

Catalytic Olefin Hydroamination with Aminium Radical Cations: A Photoredox Method for Direct C–N Bond Formation

Andrew J. Musacchio, Lucas Q. Nguyen, G. Hudson Beard, and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

S Supporting Information

ABSTRACT: While olefin amination with aminium radical cations is a classical method for C–N bond formation, catalytic variants that utilize simple 2° amine precursors remain largely undeveloped. Herein we report a new visible-light photoredox protocol for the intramolecular anti-Markovnikov hydroamination of aryl olefins that proceeds through catalytically generated aminium radical intermediates. Mechanistic studies are consistent with a process involving amine oxidation via electron transfer, turnover-limiting C–N bond formation, and a second electron transfer step to reduce a carbon-centered radical, rendering the overall process redox-neutral. A range of structurally diverse *N*-aryl heterocycles can be prepared in good to excellent yields under conditions significantly milder than those required by conventional aminium-based protocols.

The addition of aminium radical cations to olefins is an attractive method for C–N bond formation, exhibiting both low activation barriers and reliable anti-Markovnikov regioselectivity.¹ In recent years, aminium formation via amine oxidation has been incorporated as an elementary step in numerous visible-light photoredox processes.² However, in most examples these intermediates are transient, being further converted to α -amino radicals or iminium ions that participate in bond-forming reactions at carbon.³ Photocatalytic methods that engage aminium radicals directly to enable C–N bond formation are rare, with the only example reported to date being a notable oxidative indole synthesis reported by Maity and Zheng.⁴ We questioned whether these electrophilic nitrogen-centered radicals might be utilized more generally to enable the development of a broadly useful set of olefin functionalization protocols. Toward this end, we report here a catalytic method for the hydroamination of styrenes that proceeds through aminium radical intermediates. The development, scope, and mechanistic evaluation of this new process are presented below.

Reaction design and optimization. Our reaction design was grounded in the classical mechanism of aminium-based olefin aminations (Figure 1) and related Hofmann–Löffler–Freitag reactions.¹ In these methods, the amine starting materials are first stoichiometrically converted to their *N*-halogenated or *N*-nitrosylated analogues and then subjected to ultraviolet photolysis in the presence of a strong Brønsted acid. Mechanistically, the amine precursor undergoes photomediated N–X homolysis and subsequent N-protonation to furnish the

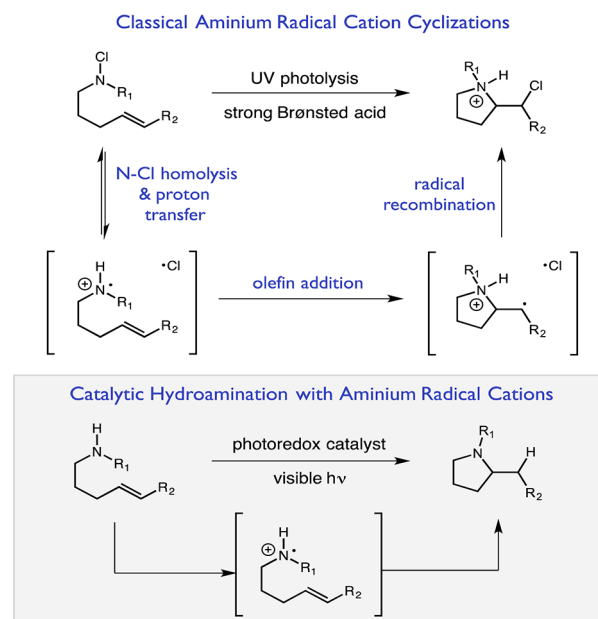


Figure 1. Classical olefin functionalizations with aminium radical cations as the basis for a new catalytic protocol.

requisite aminium intermediate. Addition to a pendant olefin occurs readily, and the resulting carbon-centered radical recombines with X· to yield a 1,2-amino-functionalized product. While powerful, both the forcing reaction conditions and the requirement of substrate prefunctionalization have significantly limited the applications of these protocols in synthesis.

We reasoned that the salient bond-forming aspects of this process could be retained in the absence of such restrictions and utilized in the development of a catalytic photoredox hydroamination protocol that operates through sequential single electron transfer steps (Figure 1).^{5,6} Specifically, an identical aminium ion could be generated via one-electron oxidation of a simple 2° amine precursor such as **1** by the excited state of an appropriate redox catalyst (Figure 2). In turn, this intermediate should be competent to undergo olefin addition, resulting in C–N bond formation and the generation of an adjacent carbon-centered radical. If the reduced form of the redox catalyst can function as an electron donor to convert this carbon-centered radical to its corresponding carbanion, a favorable proton transfer reaction would transform the resulting

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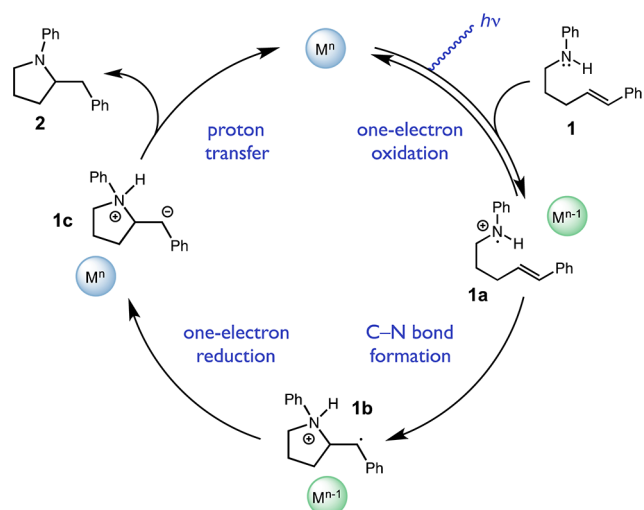


Figure 2. Proposed catalytic cycle for hydroamination.

zwitterion to the desired hydroamination product and close the catalytic cycle. Such a hydroamination process would be mechanistically complementary to both the catalytic photoredox system recently described by Nicewicz that operates through olefin oxidation and classical singlet exciplex mechanisms pioneered by Lewis.⁷

To enable such an approach, an effective catalyst must possess a range of redox potentials broad enough to mediate both of the proposed electron transfer events. For a model substrate such as **1**, aryl amine oxidation occurs at potentials near +0.4 V vs Fc in MeCN, while reduction of a typical benzylic radical by electron transfer requires potentials near -1.8 V vs Fc in MeCN.⁸ In considering these values, we initially elected to investigate the catalytic viability of Ru(bpy)₃Cl₂ (**3**) in mediating the conversion of **1** to **2**. The metal-to-ligand charge transfer excited state of this archetypal Ru(II) complex has a reduction potential of +0.39 V vs Fc in MeCN, while the resulting Ru(I) state has a potential of -1.71 V vs Fc in MeCN; these are comparable to the relevant potentials of **1**.⁹ Indeed, initial experiments demonstrated that exposing a solution of **1** and 2 mol % **3** in MeCN to visible-light excitation from a 26 W compact fluorescent lamp provided a 4% yield of the desired product **2** after 12 h at room temperature (rt) (Table 1, entry 1). Further solvent evaluation was largely unsuccessful, though a markedly improved yield of 43% was obtained in methanol (Table 1, entries 2–5).

In these reactions, small amounts of material resulting from C–C homocoupling of the cyclized benzylic radical intermediate **1b** (Figure 2) were also observed. While consistent with the proposed mechanism, these oxidative dimerization adducts are also indicative of an irreversible catalyst deactivation pathway wherein the Ru catalyst is sequestered in its reduced state and unable to re-enter the catalytic cycle. This observation suggested to us that the second electron transfer between the reduced Ru(I) state of the photocatalyst and the benzylic radical was not sufficiently rapid to outcompete this undesired dimerization pathway. Accordingly, we reasoned that this limitation might be overcome through the use of a more reducing photocatalyst, such as Ir(ppy)₂(dtbbpy)PF₆ (**4**). This Ir complex is slightly less oxidizing than **3** in its excited state ($E^* = +0.28$ V vs Fc), but its reduced Ir(II) state ($E = -1.89$ V vs Fc) is nearly 200 mV more reducing than the analogous Ru(I) complex.¹⁰

Table 1. Optimization Studies

entry	catalyst	solvent	yield of 2 (%)
1	Ru(bpy) ₃ Cl ₂	MeCN	4
2	Ru(bpy) ₃ Cl ₂	DMSO	3
3	Ru(bpy) ₃ Cl ₂	DMF	1
4	Ru(bpy) ₃ Cl ₂	acetone	1
5	Ru(bpy) ₃ Cl ₂	MeOH	43
6	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	69
7	Ir(ppy) ₂ (dtbbpy)PF ₆	DMSO	66
8	Ir(ppy) ₂ (dtbbpy)PF ₆	DMF	38
9	Ir(ppy) ₂ (dtbbpy)PF ₆	acetone	78
10	Ir(ppy) ₂ (dtbbpy)PF ₆	MeOH	88

Optimization reactions were performed on a 0.05 mmol scale. Yields were determined by GC analysis of the crude reaction mixture relative to an internal standard. Irradiation was provided by 26 W fluorescent lamps.

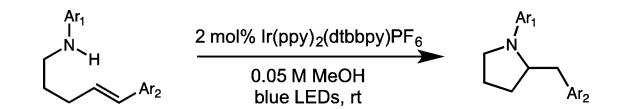
Gratifyingly, the use of catalyst **4** provided a significant improvement in reaction efficiency across all of the solvents evaluated (Table 1, entries 6–9). Methanol was again identified as the optimal reaction solvent, providing pyrrolidine **2** in 88% yield in 12 h at rt (Table 1, entry 10). Further optimization revealed that the use of blue LEDs in place of fluorescent lamps resulted in shorter reaction times, particularly for reactions run on preparative scales.

Substrate scope. With these optimized reaction conditions, we next examined the scope of this hydroamination method. First, a variety of substituted aniline substrates were investigated. On a 0.5 mmol scale, model compound **1** cyclized to give **2** in 85% isolated yield after 10 h at rt (Table 2, entry 1).¹¹ Ortho, meta, and para substituents on the aniline ring were all well-tolerated (Table 2, entries 2–4). Similarly, various halogenated and biaryl anilines were found to provide the desired adducts in good yields (Table 2, entries 5–7). Notably, a *p*-methoxyphenyl-substituted pyrrolidine product, which can be deprotected to give the free secondary amine, could also be accessed using this method (Table 2, entry 8).

We next explored the scope of the styrenyl acceptor. With catalyst **4**, a variety of electron-rich styrenes performed well despite the more negative potentials ostensibly required for benzylic radical reduction (Table 2, entries 9 and 10). A sterically hindered mesityl acceptor also cyclized in good yield but required 24 h to reach full conversion (Table 2, entry 11). A range of increasingly electrophilic styrenes were well-tolerated, resulting in high-yielding cyclizations (Table 2, entries 12–14). Ortho-, meta-, and para-halogenated styrenes could all be successfully utilized, providing useful handles for further product functionalization (Table 2, entries 15–17).

Heterocyclic olefin acceptors were effective, as pyridine-, furan-, and thiophene-containing substrates could all be cyclized without difficulty (**21**–**23**; Table 3). Similarly, cyclization reactions to form piperidine **24**, morpholine **25**, and piperazine **26** were also found to be successful, though with somewhat diminished yields. Fused bicyclic systems were readily synthesized, as demonstrated by the formation of products **27** and **28**. Lastly, various regioisomeric alkyl-substituted pyrrolidine and piperidine products could be obtained in high yields, although with low to modest levels

Table 2. Substrate Scope



entry	Ar ₁	Ar ₂	product	yield (%)
1	C ₆ H ₅	C ₆ H ₅	2	85
2	2-(Me)C ₆ H ₄	C ₆ H ₅	5	77
3	3-(Me)C ₆ H ₄	C ₆ H ₅	6	95
4	4-(Me)C ₆ H ₄	C ₆ H ₅	7	86
5	4-(F)C ₆ H ₄	C ₆ H ₅	8	91
6	2-(Cl)C ₆ H ₄	C ₆ H ₅	9	91
7	4-(Ph)C ₆ H ₄	C ₆ H ₅	10	73
8	4-(MeO)C ₆ H ₄	C ₆ H ₅	11	54
9	C ₆ H ₅	4-(MeO)C ₆ H ₄	12	88
10	C ₆ H ₅	4-(tBu)C ₆ H ₄	13	94
11	C ₆ H ₅	2,4,6-(Me) ₃ C ₆ H ₂	14	63
12	C ₆ H ₅	4-(F)C ₆ H ₄	15	93
13	C ₆ H ₅	4-(CF ₃)C ₆ H ₄	16	77
14	C ₆ H ₅	4-(CN)C ₆ H ₄	17	73
15	C ₆ H ₅	2-(Cl)C ₆ H ₄	18	91
16	C ₆ H ₅	3-(Br)C ₆ H ₄	19	83
17	C ₆ H ₅	4-(Br)C ₆ H ₄	20	83

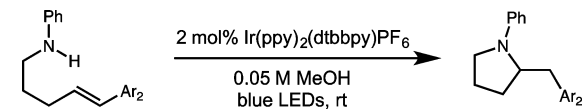
Reactions were performed on a 0.5 mmol scale. Yields are for isolated materials following chromatography.

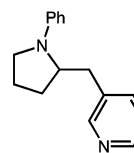
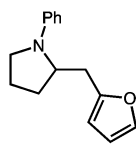
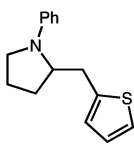
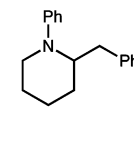
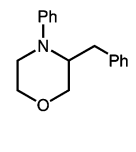
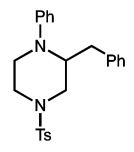
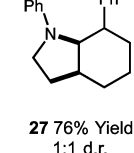
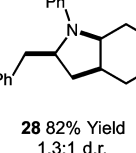
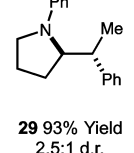
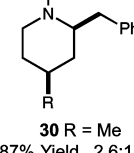
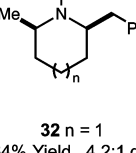
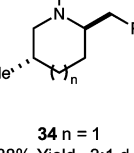
of diastereoselectivity (29–35; Table 3). Intermolecular couplings were found to be unsuccessful under the standard reaction conditions, likely because of the inability of bimolecular C–N bond formation to outcompete favorable electron back-transfer from the Ir(II) complex to the aminium ion intermediate.

Mechanistic studies. Having outlined the scope of this hydroamination process, we next focused on evaluating specific aspects of the proposed reaction mechanism. First, luminescence quenching assays demonstrated that the electron transfer between the excited state of Ir(ppy)₂(dtbbpy)PF₆ ($E^* = +0.28$ V vs Fc in MeCN) and aniline **1** ($E \approx +0.4$ V vs Fc in MeCN)^{8a} that furnishes the key aminium intermediate is kinetically facile ($k\tau = 1200$ M⁻¹). As all subsequent steps in the proposed catalytic cycle involve changes in bonding or oxidation state at the benzylic position of the styrenyl acceptor, we reasoned that a Hammett analysis might shed light on the identity of the turnover-limiting step. In accord with literature precedent, we expected that rate-limiting addition of the electrophilic aminium radical to the π -nucleophilic olefin should result in a negative ρ value.¹² In contrast, the rates of electron transfer leading to benzylic anion formation would be expected to trend with the potentials of the radical intermediates, resulting in a positive Hammett slope. A comparison of hydroamination rates for a series of para-substituted styrene acceptors revealed a linear correlation with σ_p ($R^2 = 0.96$) and a modestly negative ρ value of -0.56 , consistent with turnover-limiting C–N bond formation (see the Supporting Information). Notably, as neutral aminyl radicals exhibit positive ρ correlations in their addition reactions to para-substituted styrenes, this result also provides strong support for the involvement of a protonated aminium radical cation in the addition step.^{13–15}

Notably, the interpretation of the Hammett analysis presented above is valid only if the initial excited-state electron transfer step is reversible relative to C–N bond formation.¹⁶ To substantiate this assumption, we carried out a competition

Table 3. Substrate Scope



		
21 86% Yield	22 76% Yield	23 61% Yield
		
24 66% Yield	25 44% Yield	26 58% Yield ^a
		
27 76% Yield 1:1 d.r.	28 82% Yield 1.3:1 d.r.	29 93% Yield 2.5:1 d.r.
		
30 R = Me 87% Yield, 2.6:1 d.r.	32 n = 1 64% Yield, 4.2:1 d.r.	34 n = 1 88% Yield, 3:1 d.r.
31 R = <i>i</i> Pr 87% Yield, 3.2:1 d.r.	33 n = 0 88% Yield, 1:1 d.r.	35 n = 0 89% Yield, 2:1 d.r. ^b

Reactions were performed on a 0.5 mmol scale. Yields are for isolated materials following chromatography. Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixtures. ^aThe reaction was run in acetone. ^bThe cis isomer was the major product.

experiment wherein equal concentrations of **1** and a *p*-CN-substituted styrene (Table 2, entry 14) were placed in the same flask and subjected to the standard hydroamination conditions. Significantly, the ratio of observed rate constants in the competition experiments ($k_H/k_{CN} = 4$) differs measurably from the ratio obtained from independent reactions of each substrate ($k_H/k_{CN} = 2.6$). This outcome is not consistent with irreversible amine oxidation, for which an identical ratio would be expected. As a corollary to this understanding, the observed rate constant and quantum yield for each substrate should be directly proportional.

Lastly, though it occurs after the rate-limiting step, additional support for the proposed electron transfer/proton transfer mechanism for radical reduction was obtained through solvent-labeling studies. Specifically, we observed that cyclization products from reactions performed in CD₃OH exhibited no deuterium incorporation at the benzylic position, while reactions carried out in CH₃OD were fully deuterium-labeled.¹⁷ These observations argue against a solvent-mediated hydrogen atom transfer mechanism for radical reduction^{18,19} but are consistent with proton transfer to a transient carbanion acceptor.

In conclusion, we have developed a novel photoredox protocol for intramolecular olefin hydroamination that operates through sequential catalyst-mediated electron transfer steps spanning a range of potentials of over 2.2 V. This work represents a rare example of the use of aminium radical cations derived from simple amine precursors in catalytic C–N bond formation. Efforts are currently underway to apply the elements of reaction design presented here to other catalytic olefin amino-functionalization processes.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures, characterization data, and kinetic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

rknowles@princeton.edu

Notes

The authors declare no competing financial interest.

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- (14) Consistent with this view, proton transfer from an N–H bond in the aminium ion ($pK_a \approx 17$ in MeCN) or an adjacent methylene C–H bond ($pK_a \approx 18$ in MeCN) to the starting material ($pK_a \approx 11$ in MeCN for *N*-methylanilinium ion) is significantly endergonic.
- (15) A negative ρ value might also result from protonation of increasingly basic carbanion intermediates. However, cyclization rates of **1** evaluated in either CH₃OH or CD₃OD resulted in a k_H/k_D of 1.1, indicative that C–H bond formation is not rate-limiting.
- (16) Back electron transfer from the reduced Ir(II) complex to the aminium radical is exergonic by ~ 2.3 V.
- (17) For reactions run in CH₃OD, the deuterium-bearing stereocenter was formed as a 1:1 mixture of diastereomers.
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- (19) Consistent with this view, hydrogen atom transfer to the benzylic radicals from the C–H bonds in MeOH is endergonic by ~ 7 kcal/mol.