N*-oxide, water, and the photocatalyst to observe reactivity (SI).

We next examined electron-deficient alkenes as radical acceptors in the anti-Markovnikov carbohydroxylation of 2-ethyl-1-butene (*Condition A*) and 1-hexene (*Condition B*). Various electron-deficient alkenes, including vinylpyridines, vinylpyrazine, *tert*-butyl methacrylate, and α-(trifluoromethyl)styrene, reacted smoothly generating the corresponding primary alcohols in good to moderate yields (Table 2, **6-12**). It is presumed that vinylpyridines were activated by protonation with TFA to deliver the products, while 4-vinylpyridine was less reactive than 2-vinylpyridine producing **8** in 58% yield. With regard to the omnipresence of the pyridine scaffold in pharmaceuticals, agrochemicals, and natural products, we then conducted the scope of *α*-olefins using 2-vinylpyridine as the radical acceptor. Generally, *β*, *β*-disubstituted *α*-olefins (Condition A) exhibited higher reactivity than mono-substituted *α*-olefins (Condition B). 2-Methyl-1-pentene underwent

Table 2. Substrate Scope of anti-Markovnikov Carbohydroxylation.

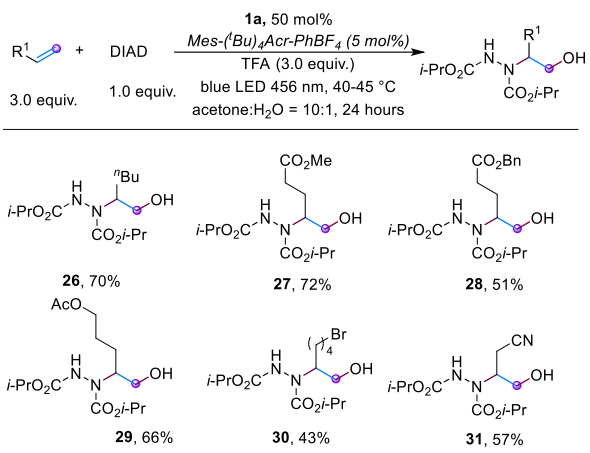


efficient anti-Markovnikov selective carbohydroxylation (**13**). Exomethylene containing 4-methylene-1-tosylpiperidine reacted successfully to generate **14** in 75% yield. The structure of anti-Markovnikov addition product **14** was identified spectroscopically and confirmed by X-ray diffraction analysis.[19] Furthermore, we evaluated *α*-olefins with various functional groups (**15-20**). Olefines containing ketones, esters, nitrile, and chloro-substituent were compatible with this reaction affording primary alcohols in good to moderate yields (**15-19**). However, bromo-substituted alkene furnished the desired product **20** in low yield (32% yield) even with 50 mol% *N*-oxide loading. In addition to terminal olefins, internal and cyclic alkenes (**21-23**) were carbohydroxylated to give the corresponding alcohol products in moderate reaction yields with low diastereoselectivities. Notably, camphene was a good substrate for this transformation giving the anti-Markovnikov selective carbohydroxylation product **24** in 71% yield with a stereoselectivity ratio of 10:1. Moreover, this protocol can be applied to the anti-Markovnikov carbohydroxylation of terminal alkene tethered Ibuprofen derivative (**25**). The present method for anti-Markovnikov carbohydrox-

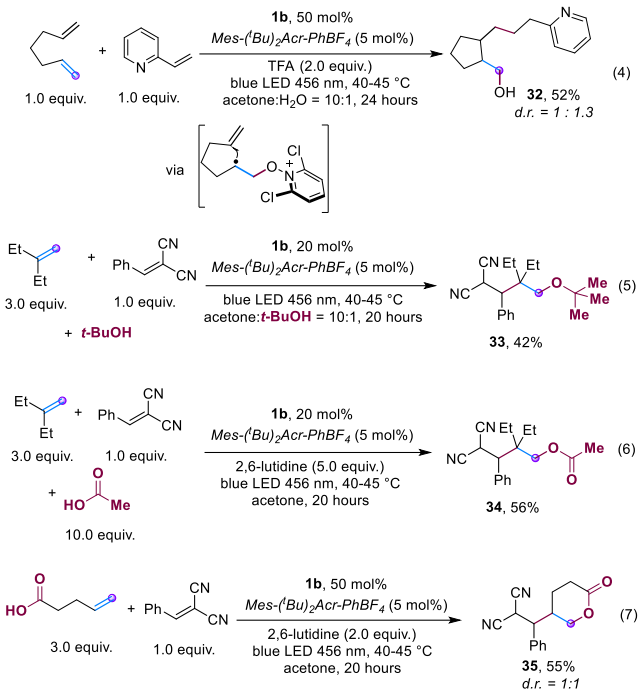
ylation allows the generation of various primary alcohols from unactivated α-olefins. Remarkably, it provides a direct approach to the synthesis of primary alcohols containing β-quaternary carbon center.

In order to fully explore the synthetic potential of the photoredox catalyzed anti-Markovnikov addition, we next applied this protocol to the aminohydroxylation of α-olefins using diisopropyl azodicarboxylate (DIAD) as radical acceptors (Table 3). Gratifyingly, upon employing 50 mol% **1b** and Mes-(^{t}Bu)$_2$Acr-PhBF$_4$ (*Condition B*), the desired aminohydroxylation products were successfully produced from various α-olefins in acceptable to good yields (**26-31**).

Table 3. Substrate Scope of anti-Markovnikov Aminohydroxylation.



To formulate a plausible mechanistic working hypothesis, we next carried out an array of experiments including fluorescence quenching experiments, electrochemical studies, and radical trapping experiments. The Stern–Volmer fluorescence quenching analysis determined that the light-excited photocatalyst Mes-(^{t}Bu)$_2$Acr^{+}* was quenched by 2,6-dichloropyridine *N*-oxide (**1b**, K_{sv} = 34.2, see SI) rather than α-olefin or benzalmalononitrile. It is consistent with our electrochemical studies that the excited photocatalyst Mes-(^{t}Bu)$_2$Acr^{+}* (E^*_{red} = 2.15 V vs SCE) oxidizes 2,6-dichloropyridine *N*-oxide (**1b**, $E_{1/2}^{ox}$ = +2.06 V vs SCE) via photoinduced single-electron oxidation, while α-olefins (e.g. 1-hexene: $E_{1/2}^{ox}$ > +2.50 V vs SCE; 2-ethyl-1-butene: $E_{1/2}^{ox}$ = +2.43 V vs SCE, see SI) are outside of the oxidation range of the acridinium excited state. These results demonstrate the feasibility for photocatalyzed 2,6-dichloropyridine *N*-oxy radical generation and exclude the pathway of photocatalyzed single-electron oxidation of α-olefins. Furthermore, carbon radical intermediates in the reaction were implicated by carbohydroxylation of 1,6-heptadiene (eq 4), which afforded a disubstituted cyclopentane **32** in 52% yield through an intramolecular radical addition to the pendant alkene. Our control experiment demonstrated the necessity of water for the production of desired carbohydroxylation products. We envisioned that the employment of other nucleophiles, e.g. alcohols and carboxylates, would be compatible to afford corresponding carbooxygenation products. Indeed, as shown in eq 5 and 6, the desired anti-Markovnikov carboetherification and carboesterification products **33** and **34** were formed from *tert*-butanol and carboxylate under anhydrous conditions. Moreover, a γ-substituted δ-lactone **35** (eq 7) was successfully obtained from 4-pentenoic acid through radical addition/cyclization. Although the unoptimized conditions produced **33**-**35** in moderate yields, these results provide not only mechanistic support for the proposed nucleophilic substitution step but also proof of principle for this protocol in the development of anti-Markovnikov additions and heterocycle synthesis from α-olefins.



In accordance with our experimental evidence and previous reports, the proposed mechanism of the *anti*-Markovnikov carbohydroxylation of α-olefins is displayed in Scheme 3. After photoexcitation, the excited photocatalyst (Mes-(^{t}Bu)$_2$Acr^{+}*) oxidizes 2,6-dichloropyridine *N*-oxide **1b** to the *N*-oxy radial. The electrophilic *N*-oxy radial undergoes *anti*-Markovnikov radical addition to α-olefin affording the carbon radical intermediate **I,** which then reacts with an electron-deficient alkene. The resulting electrophilic carbon radical alpha to the EWG (**II**) is reduced by the acridine radical Mes-(^{t}Bu)$_2$Acr· followed by protonation generating the *N*-alkoxypyridinium **III**, which was detected by ESI/MS (see SI). It is rationalized that the addition of TFA may facilitate the protonation step. Subsequently, the intermediate **III** reacts with H_2O through substitution to release **1b** and the primary alcohol product. Our experimental success for the carboetherification and carboesterification reactions of α-olefins (eq 5-7) supports the proposed substitution step.

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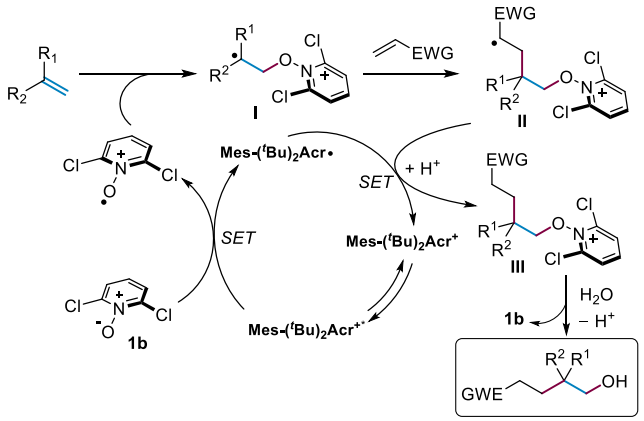
Scheme 3. Proposed Reaction Mechanism.



In summary, we have developed a direct and catalytic strategy for anti-Markovnikov carbohydroxylation of α-olefins via pyridine *N*-oxide and photoredox catalysis. The demonstrated concept was extended to anti-Markovnikov aminohydroxylation of unactivated olefins with azodicarboxylates. We anticipate that with improved understanding of the reactivity and selectivity of pyridine *N*-oxy radicals, it will be possible to further expand the diversity of anti-Markovnikov reaction classes capable of interfacing with pyridine *N*-oxide/photoredox catalysis. This may allow us to approach the enduring challenge of the anti-Markovnikov hydration of α-olefins and apply this strategy in new synthetic contexts.

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Author Contributions

The manuscript was written through contributions of all authors.

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