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Anti-Markovnikov Hydroamination of Alkenes Catalyzed by an Organic Photoredox System

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Abstract

Herein we report a metal-free method for the direct anti-Markovnikov hydroamination of unsaturated amines. Irradiation of the amine substrates with visible light in the presence of catalytic quantities of easily synthesized 9-mesityl-10-methylacridinium tetrafluoroborate and thiophenol as a hydrogen atom donor furnished the nitrogen containing heterocycles with complete regio-control. Two examples of in termolecular anti-Markovnikov alkene hydroamination are also disclosed.

The direct addition of N-H across an alkene[1] provides an efficient, atom-economical route to highly valuable, biologically active nitrogen containing compounds.[2] Considerable effort has been devoted to the development of catalyst systems for alkene hydroamination, with the majority of these strategies exhibiting preferential Markovnikov selectivity.[3, 4] Thus, accessing anti-Markovnikov reactivity has proven quite challenging and considerably fewer reports exist in this arena. Catalytic intermolecular anti-Markovnikov olefin hydroamination reactions have been demonstrated using transition metals,[5] alkaline earth metals,[1, 5] and to a limited extent, photosensitizers.[6, 7]To our knowledge, there exists a single report of an intramolecular anti-Markovnikov hydroamination of styrenes reported by the Hartwig group in 2006 employing a Rh catalyst at elevated temperatures (eq. 1).[8, 9] Recently, our group reported an anti-Markovnikov hydroalkoxylation reaction using a photocatalyst and hydrogen atom donor system.[10] Given the paucity of intramolecular anti-Markovnikov hydroamination reports, we saw an opportunity to further demonstrate the utility of our catalytic strategy towards this end. Here, we report a metal-free, anti-Markovnikov hydroamination of unsaturated amines using 9-mesityl-10-methylacridinium and thiophenol as a hydrogen atom donor (Figure 1, eq. 2).

In our previously reported hydroalkoxylation reaction, we took advantage of the well-documented single electron oxidation of alkenes to provide unique radical cations that give rise to anti-Markovnikov reactivity.[11–13] We proposed to apply this strategy to the hydroamination reaction, although we anticipated some challenges associated with amine oxidation.[14] Sufficiently electron-rich amines are susceptible to oxidation at nitrogen and numerous groups have taken advantage of this reactivity.[15]While this pathway could lead to

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Supporting Information Placeholder

ASSOCIATED CONTENT

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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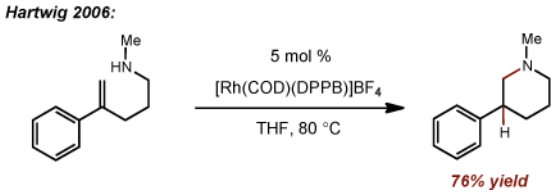
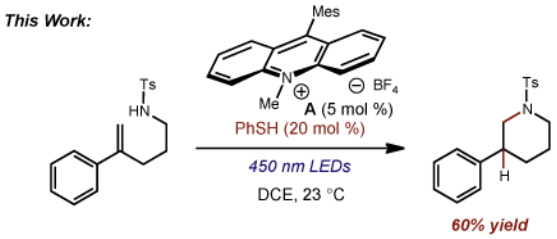
productive hydroamination, it may also result in undesirable side reactions stemming from amine cation radical intermediates. Judicious selection of the amine protecting group could circumvent these potential issues and for this reason, we elected to first examine the use of a sulfonyl group as it should be adequately withdrawing to suppress amine oxidation, yet still render the amine nucleophilic.



(1)



(2)

We began our studies by submitting the *p*-toluenesulfonyl-protected isoprenyl amine **9a** to our previously reported conditions for the anti-Markovnikov hydroalkoxylation reaction. Despite the low yield obtained, complete anti-Markovnikov regioselection (>20:1) was observed in the formation of the desired pyrrolidine product after 3 days (16%, Table 1, entry 1). After additional efforts at reaction optimization (solvent, addition of organic and inorganic bases, concentration, etc.) failed to increase the reaction efficiency, we turned our attention to the identity of the hydrogen atom donor. While 9-cyanofluorene gave essentially the same result (entry 2) as did phenylmalononitrile, heteroatom hydrogen donor thiophenol provided a 2-fold increase in yield (entry 3).[16] Upon decreasing the thiophenol loading to 20 mol %, we were pleased to find that pyrrolidine **9b** could be obtained in a 70% yield as a single regioisomer (entry 4). To our knowledge, this result represents a rare example of an intramolecular anti-Markovnikov hydroamination of a non-activated olefin.[3b, 4a]

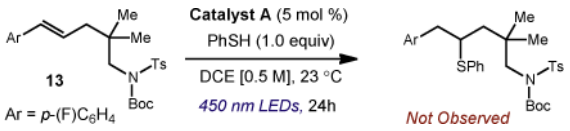
Control experiments revealed that the thiophenol, light and photocatalyst were all necessary for productive reactivity (entries 8–10). The use of thiophenol as the hydrogen atom donor allowed us to explore the use of alternative common protecting groups for amines. While a benzyl protecting group afforded only small amounts of the pyrrolidine adduct (15% yield, entry 6), presumably due to the formation of numerous unidentified side products, we found that the Boc protecting group was suitable in this context (65% yield, entry 7). This supports our hypothesis that electron rich amines would be poor substrates as they are susceptible to oxidation. While the use of a Boc protecting group was quite appealing owing to the ease of its removal, we elected to evaluate tosylamine substrates for their straightforward characterization.

We next shifted our focus to the investigation of the alkene hydroamination reaction scope. Amine substrates bearing pendant styrenes underwent smooth 5-*exo* cyclization to furnish the corresponding regioisomerically pure pyrrolidines (entries 1–6). It should be noted that similar reactivity can be obtained with catalytic quantities of strong bases.[17] The presence of electron releasing (-OMe) and withdrawing (-F) groups had little effect on the reaction efficiencies (entries 2–5). Substitution at the *ortho* position of the styrene was tolerated, giving desired pyrrolidine **4b** in 69% yield (entry 4). Importantly, 6-*endo* cyclizations of 1,1 disubstituted styrenes to give tosylpiperidine products **7b** and **8b** also proceeded in good yields and with complete regiocontrol (entry 7, 8). We observed that geminal substitution in the backbone was not required for reactivity, and saw only slight decreases in yield as compared to their dimethyl substituted analogs, albeit longer reaction times were generally required (cf. entries 3&5; 7&8). For styrenyl substrates, the major byproduct was the cyclized deprotected product. Re-protection or deprotection of the reaction mixture can easily convert the remainder of the mass balance as desired.

Inclusion of a stereocenter neighboring the amino group (**10a**) gave stereocontrol during the ring-forming event, albeit in modest levels (3:1 d.r., entry 10). We were pleased to find that a more geometrically-challenging 5-*endo* cyclization could be achieved employing unsaturated amine **11a** to afford the fully-saturated indole derivative **11b** in 72% yield and 12:1 dr (entry 11). Furthermore, the method is not limited to tosylamine as the sulfamate proved to be a competent nucleophile, givingaccess to a unique 6-exo cyclization (entry 12).

From the beginning of our studies, we presumed that the role of the thiophenol was to act as a hydrogen atom donor and the subsequent thiyl radical could serve to reoxidize the reduced form of **A**. To exclude alternative mechanistic pathways, we conducted several control experiments. We considered that thiophenol could participate in a thiol-ene reaction that could be catalyzed by the acridinium catalyst.[18] Following the thiol-ene reaction, subsequent nucleophilic displacement of the resultant phenylthioether could furnish the observed products. However, this prospect seemed unlikely given that the limited examples of this reactivity require either strong exogenous base or elevated temperatures. To probe the potential involvement of this reaction pathway, we prepared Boc-protected unsaturated amine **13** and submitted it to the reaction conditions shown in eq 3. As we only observed unchanged starting material and no incorporation of thiophenol into the molecule, we believe that the thiol-ene pathway is likely not operative in this transformation.

We also considered that thiophenol was acting solely as a hydrogen atom shuttle.[19] In this context, we submitted isoprenyl amine **9a** to thiophenol with either di-*tert*-butyl peroxide or AIBN as thermal radical initiators (Conditions A and B, eq 4). No reactivity was observed in either case, suggesting that formation of nitrogen-centered radical intermediates was also unlikely.



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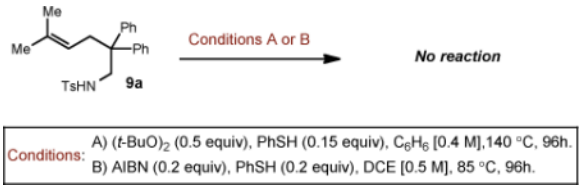
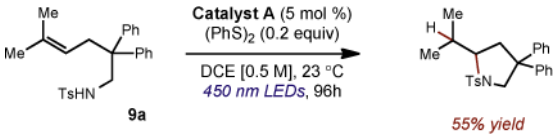


(4)

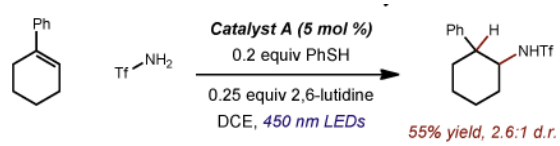
Finally, after the observation of varying quantities of PhSSPh in the crude reaction mixtures, we questioned whether this byproduct was active in the catalytic cycle. Subjection of **9a** to the reaction conditions employing PhSSPh instead of PhSH afforded the anti-Markovnikov hydroamination product in 55% yield (eq 5). While this observation is not fully understood at this time, it is conceivable that diphenyl disulfide could serve as a reservoir of phenyl thiyl radical via oxidation of the disulfide (E_p^{ox} = +1.51 V vs. SCE)[20] and subsequent fragmentation. It is possible that the phenyl thiyl radical then can act as an oxidant for the reduced form of catalyst **A** in a manner similar to the mechanism invoked in our prior communication.[10]



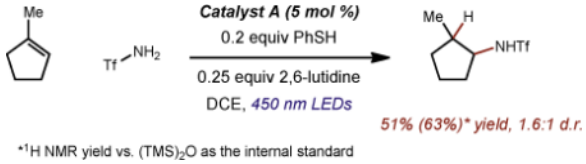
(5)

Based on these experiments and the reactivity observed in this study, we have developed the working mechanistic hypothesis depicted in Scheme 1. After oxidation of the unsaturated amine (**9a**) by the excited state of the catalyst (**A***), anti-Markovnikov addition of the amine would furnish intermediate cation radical **14**. Hydrogen atom transfer from thiophenol to **14** would furnish the desired amine heterocycle (**9a**) after proton loss. The subsequent thiyl radical (**15**) could serve as an oxidant for **14** to reset catalyst **A** and generate thiophenoxide anion. Given the known reduction potential of **16** (E_p = +0.45 V vs. SCE)[21] and the oxidation potential of **15** ($E_{1/2}$ = −0.57 V vs. SCE),[22] we estimate this electron transfer should be exergonic. Thiophenoxide then should serve as a mild base to neutralize the acid generated during the course of the reaction.

We were pleased to find that this protocol could be extended to include examples of in termolecular alkene hydroamination (eqns 6 & 7). Treatment of a styrenyl and alkenyl substrate with 3.0 equiv trifylamide under our standard reaction conditions with the addition of 0.25 equiv of 2,6-lutidine gave the desired products in modest yields as single regioisomers. To our knowledge, this represents the first example of an organocatalytic intermolecular anti-Markovnikov alkene hydroamination.



(6)



(7)

In conclusion, we have reported an intramolecular anti-Markovnikov hydroamination method using catalytic amounts of thiophenol and an organic photocatalyst promoted by visible light. The reaction conditions are mild and effect a range of cyclization modes to give important nitrogen-containing heterocycles. We have also demonstrated that this protocol can be extended to inter-mo lecular reactions. Efforts to further understand the mechanism of this transformation are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. For reactions of amines with electrochemically-generated alkene cation radicals, see:(a) Ashikari Y, Nokami T, Yoshida J. J Am Chem Soc. 2011; 133:11840. [PubMed: 21744849] (b) Campbell JM, Xu H, Moeller KD. J Am Chem Soc. 2012; 134:18338. [PubMed: 23061483] (c) Xu H, Moeller KD. Org Lett. 2010; 12:5174. [PubMed: 20945849] (d) Xu H, Moeller KD. J Am Chem Soc. 2010; 132:2839. [PubMed: 20131795] (e) Xu H, Moeller KD. J Am Chem Soc. 2008; 130:13542. [PubMed: 18808122]
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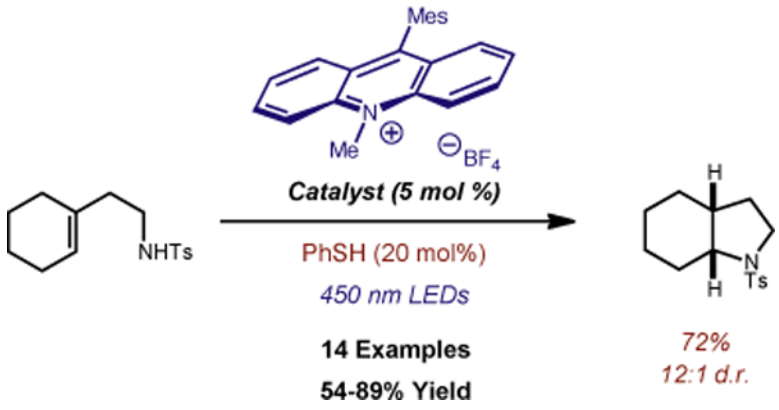
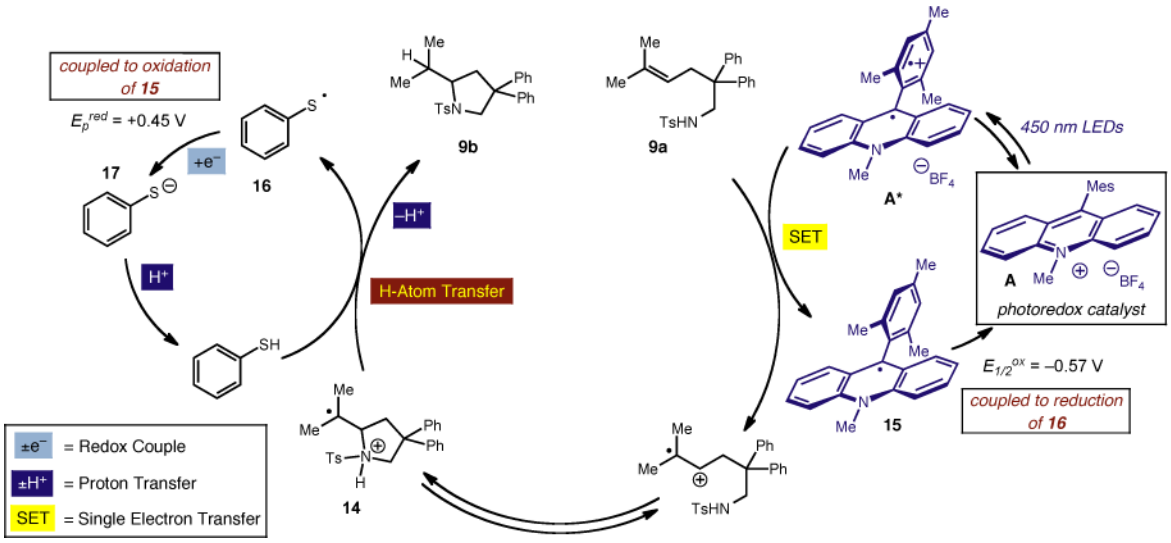


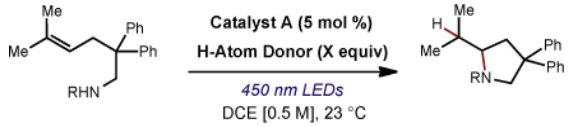
Figure 1.
Catalytic Anti-Markovnikov Intramolecular Hydroamination



Scheme 1.
Working Mechanism for Direct Anti-Markovnikov Hydroamination of Alkenes

Table 1

Optimization Studies[a]



Entry	R	H-Atom Donor	Time	Yield[b]
1	Ts	1.0 equiv $PhCH(CN)_2$	72	16%
2	Ts	1.0 equiv 9-Cyanofluorene	72	12%
3	Ts	1.0 equiv PhSH	72	41%
4	Ts	0.2 equiv PhSH	96	70%[c]
5	H	0.2 equiv PhSH	96	<5%
6	Bn	0.2 equiv PhSH	96	15%
7	Boc	0.2 equiv PhSH	96	65%
8	Ts	None	96	<5%
9	Ts	0.2 equiv PhSH without photocatalyst	24	<5%
10	Ts	0.2 equiv PhSH without light	24	<5%

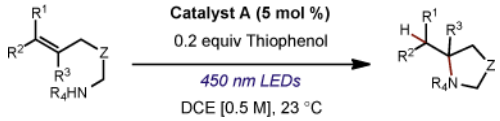
[a] All reactions irradiated with a 15W 450 nm LED flood lamp.

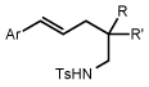
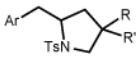
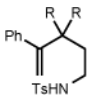
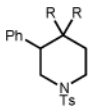
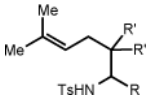
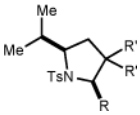
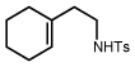
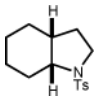
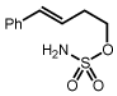
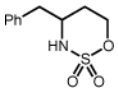
[b] Determined by ^{1}H NMR analysis.

[c] Isolated yield

Table 2

Scope of the Intramolecular Anti-Markovnikov Hydroamination Reactions of Unsaturated Amines[a]



Entry	Alkenol	Product	Time	Yield
				
1	**1a** Ar = C_6H_5, R, R′ = Me	**1b**	24h	82%
2	**2a** Ar = 4-(F)C_6H_4, R, R′ = Me	**2b**	24h	89%
3	**3a** Ar = 4-(MeO)C_6H_4, R, R′ = Me	**3b**	30h	88%
4	**4a** Ar = 2-(MeO)C_6H_4, R, R′ = Me	**4b**	40h	69%
5	**5a** Ar = 4-(MeO)C_6H_4, R, R′ = H	**5b**	48h	79%
6	**6a** Ar = 4-(MeO)C_6H_4, R = H, R′ = *i*-Pr	**6b**	39h	88%
				1.6:1 d.r.[b]
7	**7a** R = Me	**7b**	48h	79%
8	**8a** R = H	**8b**	96h	60%
				
9	**9a** R = H; R′ = Ph	**9b**	96h	70%
10	**10a** R = Me; R′ = H	**10b**	96h	56%
				3:1 d.r.[b]
11	**11a**	**11b**	96h	72%
				12:1 d.r.[b]
12	**12a**	**12b**	96h	54%

[a] All reactions irradiated with a 15W 450 nm LED flood lamp. Reported as isolated yields, average of two trials.

[b] Determined by ^{1}H NMR analysis of the crude reaction mixtures.