

## Metal-free Photocatalytic Intermolecular anti-Markovnikov Hydroamination of Unactivated Alkenes

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The development of photocatalytic intermolecular hydroamination reaction between N-aminated dihydropyridines and unactivated alkenes is reported. Metal-free co-catalysts, rhodamine 6G and thiophenol, in presence of visible light are used to initiate the process. The transformation shows a broad substrate scope, both alkenes and amidyl radical can act as coupling partners. The radical strategy provides excellent anti-Markovnikov selectivity and regioselectivity in diene substrates.

## Introduction

Nitrogen-containing structural motif is prevalent in organic compounds, such as pharmaceuticals, agrochemicals, and modern materials.<sup>[1]</sup> Therefore, new synthetic methods towards C-N bond formation have been always attractive for the synthetic community. Comparing to the well-studied nucleophilic N-species, N-centered radicals would potentially offer unique synthetic opportunities.<sup>[2-4]</sup> For example, amidyl radicals represent a very useful class of reactive species with potentially broad applications in the construction of C-N bonds and preparation of N-containing molecules.<sup>[5-11]</sup> Ingold's pioneering works<sup>[5]</sup> suggested that amidyl radicals display remarkably high electrophilic character, which gives the radical species an umpolung reactivity comparable to the typical nucleophilic character of N-species in classic polar reaction modes.<sup>[12]</sup> The development of N-centered radical reaction has been limited by the harsh requirement of the radical generation, commonly involving hazardous radical initiators, elevated temperature, or high energy UV irradiation. However, mild and efficient generation of N-radicals has been achieved by visible light photoredox catalysis recently.<sup>[13]</sup> Particularly, amidyl radicals have been achieved by a variety of elegant designs. Besides the challenging direct access to amidyl radical from amides by Knowles<sup>[14]</sup> and Rovis,<sup>[15]</sup> a series of functionalized amide precursors for the generation of amidyl radical has been

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reported by Sanford,<sup>[16]</sup> Lee,<sup>[17]</sup> Studer,<sup>[18]</sup> MacMillan,<sup>[19]</sup> Yu,<sup>[20]</sup> Luo,<sup>[21]</sup> and Leonori<sup>[22]</sup> (Scheme 1). These methodologies have been leading broad synthetic application of amidyl radicals, constructing C–N bonds, and preparing N-heterocycles.

The direct hydroamination reaction of unactivated alkenes is one of the most effective approaches for the formation of valuable nitrogen building blocks. As a result, tremendous efforts have been made in the synthetic community on this C–N bond formation by using organometallic agents as reagents or catalysts.<sup>[23–27]</sup> In 2008, Studer reported thiolcatalyzed hydroamination of olefins where N-aminated dihydropyridines were used as amidyl radical precursors.<sup>[28]</sup> More recently, Knowles reported an intermolecular hydroamination of unactivated alkenes by [Ir] catalyst and thiol catalyst upon visible-light-irradiation.<sup>[29]</sup> Continuing our interest in organic photoredox catalysis,<sup>[30]</sup> we herein reported our application of the N-aminated dihydropyridines to the metal-free photocatalytic intermolecular hydroamination reactions.

We initiated our studies by examining the hydroamination reaction between cyclohexene 1 and N-radical precursor 2 (Table 1). A series of organic photocatalysts were carefully investigated (entries 1–8) under blue light-emitting diode (LED) irradiation. Among them, 9-mesityl-10-methylacridinium salts (A and B), 4-Me–TPT (C), and rhodamine 6G could successfully

a. Functionalized amide as N-radical precusors for photoredox transformation



b. Studer's hydroamination of olefins with N-aminated dihydropyridines





Scheme 1. Functionalized amides as amidyl radical precursor.





[a] Reactions conducted by irradiating **1** (0.6 mmol), **2** (0.2 mmol), PhSH (5 mol%) and photocatalyst (2 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) with two 12 W, 450 nm light-emitting diode (LED) flood lamps for 3 h. [b] Isolated yield. [c] Reaction conducted in the dark. [d] Yield determined by <sup>1</sup>H NMR with mesitylene as a quantitative internal standard.

promote the hydroamination reaction in useful yields (entries 1-4, 53%, 50%, 58%, and 65% respectively). On the other hand, riboflavin, eosin Y, rose Bengal were only able to catalyze the reaction inefficiently (entries 5-7). Methylene Blue is found not effective at all in this reaction (entry 8). Screening different thiols (aliphatic thiol, substituted phenyl thiol, sterically hindered thiols) has shown that rhodamine 6G and PhSH cocatalysts provided the best outcome (entries 4, 9-12), providing 65% isolated yield of the hydroamination product 3. In addition, CH<sub>2</sub>Cl<sub>2</sub> was found to be the optimal solvent after careful screening of various solvents (CH<sub>2</sub>Cl<sub>2</sub>, THF, MeCN, Toluene, DMSO, and CICH<sub>2</sub>CH<sub>2</sub>CI). Control experiments (entries 13-16) have verified that photocatalyst, PhSH, and light irradiation are necessary to keep the reaction efficiency. While light irradiation is essential for the transformation (entry 16), reactions without photocatalyst or PhSH (entries 13 and 14) were able to deliver the desired product in low yields, presumably due to non-negligible absorption of light by the Nradical precursor 2. In addition, it is worth noting that although blue-LEDs, comparing with white LEDs and green LEDs, delivered the best outcome with rhodamine 6G and PhSH, we can not rule out the possibilities that the inefficiency of other catalysts is due to the mismatch between their absorption spectra and the emission spectrum of blue LEDs.

With the optimal reaction condition in hand, we next evaluated the scope of the photocatalytic hydroamination reaction. Scheme 2 summarized experiments probing the scope of olefins that can accept N-radical. In addition to cyclohexene, a series of cycloalkenes could react with N-aminated dihydropyridines to generate Boc-protected amine (Scheme 2, **3**–**7**, 57%–72%). We were pleased to find that mono-substituted alkene, 1,1-disubstituted, 1,2-disubstituted alkene, tri-substituted, and tetra-substituted alkene substrates all worked well by the procedure, providing the corresponding hydroamination



Gaoyuan Zhao received his B. Sc. in chemistry from Lanzhou University in 2011 and he pursued his Ph.D. studies at Lanzhou University under the supervision of Prof. Xuegong She (2011–2016). After obtaining his Ph.D. degree in 2016, he joined Prof. Ting Wang's group as a postdoctoral fellow at the University at Albany-SUNY (2016–2019). In 2019, he joined Prof. Ming-yu Ngai's group as a postdoctoral fellow at Stony Brook University. Currently, his research interests mainly focus on the development of new methods to functionalize carbohydrates.



Juncheng Li graduated from Southern University of Science and Technology in Shenzhen, China. His undergraduate research included trifluoromethylsulfation, glycosylation, and asymmetric addition with the ligand of chiral diene. In the fall of 2018, he joined Prof. Ting Wang's group for graduate studies at SUNY-Albany. His research focuses on the development of new photocatalysts and their applications in organic synthesis.



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Scheme 2. Scope of alkenes.

products in moderate to good yields (Scheme 2, 8–15, 54%–73%). Moreover, this radical hydroamination process was compatible with a variety of functional groups, such as silane, silyl ether, unprotected alcohol, acetonides, hemiaminol, and tertiary amide (Scheme 2, 16–20). In all cases, high anti-Markovnikov regioselectivity was observed, which was consistent with the proposed radical reaction process.

We next focused our attention on testing the scope of the N-radicals in the coupling process (Scheme 3). Aromatic amidyl radicals, bearing alkyl substitution, halogen substitution, and alkoxy substitution, worked well with cyclohexene in this transformation (Scheme 3, **21–27**, 55%–78%). Particularly, fluoro-substituted substrate provided a slightly better yield (Scheme 3, **25**, 78%). In addition, aliphatic amidyl radicals were able to deliver the corresponding coupling products (Scheme 3, **28–30**, 61%–67%). Moreover, the photocatalytic method could also be useful to generate amines bearing common protecting groups (Scheme 3, **31–33**) and functionalized amide in complex a molecular setting (Scheme 3, **34**).

Encouraged by the success of this visible-light-driven hydroamination of unactivated alkenes, we next questioned that if this radical process could differentiate different kinds of alkene partners. Mechanistically, after the amidyl radical reacted alkenes, the resulting carbon radical should be more stable on a more alkyl-substituted carbon. Therefore, it might be possible that the hydroamination reaction would favor the more substituted alkene coupling partner. Gladly, the idea was validated by several regioselective hydroamination reactions (Scheme 4a). In all examples, the amidyl radicals reacted with the tri-substituted alkene motif in the presence of monosubstituted one, affording masked secondary amine in moderate yields (36, 50%; 38, 50%; 41, 47%). We then applied the methodology to a synthesis of pyrrolizidine 5-5-6 tricycles. The synthesis of the heterocycles began with photocatalytic hydroamination between N-radical precursor 2 and 1,5-cycloocta-



Scheme 3. Scope of N-radical coupling partner.

diene, providing **43** in 57% yield. A ROM strategy by using Hoveyda-Grubbs 2G catalyst were employed to synthesize **44**, which was then cyclized to 5-5-6 tricycles **45** and **46** by treating with Lewis acid Sn(OTf)<sub>2</sub> (Scheme 4b).<sup>[31]</sup>

A plausible mechanism for the reaction is outlined in Scheme 5. According to the Stern-Volmer emission quenching studies (Supporting Information), we propose that photoexcita-



a. Regioselective hydroamination



PhMe 40%, 1:1

<sup>H</sup> CO<sub>2</sub>E1

Scheme 4. Regioselective hydroamination and synthetic application.



Scheme 5. Proposed mechanism.

tion of catalyst PC afforded an oxidizing state (PC\*)<sup>[32]</sup> that can oxidize N-aminated dihydropyridine (2), generating the amino radical cation 47 and one electron reduced photocatalyst PC<sup>•-</sup>. The N-radical 48, afforded through fragmentation of 47, would couple the alkene 50 with anti-Markovnikov selectivity. The resulting alkyl radical 51 then abstracted a hydrogen atom from PhSH to afford the hydroamination product 54 and generate thiyl radical PhS<sup>•</sup>53 which would quickly recombine to disulfide PhSSPh 55. PhSSPh 55 could be redox-coupled with PC<sup>•-</sup> to regenerate photocatalyst and afford PhSSPh<sup>•-</sup> 56 which would then generate PhS<sup>•</sup> and PhS<sup>-</sup>. The resulting PhS<sup>-</sup> would facilitate the proton transfer step in forming 49 and reproduce PhSH. Although we can not rule out the possibilities of chain reaction in the process, the light on/off experiments have shown that continuous light irradiation is necessary for the reaction to reach complete (Scheme S1 in the Supporting Information). The quantum yield for this reaction is 0.2203 (Supporting Information).

In summary, we have reported a metal-free intermolecular hydroamination reaction induced by visible light. These reactions show great generality of a variety of N-radicals and alkenes, providing direct access to various masked amines with excellent regio-selectivity. Applications of this hydroamination reaction in more complicated molecular settings are ongoing in our laboratory.



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## **Conflict of Interest**

The authors declare no conflict of interest.

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