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Communication

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Anti-Markovnikov Hydroamination of Unactivated Alkenes with Primary Alkyl Amines

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Supporting Information Placeholder

ABSTRACT: We report here a photocatalytic method for the intermolecular anti-Markovnikov hydroamination of unactivated olefins with primary alkyl amines to selectively furnish secondary amine products. These reactions proceed through aminium radical cation (ARC) intermediates and occur at room temperature under visible light irradiation in the presence of an iridium photocatalyst and an aryl thiol hydrogen atom donor. Despite the presence of excess olefin, high selectivities are observed for secondary over tertiary amine products, even though the secondary amines are established substrates for ARC-based olefin amination under similar conditions.

Hydroamination reactions between primary alkyl amines and olefins are attractive technologies for the construction of secondary amines,[1–4] which are prevalent structural features in pharmaceuticals, natural products, and other biologically-active small molecules.[5–7] Accordingly, numerous catalytic protocols have been reported in recent years for the coupling of olefins and primary alkyl amines, though significant limitations with respect to both scope and selectivity have yet to be addressed. While intramolecular cyclizations of aminoalkenes are common,[2] intermolecular variants that accommodate unactivated alkenes remain rare, with seminal examples having been reported by Marks[8–10] and Hultzsch.[11–13] Modular control of regioselectivity poses an additional challenge, as these methods provide Markovnikov addition products when unactivated olefins are employed (Figure 1A). Though the state of the art in hydroamination catalysis has advanced significantly in recent years,[14–21] no general protocol for the intermolecular anti-Markovnikov hydroamination of unactivated alkenes with primary alkyl amines has yet been reported.

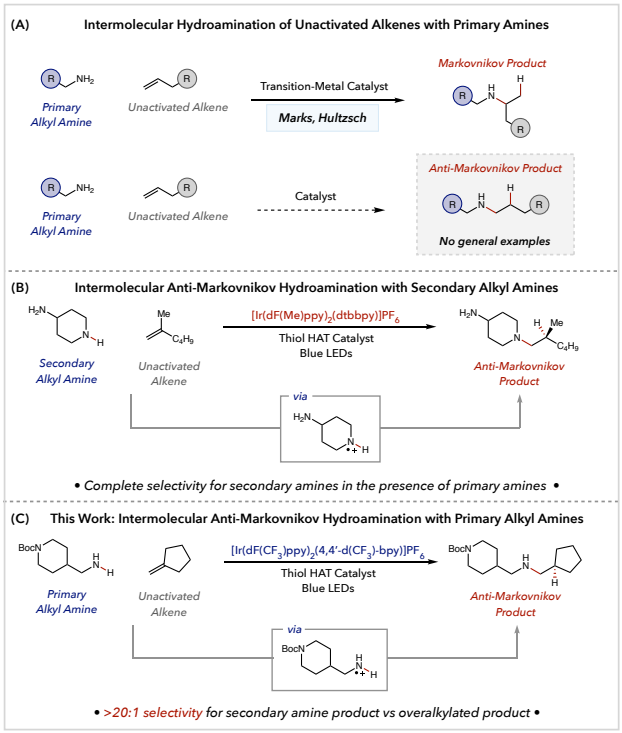


Figure 1. (A) Transition-metal catalyzed intermolecular hydroamination of unactivated alkenes with primary alkyl amines. (B) Photocatalytic anti-Markovnikov hydroamination of unactivated olefins with secondary alkyl amines. (C) Intermolecular anti-Markovnikov hydroamination of unactivated olefins with primary alkyl amines.

Seeking to address this challenge, our laboratory has recently developed several photocatalytic methods for alkene hydroamination involving aminium radical cations (ARCs), which undergo addition to alkenes with low activation barriers and predictable anti-Markovnikov regioselectivity.[22–25] In 2017, we demonstrated that ARCs generated *via* electron transfer (ET) between the excited state of $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ (**A**) and a secondary amine could undergo intermolecular addition to unactivated alkenes to furnish tertiary amine products

(Figure 1B) in the presence of a thiol co-catalyst.[14] While this protocol exhibits a broad scope with respect to both the alkene and secondary amine components, primary alkyl amines were found to be unreactive. This selectivity was attributed to the large difference in oxidation potentials between the two amine classes; while secondary amines ($E_{p/2}$ for piperidine = 0.56 V vs. Fc^+/Fc in MeCN)[26] could undergo favorable ET with the excited state of **A** ($E_{1/2}$ ($^*Ir^{III/II}$) = 0.59 V vs. Fc^+/Fc in MeCN),[27] the oxidation of primary amines ($E_{p/2}$ for isopropylamine = 1.16 V vs. Fc^+/Fc in MeCN)[28] was prohibitively endergonic. Here, we present a complementary photocatalytic method that inverts this chemoselectivity, enabling direct intermolecular anti-Markovnikov olefin hydroamination with primary amines to furnish secondary amine products that do not readily undergo further alkylation. The discovery, optimization, and scope of this process are described herein (Figure 1C).

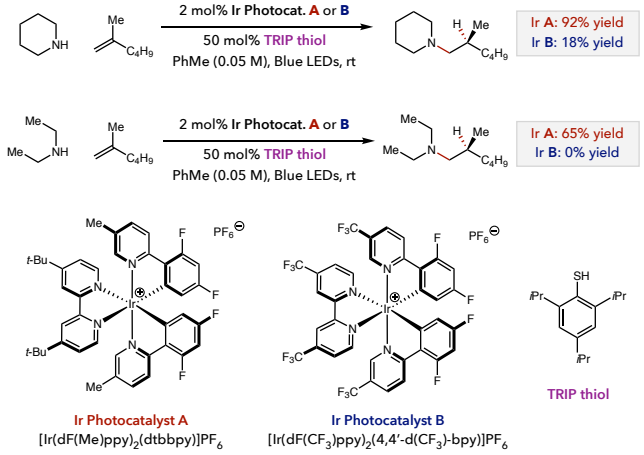


Figure 2. Observation of divergent reactivity between cyclic and acyclic amines with photocatalysts **A** and **B**.

This work finds its basis in observations made during the optimization of the secondary amine hydroamination reaction described above (Figure 2). Under optimized conditions using photocatalyst **A**, hydroamination of 2-methyl-1-hexene with piperidine yielded the desired tertiary amine product in 92% yield, while an analogous reaction with diethylamine proved moderately less efficient (65% yield). However, when the same reaction partners were studied using the more highly oxidizing photocatalyst $[Ir(dF(CF_3)ppy)_2(4,4'\text{-}d(CF_3)\text{-}bpy)]PF_6$ (**B**) ($E_{1/2}$ ($^*Ir^{III/II}$) = 1.27 V vs. Fc^+/Fc in MeCN),[29] we observed only 18% conversion to the piperidine product, while reactions with diethylamine provided only unreacted starting materials. The latter results were surprising given that both amines are readily oxidized to their corresponding ARCs by the excited state of **B**, and both ARCs are kinetically competent hydroamination partners. In fact, prior work by Lusztyk and co-workers demonstrated that the operative C–N bond forming steps are rapid, with the piperidinium radical cation undergoing addition to 2-methyl-1-butene with a second-order rate constant of 1.8×10^8 $M^{-1}s^{-1}$ in MeCN at rt, while the diethyl aminium radical cation reacts with the same olefin approximately an order of magnitude more slowly ($k = 2.6 \times 10^7$ $M^{-1}s^{-1}$).[23]

We hypothesized that these divergent outcomes may result from a kinetic competition between productive olefin addition and back-electron transfer (BET) to the ARCs from the reduced Ir^{II} state of **B**, regenerating the amine starting material and Ir^{III} photocatalyst.[30,31] In this proposal, we speculated that the rate of olefin addition for piperidine may be kinetically competitive with back-electron transfer, resulting in observable product formation. However, the slower rate of olefin addition for the diethyl aminium radical cation would permit BET to dominate, effectively precluding productive C–N bond formation.

Table 1. Reaction optimization[a]

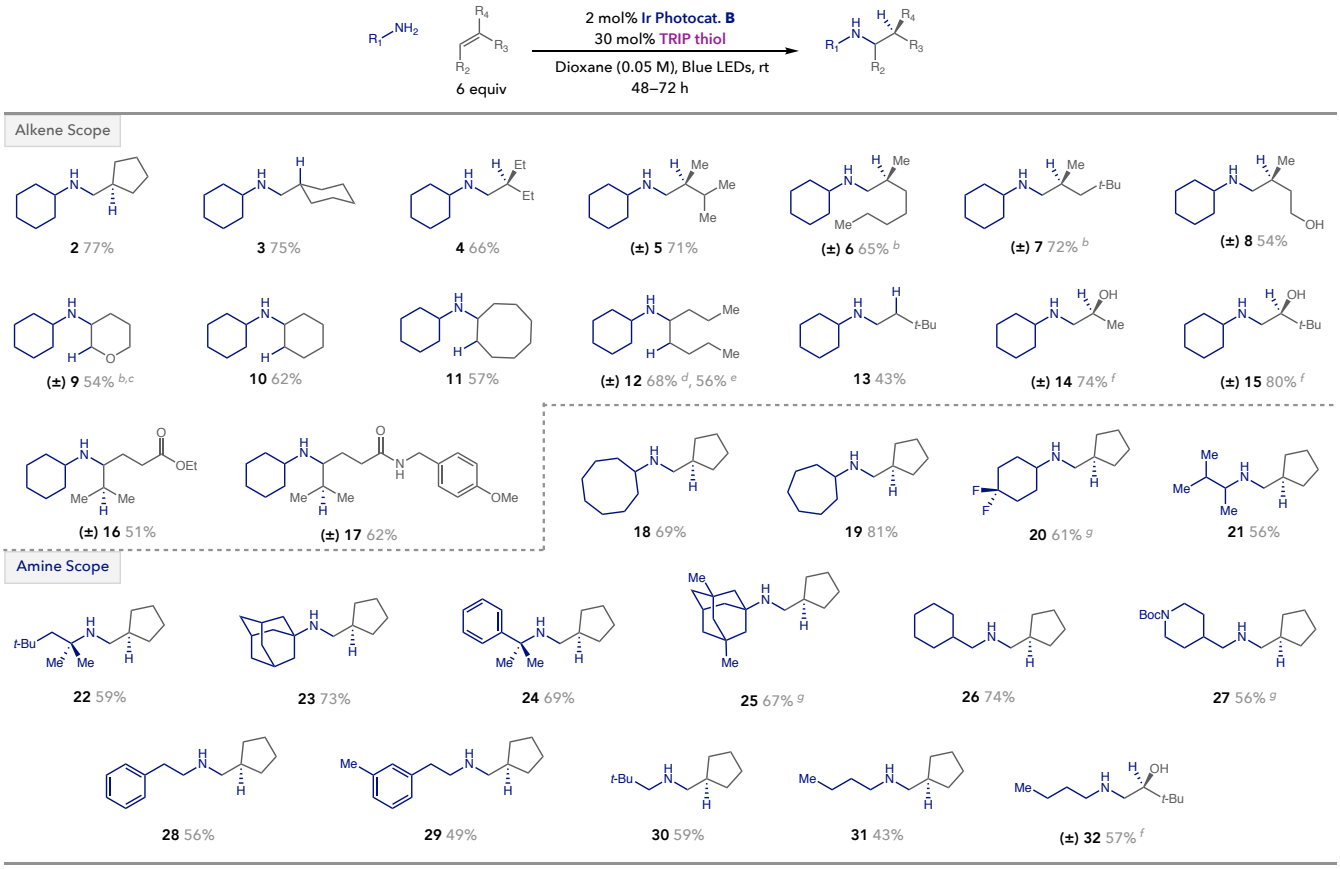
Entry	Solvent	TRIP thiol (mol%)	Concentration (M)	Equiv Alkene	Yield 2 (%)	Yield 2a (%)
1	PhMe	30	0.05	6	8	0
2	EtOAc	30	0.05	6	34	0
3	Dioxane	30	0.05	6	84	2
4	Dioxane	30	0.2	3	69	2
5[b]	Dioxane	30	0.05	6	8	0
6[c]	Dioxane	30	0.05	6	76	2
7	Dioxane	0	0.05	6	0	0
8[d]	Dioxane	30	0.05	6	0	0
9[e]	Dioxane	30	0.05	6	0	0

[a] Optimization reactions were performed on a 0.2j mmol scale and run for 24 h. Yields were determined *via* GC analysis of the crude reaction mixture relative to biphenyl as an internal standard. [b] **1**•HCl used instead of **1**. [c] **1**•HCl used with 1 equiv LiOH. [d] 0 mol% Ir photocatalyst **B**. [e] No irradiation.

Considering these ideas more broadly, we reasoned that this framework might enable the development of a complementary olefin hydroamination method with primary alkyl amines that would furnish secondary amine products selectively. First, the excited-state reduction potential of catalyst **B** suggests that it should be competent to oxidize primary amines to their corresponding ARCs.[28] Second, we expected that the resulting primary amine-derived ARCs would be significantly more reactive than secondary ARCs, enabling C–N bond formation to outcompete BET and resulting in a productive hydroamination reaction. However, once formed, we inferred from the diethyl amine studies that the nascent acyclic secondary amine product should be inert to further reaction.

To evaluate this hypothesis, we elected to study the hydroamination of methylene cyclopentane with cyclohexylamine (**1**) as a model reaction. Combining the olefin and amine together with 30 mol% 2,4,6-triisopropylbenzenethiol (TRIP thiol) as the H-atom transfer (HAT) catalyst and 2 mol% of **B** in PhMe solution

Table 2. Scope of the Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes[a]



[a] Yields are for isolated and purified material and are the average of two experiments. Reactions were conducted on 0.5 mmol scale. [b] 3 equiv olefin was used with 0.2 M dioxane. [c] An additional 18% of the Markovnikov addition product also was formed. [d] *cis*-4-Octene was used as the olefin. [e] *trans*-4-Octene was used as the olefin. [f] Substrate is the corresponding trimethylsilyl enol ether. [g] Amines were used as their corresponding HCl salts with 1 equiv LiOH.

(0.05 M) under blue light irradiation furnished secondary amine **2** in 8% yield after 24 hours with no observable amount of overalkylated **2a** (Table 1, Entry 1).Employing ethyl acetate as solvent increased reactivity, providing **2** in 34% yield (Entry 2). Further solvent evaluation revealed dioxane to be the optimal medium for this protocol, giving the desired secondary amine in 84% yield, with only 2% of **2a** observed (Entry 3). We also found that it was possible to obtain similar yields of the product under more concentrated reaction conditions with lower loadings of the alkene (Entry 4), though these conditions were not general for all substrates examined. While **1**•HCl is not a viable substrate in the reaction (Entry 5), the inclusion of 1 equivalent of LiOH restores reactivity (Entry 6). The ability to use amine hydrochloride salts in the reaction directly is of practical significance due to their enhanced stability and ease of handling relative to free amines, particularly for volatile, low molecular weight substrates. Control reactions revealed that absence of TRIP thiol, photocatalyst **B**, or light results in a complete loss of hydroamination activity (Entries 7–9).

Having identified effective reaction conditions, we next explored the substrate scope of this process (Table 2). A number of alkene classes could be successfully aminated, including both symmetrical (**2**–**4**) and unsymmetrical 1,1-disubstituted olefins (**5**–**8**). Cyclic enol ethers were competent substrates, as well, though they yielded a 3:1 ratio of the desired anti-Markovnikov product to the Markovnikov product (**9**). We hypothesize that this undesired isomer likely results from competitive Brønsted acid catalysis, given the low pK_a of primary ARC intermediates (pK_a ~5 in MeCN).[28,32] Amination of 1,2-disubstituted cyclic olefins gave **10** and **11** in moderate yields. Hydroamination of *trans*-4-octene and *cis*-4-octene with cyclohexylamine furnished **12** in 68% and 56% yield, respectively. Terminal olefins, which are comparatively less nucleophilic, proved to be a particularly challenging substrate class, with 3,3-dimethyl-1-butene providing **13** in 43% yield. Silyl enol ethers were excellent substrates, resulting in useful 1,2-amino alcohol products following an acidic, desilylative workup (**14**, **15**). Esters and amides are also tolerated in the reaction, furnishing **16** and **17**, respectively, in moderate

yields. Notably, no intramolecular hydroamidation of **17** is observed,[17,33,34] suggesting that the amide N–H bond is not activated *via* a proton-coupled electron transfer process under these reaction conditions. Similarly, oxidation of the trisubstituted olefin to the alkene radical cation would likely favor cyclization over intermolecular hydroamination, further supporting the intermediacy of the key aminium radical cation. With respect to limitations, styrene was found to be a comparatively poor substrate in this protocol.

Following our investigations of the olefin scope, we turned our attention to the scope of the amine component. Both cyclooctylamine and cycloheptylamine gave good to excellent yields of **18** and **19**, respectively. The HCl salt of 4,4-difluorocyclohexan-1-amine provided **20** in 61% yield with the addition of an equivalent of LiOH. Amines bearing secondary and tertiary branching in the α-position could be alkylated in good to moderate yields (**21**–**24**). Given that the cumyl group of **24** can be readily deprotected with trifluoroacetic acid,[35] this protocol represents a convenient and complementary method for the installation of an ammonia surrogate for the synthesis of primary amines *via* hydroamination. Memantine•HCl, used to treat dementia associated with Alzheimer's disease, was cleanly alkylated in 67% yield (**25**). Linear primary amines bearing no substitution at the α-position were also amenable substrates (**26**–**30**), with butylamine giving **31** in 43% yield. Switching from methylene cyclopentane to a silyl enol ether provided the amino alcohol **32** in 57% yield.

Monoalkylation of primary amines is a long-standing synthetic challenge, with few methods capable of generating secondary amines selectively.[5,36–41] In all the reactions described in Table 2, no tertiary amine side products were observed by ^{1}H-NMR analysis of the crude reaction mixtures. In order to quantify the degree of overalkylation more precisely, the tertiary amine side products of **19** and **26** were independently synthesized. The ratio of monoalkylated versus dialkylated products was found to be 59:1 for **19** and 34:1 for **26**, respectively. Additionally, no Markovnikov addition products other than for **9** were observed, highlighting the robust selectivity profile of this method.

While the mechanistic hypothesis described above guided our thinking in the design and evaluation of this system, we emphasize that it remains speculative and further mechanistic work will be necessary to evaluate its validity. However, we note that both the primary amine starting material **1** and secondary amine product **2** effectively quench the luminescence of the excited state of **B** (K_{SV} = 45 M^{-1} for **1** and 941 M^{-1} for **2**), consistent with the conversion of both amine classes to their respective ARCs under these reaction conditions. Moreover, single electron transfer between the excited state of **B** and the alkenes employed in this study are predicted to be prohibitively endergonic (ΔE ~ +730 mV and +330 mV for disubstituted and trisubstituted alkenes, respectively), suggesting that alkene radical cations are unlikely intermediates in these reactions.[26] If correct, this mechanism represents an interesting example of how nonintuitive selectivities can be achieved in photocatalysis by using BET to limit the reaction channels available to an otherwise kinetically competent radical intermediate. Regardless of the ultimate basis for selectivity, these reactions address a long-standing gap in the hydroamination literature. As such, we are optimistic that this protocol will provide both new opportunities for the construction of secondary amines and serve as the basis for future work in this area.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)

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Notes

No competing financial interests have been declared.

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REFERENCES

(1) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596–2697.

(2) Reznichenko, A. L.; Hultzsch, K. C. Hydroamination of Alkenes. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2015; Vol. 88, pp 1–554.

(3) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **2008**, *108*, 3795–3892.

(4) Reznichenko, A. L.; Hultzsch, K. C. C1-Symmetric Rare-Earth-Metal Aminodiolate Complexes for Intra- and Intermolecular Asymmetric Hydroamination of Alkenes. *Organometallics* **2013**, *32*, 1394–1408.

(5) Salvatore, R. N.; Yoon, H.; Woon, K. Synthesis of Secondary

Amines. *Tetrahedron* **2001**, *57*, 7785–7811.

(6) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley: Weinheim, 2008.

(7) Marvin, C. C. Synthesis of Amines and Ammonium Salts. In *Comprehensive Organic Synthesis: Second Edition*; 2014; Vol. 6, pp 34–99.

(8) Li, Y.; Marks, T. J. Diverse Mechanistic Pathways and Selectivities in Organo-f-Element-Catalyzed Hydroamination. Intermolecular Organolanthanide-Catalyzed Alkyne and Alkene Hydroamination. *Organometallics* **1996**, *15*, 3770–3772.

(9) Ryu, J. S.; Li, G. Y.; Marks, T. J. Organolathanide-Catalyzed Regioselective Intermolecular Hydroamination of Alkenes, Alkynes, Vinylarenes, Di- and Trivinylarenes, and Methylenecyclopropanes. Scope and Mechanistic Comparison to Intramolecular Cyclohydroaminations. *J. Am. Chem. Soc.* **2003**, *125*, 12584–12605.

(10) Yuen, H. F.; Marks, T. J. Phenylene-Bridged Binuclear Organolanthanide Complexes as Catalysts for Intramolecular and Intermolecular Hydroamination. *Organometallics* **2009**, *28*, 2423–2440.

(11) Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines. *Angew. Chemie - Int. Ed.* **2010**, *49*, 8984–8987.

(12) Reznichenko, A. L.; Hultzsch, K. C. *C* 1 -Symmetric Rare-Earth-Metal Aminodiolate Complexes for Intra- and Intermolecular Asymmetric Hydroamination of Alkenes. *Organometallics* **2013**, *32*, 1394–1408.

(13) Nguyen, H. N.; Lee, H.; Audörsch, S.; Reznichenko, A. L.; Nawara-Hultzsch, A. J.; Schmidt, B.; Hultzsch, K. C. Asymmetric Intra- and Intermolecular Hydroamination Catalyzed by 3,3′-Bis(Trisarylsilyl)- and 3,3′-Bis(Arylalkylsilyl)-Substituted Binaphtholate Rare-Earth-Metal Complexes. *Organometallics* **2018**, *37*, 4358–4379.

(14) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic Intermolecular Hydroaminations of Unactivated Olefins with Secondary Alkyl Amines. *Science (80-.).* **2017**, *355*, 727–730.

(15) Utsunomiya, M.; Hartwig, J. F. Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *J. Am. Chem. Soc.* **2004**, *126*, 2702–2703.

(16) Zhu, S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916.

(17) Nguyen, T. M.; Nicewicz, D. A. Anti-Markovnikov Hydroamination of Alkenes Catalyzed by an Organic Photoredox System. *J. Am. Chem. Soc.* **2013**, *135*, 9588–9591.

(18) Ensign, S. C.; Vanable, E. P.; Kortman, G. D.; Weir, L. J.; Hull, K. L. Anti-Markovnikov Hydroamination of Homoallylic Amines. *J. Am. Chem. Soc.* **2015**, *137*, 13748–13751.

(19) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. Synthesis of Tertiary Alkyl Amines from Terminal Alkenes: Copper-Catalyzed Amination of Alkyl Boranes. *J. Am. Chem. Soc.* **2012**, *134*, 6571–6574.

(20) Zhu, Q.; Graff, D. E.; Knowles, R. R. Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 741–747.

(21) Lardy, S. W.; Schmidt, V. A. Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination Using N-Hydroxyphthalimide. *J. Am. Chem. Soc.* **2018**, *140*, 12318–12322.

(22) Chow, Y. L.; Nelsen, S. F.; Rosenblatt, D. H. Nonaromatic Aminium Radicals. *Chem. Rev.* **1978**, *78*, 243–274.

(23) Wagner, B. D.; Ruel, G.; Lusztyk, J. Absolute Kinetics of Aminium Radical Reactions with Olefins in Acetonitrile Solution 1. *J. Am. Chem. Soc.* **1996**, *118*, 13–19.

(24) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. Kinetics of Dialkylaminium Cation Radical Reactions: Radical Clocks, Solvent Effects, Acidity Constants, and Rate Constants for Reactions with Hydrogen Atom Donors. *J. Am. Chem. Soc.* **1995**, *117*, 11124–11133.

(25) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. Catalytic Olefin Hydroamination with Aminium Radical Cations: A Photoredox Method for Direct C-N Bond Formation. *J. Am. Chem. Soc.* **2014**, *136*, 12217–12220.

(26) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2016**, *27*, 714–723.

(27) Ladouceur, S.; Fortin, D.; Zysman-Colman, E. Enhanced Luminescent Iridium(III) Complexes Bearing Aryltriazole Cyclometallated Ligands. *Inorg. Chem.* **2011**, *50*, 11514–11526.

(28) Bourdelande, J. L.; Gallardo, I.; Guirado, G. Inductive vs Solvation Effects in Primary Alkyl Amines: Determination of the Standard Potentials. *J. Am. Chem. Soc.* **2007**, *129*, 2817–2821.

(29) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C-H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539*, 268–271.

(30) Ruccolo, S.; Qin, Y.; Schnedermann, C.; Nocera, D. G. General Strategy for Improving the Quantum Efficiency of Photoredox Hydroamidation Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14926–14937.

(31) Gould, I. R.; Farid, S. Dynamics of Bimolecular Photoinduced Electron-Transfer Reactions. *Acc. Chem. Res.* **1996**, *29*, 522–528.

(32) Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. Heats of Formation and Ionization Potentials of Some Alpha-Aminoalkyl Radicals. *J. Am. Chem. Soc.* **1983**, *105*, 4701–4703.

(33) Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with N-Alkyl Amides. *ACS Catal.* **2019**, *9*, 4502–4507.

(34) Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 13492–13495.

(35) Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: Hoboken, NJ, 2007; Vol. 33.

(36) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707–17710.

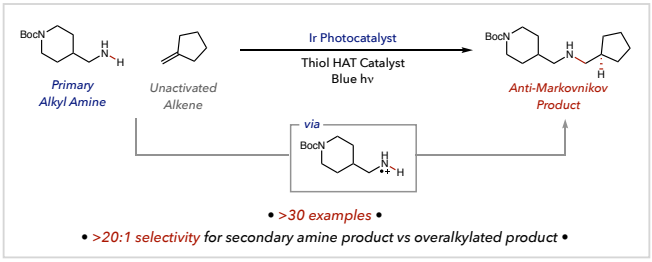
(37) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. Cesium Hydroxide Promoted Chemoselective N -Alkylation for the Generally Efficient Synthesis of Secondary Amines. *Org. Lett.* **1999**, *1*, 1893–1896.

(38) Salvatore, R. N.; Nagle, A. S.; Kyung, W. J. Cesium Effect: High Chemoselectivity in Direct N-Alkylation of Amines. *J. Org. Chem.* **2002**, *67*, 674–683.

(39) Kumpaty, H. J.; Bhattacharyya, S.; Rehr, E. W.; Gonzalez, A. M. Selective Access to Secondary Amines by a Highly Controlled Reductive Mono-N-Alkylation of Primary Amines. *Synthesis (Stuttg).* **2003**, No. 14, 2206–2210.

(40) Bhattacharyya, S.; Pathak, U.; Mathur, S.; Vishnoi, S.; Jain, R. Selective N-Alkylation of Primary Amines with R-NH2·HBr and Alkyl Bromides Using a Competitive Deprotonation/Protonation Strategy. *RSC Adv.* **2014**, *4*, 18229–18233.

(41) Castillo, J. C.; Orrego-Hernández, J.; Portilla, J. Cs2CO3-Promoted Direct N-Alkylation: Highly Chemoselective Synthesis of N-Alkylated Benzylamines and Anilines. *Eur. J. Org. Chem.* **2016**, 3824–3835.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• >20:1 selectivity for secondary amine product vs overalkylated product •