Photochemistry

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anti-Markovnikov Hydroamination of Alkenes Catalyzed by a Two-Component Organic Photoredox System: Direct Access to Phenethylamine Derivatives**

*Tien M. Nguyen, Namita Manohar, and David A. Nicewicz**

Abstract: *Disclosed herein is a general catalytic system for the intermolecular anti-Markovnikov hydroamination of alkenes. By using an organocatalytic photoredox system, α- and β-substituted styrenes as well as aliphatic alkenes undergo anti-Markovnikov hydroamination. Heterocyclic amines were also successfully employed as nitrogen nucleophiles, thus providing a direct route to heterocyclic motifs common in medicinal agents.*

Carbon–nitrogen bonds are ubiquitous in biologically active compounds and appear as numerous but distinct structural motifs.[1] A particularly prevalent class of nitrogen-containing bioactive compounds, phenethylamine derivatives, display wide-ranging medicinal properties from antidepressants to fungicides (Figure 1). One of the most direct means of accessing amine derivatives is the hydroamination reaction of alkenes.[2] The synthetic community has developed numerous methods for the hydroamination of olefins catalyzed by late transition metals, and they generally proceed with Markovnikov selectivity. In contrast, *anti*-Markovnikov-selective methods are less prevalent and often require either a large excess of alkene, strong bases, or precious transition-metal catalysts.[3–6] In addition, hydroboration-amination strategies provide access to formal *anti*-Markovnikov hydroamination products, but they are indirect.[7]

Our lab recently demonstrated the intramolecular *anti*-Markovnikov hydroamination of unsaturated amines employing the Fukuzumi acridinium photoredox catalyst and thiophenol as a hydrogen atom donor (Figure 1 a).[8a] We hoped to expand the general utility of this catalyst system to include intermolecular examples with the goal of accessing biologically relevant amines. Herein, we report the use of a mild two-component organic photoredox catalyst system which enables a direct *anti*-Markovnikov hydroamination of alkenes to access the important phenethylamine motif, and also allows use of nitrogen heteroaromatic nucleophiles (Figure 1 b).

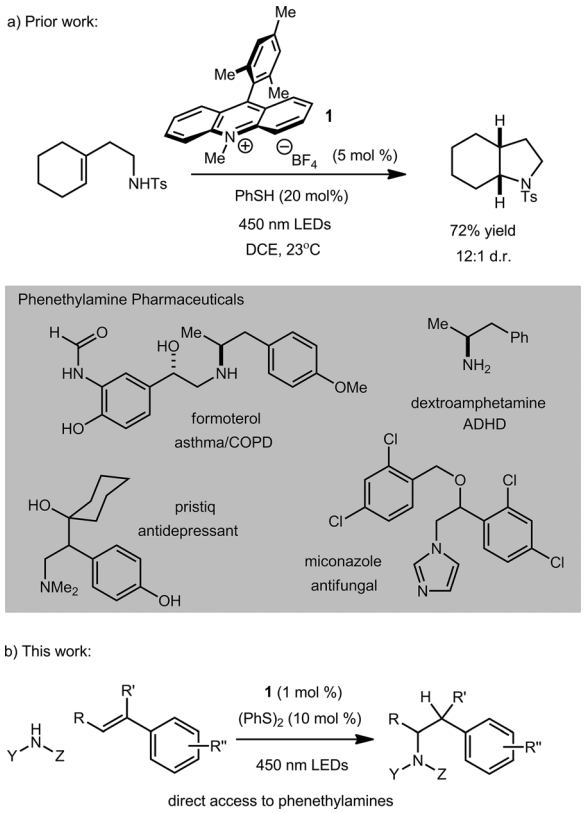

Figure 1. Photoredox strategy to access phenethylamines. DCE = 1,2-dichloroethane, Ts = 4-methylbenzenesulfonyl.

Beginning with our previously reported reaction conditions, we tested the intermolecular reaction between β-methylstyrene and amine nucleophiles (Table 1). By employing trifluoromethanesulfonamide ($TfNH_2$) as the nucleophile and thiophenol as the cocatalyst, we obtained a single regioisomer of *N*-triflylamphetamine in 87% yield (entry 1). To probe the electronic effects of the cocatalyst on the reaction, we surveyed both electron-rich (entry 2) as well as electron-deficient (entry 3) thiophenols. Neither offered an improvement over thiophenol, and 4-nitrothiophenol gave only moderate yields of the desired adduct (58%). In our previous communication,[8a] we observed that phenyl disulfide could be employed in place of thiophenol as the cocatalyst for alkene hydroamination. We found that by replacing 20 mol% thiophenol with 10 mol% phenyl disulfide, good yields could be maintained (entry 7). Diphenyl disulfide exists as an odorless solid and provides a practical advantage over thiophenol, which is a pungent and highly toxic liquid.

[*] T. M. Nguyen, N. Manohar, Prof. D. A. Nicewicz
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
E-mail: nicewicz@unc.edu
Homepage: http://www.chem.unc.edu/people/faculty/nicewicz/

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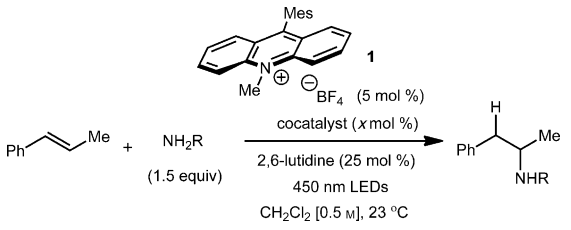
Table 1: Optimization of the *anti*-Markovnikov alkene hydroamination reaction.[a]



Entry	R	Cocatalyst	mol%	Yield [%][b]
1	Tf	thiophenol	20	87
2	Tf	2,6-dimethylthiophenol	20	80
3	Tf	4-nitrothiophenol	20	58
4	Tf	phenyl disulfide	20	78
5	Tf	–	0	<5
6	Tf	phenyl disulfide	5	35
7	Tf	phenyl disulfide	10	89
8	Tf	phenyl disulfide	100	40
9	Boc	phenyl disulfide	10	8
10	Ts	phenyl disulfide	10	<5
11	Ns	phenyl disulfide	10	<5

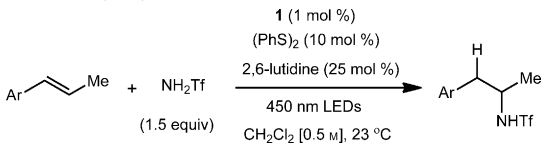
[a] All reactions irradiated with a 15 W 450 nm LED flood lamp and run on a 0.2 mmol scale. [b] Determined by ^{1}H NMR spectroscopy using $[(H_3C)_3Si]_2O$ as an internal standard. Boc = *tert*-butoxycarbonyl, Ns = 4-nitrobenzenesulfonyl, Tf = trifluoromethanesulfonyl.

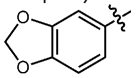
Importantly, no reaction was observed in the absence of a cocatalyst (entry 5). The inclusion of 25 mol% 2,6-lutidine resulted in slightly higher product yields and cleaner crude reaction mixtures. Attempts to use $BocNH_2$ in place of $TfNH_2$ were unfortunately unsuccessful (entry 9), as was the use of other sulfonamides (Ts, Ns; entries 10 and 11).

We then began exploring the scope of the reaction with various β-methyl-substituted styrenes as the alkene partner. Electron-rich methoxy-substituted styrenes gave the desired products in moderate to good yields (Table 2, entries 1–3). These substrates demonstrated the fastest times to completion, likely because of the ease of their oxidation. Slightly less-electron-rich methyl-substituted styrenes were obtained in uniformly good yields, with a variation in the substitution pattern having little effect (entries 4–6). Halogenated styrenes also provided the corresponding phenethylamine derivatives in good yields (entries 7–9). We obtained a lower yield for 4-*tert*-butyl-substituted styrene, and observed many oligomeric side products in the crude reaction mixture (entry 10). Styrenes with bulky arenes were also participants in the reaction, with 2,4,6-$Me_3C_6H_4$ undergoing hydroamination in good yield (entry 11). We were able to extend the reaction to include bicyclic styrenes, such as naphthalene and isosafrole, which gave the desired product in modest yields (entries 12 and 13). Heteroaromatic substitution was also tolerated, as demonstrated by the thiophene-substituted product, albeit in low yield and with a long reaction time (entry 14). All substrates gave complete *anti*-Markovnikov regioselectivity.

We then turned our attention to styrenyl substrates bearing different functional groups at the β-position (Figure 2). We were pleased to find that the reaction proceeded in good yields with esters, alcohols, and phthalimide-protected amines as substituents on the styrenes

Table 2: Scope of the intermolecular *anti*-Markovnikov hydroamination reactions with styrenyl substrates.[a]



Entry	Ar	*t* [h]	Yield [%][b]
1	2-$MeOC_6H_4$	48	55
2	3-$MeOC_6H_4$	48	69
3	4-$MeOC_6H_4$	48	73
4	2-MeC_6H_4	72	76
5	3-MeC_6H_4	72	73
6	4-MeC_6H_4	72	84
7	Ph	72	72
8	4-FC_6H_4	96	77
9	4-ClC_6H_4	72	75
10	4-*t*BuC_6H_4	72	43
11	2,4,6-$Me_3C_6H_2$	72	64
12	2-naphthyl	72	63
13		96	57
14		144	35

[a] All reactions irradiated with a 15 W 450 nm LED flood lamp. [b] Yield of isolated product (average of two trials).

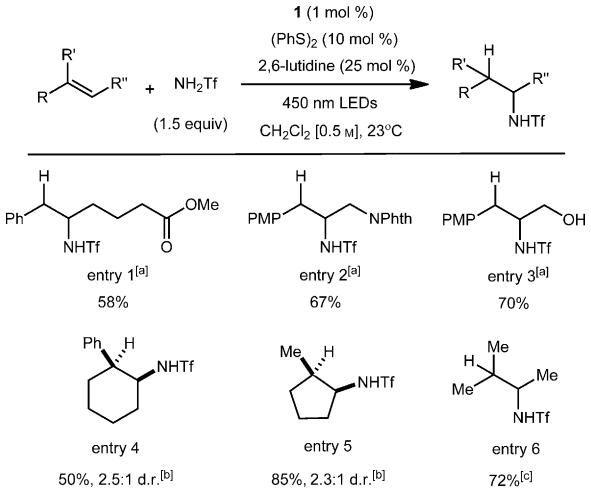
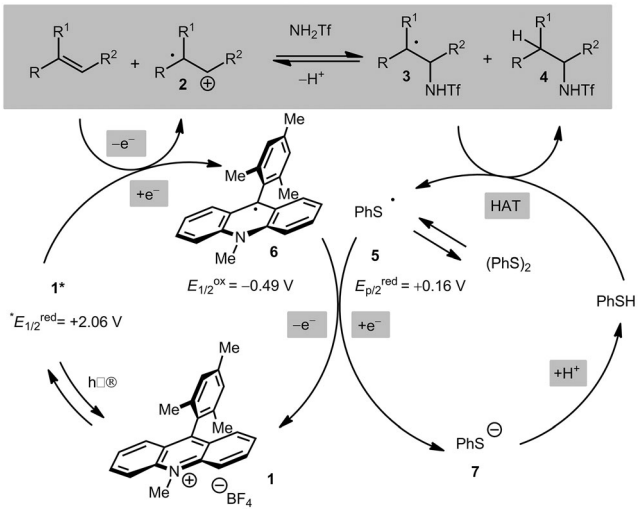


Figure 2. Scope of the intermolecular *anti*-Markovnikov hydroamination reactions with alkenes. All reactions irradiated with a 15 W 450 nm LED flood lamp. All yields are those of the isolated products (average of two trials). [a] *E*-configured styrenes employed in reaction. [b] Diastereoselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Used 3.0 equiv alkene. PMP = 4-$MeOC_6H_4$, Tf = trifluoromethanesulfonyl.

(entries 1–3). In particular, the use of allylic amines and alcohols provided 1,2-diamine and amino alcohol products, respectively (entries 2 and 3). The result in entry 3 should be underscored, as it is the only example, to our knowledge, of an alkene bearing a free alcohol undergoing a hydroamination reaction. Perhaps most impressively, trisubstituted aliphatic cyclic alkenes underwent hydroamination with complete

regioselectivity, despite having oxidation potentials in the vicinity of +2.0 V vs. SCE (entries 5 and 6). As a result of its volatility, 3.0 equivalents of 2-methyl-2-butene were employed in the reaction.

In accord with our previous work in this area, we propose that the mechanism of this transformation begins with excitation of the mesityl acridinium catalyst **1** by $\lambda = 450$ nm light, with subsequent single-electron oxidation of the alkene by **1*** (Scheme 1). Reversible addition of triflylamide to the



Scheme 1. Proposed mechanism for the intermolecular *anti*-Markovnikov alkene hydroamination reaction. HAT = hydrogen-atom transfer.

less-substituted position of **2** results in the formation of tertiary radical **3**, which reacts with a hydrogen-atom donor, presumably thiophenol, to furnish the final adduct **4**. How thiophenol is generated is less clear. One potential mechanism involves homolysis of the S–S bond, either directly by light, or by energy transfer from **1***, thus giving rise to the thiyl radical **5**. This oxidizing radical could reset the acridinium catalyst by oxidation of the long-lived acridine radical **6**. This process seems feasible given the thiyl radical/thiophenoxide redox couple ($E_{p/2} = +0.16$ V vs. SCE)[9] and the acridinium redox potential ($E_{1/2}^{ox} = -0.49$ V vs. SCE),[10] thus ensuring that the redox event would be exergonic by nearly 15 kcal mol^{-1}. Subsequent protonation generates the putative hydrogen-atom-transfer reagent, thiophenol. In previous control experiments, if thiophenol was employed as the cocatalyst, varying quantities of phenyl disulfide were observed in the crude reaction mixture, thus implicating the disulfide/thiophenol equilibrium.

Finally, we were able to employ heterocyclic amines as nucleophiles in this setting, thus providing access to potentially valuable nitrogen heterocycles (Figure 3).[11] We observed good reactivity between methoxy-substituted styrenes and pyrazole, indazole, and 1,2,3-triazole. Indazole gave a single N2 regioisomeric product, congruent with prior observations of indazole alkylation selectivity under nonbasic conditions (entry 2).[12] The addition of poorly soluble imidazole gave a slightly lower yield and attempts to improve its

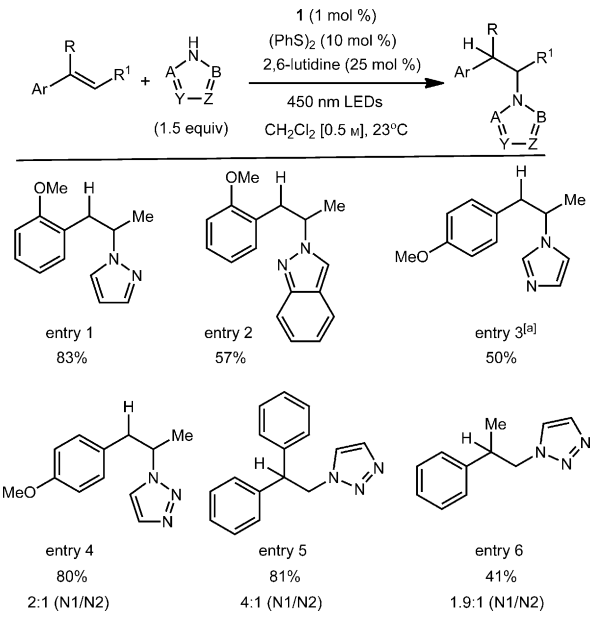


Figure 3. Scope of the intermolecular *anti*-Markovnikov hydroamination reactions with heterocyclic amines. All reactions irradiated with a 15 W 450 nm LED flood lamp. All yields are those of the isolated products (average of two trials). Values within parentheses indicate the ratio of N1 substitution to N2 substitution. [a] Used 3.0 equiv imidazole.

solubility with various solvent combinations were unsuccessful (50% yield; entry 3). 1,1-Disubstituted styrenes did not react productively with triflylamide but were reactive toward 1,2,3-triazole (entries 5 and 6). For 1,2,3-triazole, substitution at N1 was led to the major regioisomer as expected, because of the statistical advantage and increased electron density of N1/N3 over N2.[13] This reaction class should be of potential interest to the biomedical community as tool for lead-drug candidate discovery.

In conclusion, we have demonstrated an *anti*-Markovnikov intermolecular hydroamination reaction of alkenes and amines employing a novel organic photoredox catalyst system. The broad reaction scope extends to trisubstituted aliphatic alkenes and α- and β-substituted styrenes with a variety of functional groups such as halides, esters, alcohols, and protected amines. The amine coupling partner can be triflamide or heterocyclic amines. Though extended reaction times are required, this method expands the limited arena of *anti*-Markovnikov hydroamination for the direct addition of sulfonamides to alkenes. We are actively probing the mechanism of this and associated transformations as to the exact nature of the redox cycle and involvement of phenyl disulfide in the reaction mechanism.

Experimental Section

A magnetic stir bar, *N*-Me-mesityl acridinium catalyst (**1**, 1.0 mol%), phenyldisulfide (10 mol%), and the amine (1.5 equiv) were added to a flame-dried 2 dram vial. The reaction vessel was purged with nitrogen, then 2,6-lutidine (25 mol%), the alkene (1.0 equiv), and dichloromethane (sparged for 15 min, [0.5 M]) were added. The vial

was sealed with Teflon tape and irradiated with a blue LED lamp ($\lambda =$ 450 nm) at room temperature. Reactions were quenched with a solution of TEMPO (ca. 5 mg) in dichloromethane (0.2 mL) and concentrated in vacuo. The final products were purified by silica gel chromatography using the conditions given in the Supporting Information.

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