Bifunctional *N*-Aminopyridinium Reagents Enable C–H Amination, Olefin Carboamination Cascades

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Abstract C–H amination reactions provide streamlined access to nitrogen-containing small molecules. Here, we disclose benzylic C–H amination with *N*-aminopyridiniums, which are bifunctional reagents that provide avenues for further diversification. Reductive activation of the incipient N–N bonds unveils electrophilic *N*-centered radicals, which can be engaged by nucleophilic partners such as olefins, silyl enol ethers, and electron-rich heterocycles. We highlight the synthetic potential of these sequences in the synthesis of tetrahydroisoquinolines, which are important heterocycles in molecular therapeutics, via anti-Markovnikov olefin carboamination. Unlike many C–H amination reactions that provide access to protected amines, the current method installs an easily diversifiable synthetic handle that serves as a lynchpin for C–H amination, deaminative N–N functionalization sequences.

The presence of amines and other nitrogen-based functional groups can profoundly impact the chemical and biological properties of organic small molecules and thus C–N bonds are ubiquitous in pharmacologically active organic scaffolds.[1] In both biology and synthetic chemistry, installation of C–N bonds typically requires substrate pre-oxidation, which inherently limits the efficiency and versatility of synthetic approaches to these important molecules.[2] Direct C–H amination reactions based on electrophilic, subvalent nitrogen fragments, such as nitrenes or nitrogen-centered radicals (or transition metal-stabilized analogues of these species), have been

developed to streamline access to nitrogen-containing small molecules that span the organic chemical value chain (Figure 1a).[3,4] In practice, the aminating reagents employed in C–H amination often require *N*-activating groups (*i.e.*, sulfonamides, amides, or hydrazine derivatives) for efficient C–N bond construction.[5,6] Subsequent removal of these activating groups can provide access to the corresponding amines.

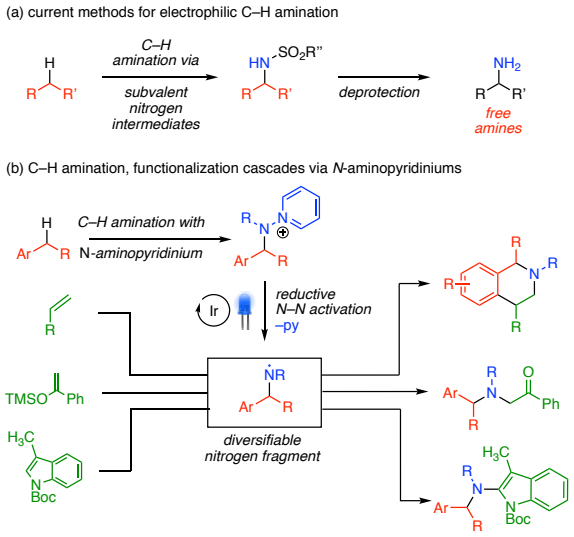


Figure 1. (a) Direct C–H amination via nitrene transfer or radical-mediated processes typically requires activation of the amine fragment with electron withdrawing substituents, which can be removed to ultimately generate free amines. (b) Here, we demonstrate C–H amination with *N*-aminopyridinium which provides the opportunity to diversify the products of C–H amination via amidyl radicals generated by reductive N–N cleavage.

Bifunctional reagents contain two distinct reactive moieties and provide the opportunity to achieve sequential functionalization reactions under orthogonal activation modes.[7] We were attracted to the possibility of achieving C–H amination with a bifunctional aminating reagent, which would provide direct access to nitrogenous products poised for synthetic diversification (Figure 1b). In this context, *N*-aminopyridiniums, which feature a nucleophilic *N*-amino group and can serve as radical precursors via reductive (photo)activation of the N–N bond, were identified as attractive reagents for C–H amination.[8] In the context of amination chemistry, *N*-sulfonylpyridines have been utilized in photoredox-promoted olefin difunctionalization[9] and

aromatic C–H amination reactions.[10,11] Broad application of *N*-aminopyridiniums as bifunctional reagents in amination chemistry is stymied by the limited methods currently available to prepare *N*-functionalized aminopyridiniums, which are accessed by either addition of hydrazines to pyrrilium salts or by sulfonylation of *N*-aminopyridiniums.[12] Here, we describe benzylic C–H amination using *N*-aminopyridium triflate to provide access to *N*-benzylaminopyridiniums. Reductive N–N bond activation enables derivatization via amidyl radical intermediates. We highlight the amination/derivatization sequence in the synthesis of tetrahydroisoquinolines, an important heterocycle in medicinal chemistry, which can be challenging to prepare by existing methods.[13] This protocol enables conversion of benzylic C–H bonds to an array of nitrogen-containing products and significantly expands the utility of *N*-aminopyridiniums as lynchpins of molecular synthesis.

We initiated the development of C–H amination with bifunctional aminating reagents by examining the amination of ethylbenzene (**1a**) with *N*-aminopyridinium triflate. Two sets of reaction conditions—one based on DDQ-promoted benzylic amidation reported by Venkateswarlu *et al.*[14] and the other based on NIS-promoted photochemical amination reported by Li *et al.*[15]—have been identified to provide efficient access to benzylic amination products (Figure 2; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, NIS = *N*-iodosuccinimide). Thermolysis of a CH_2Cl_2 solution of **1a** and *N*-aminopyridinium triflate in the presence of DDQ in a sealed tube afforded *N*-benzylaminopyridinium **2a** in 72% yield. Alternately, photolysis of a CH_2Cl_2 solution of **1a** and *N*-aminopyridinium triflate in the presence of NIS afforded **2a** in 65% yield.

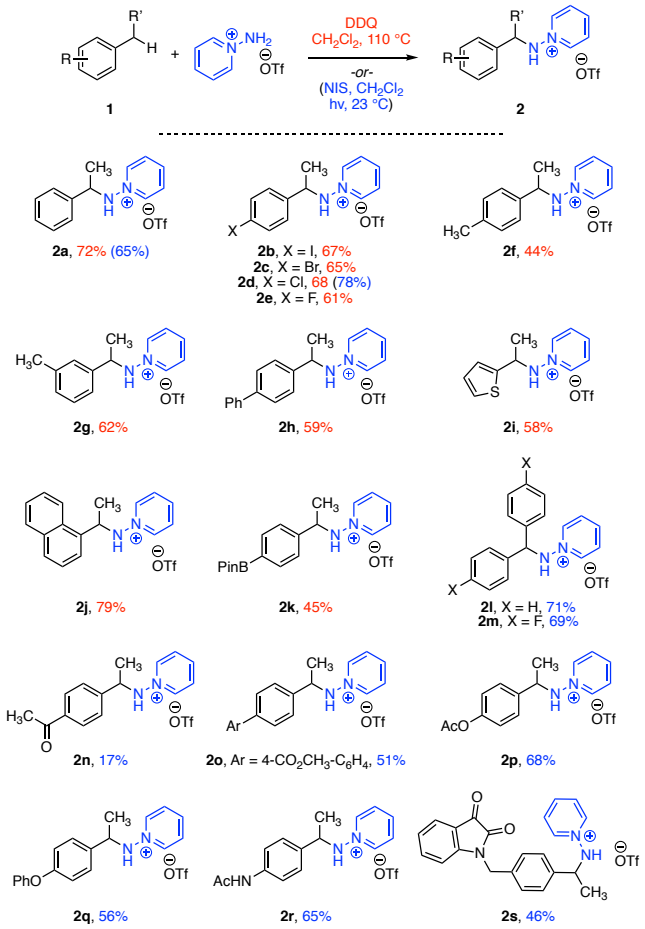
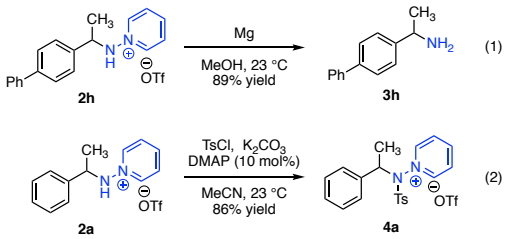


Figure 2. Benzylic C–H amination with *N*-aminopyridinium triflate affords *N*-benzylaminopyridiniums **2**. Conditions: **1** (1.3 equiv), *N*-aminopyridinium triflate (1.0 equiv), DDQ (2.3 equiv), CH_2Cl_2, 110 °C, 40 h; **1** (1.3 equiv), *N*-aminopyridinium triflate (1.0 equiv), NIS (2.2 equiv), CH_2Cl_2, 23 °C, 30 h, blue LEDs.

The two sets of C–H amination conditions display complementary substrate preferences (Figure 2). DDQ-promoted benzylic amination provided access to halogenated *N*-benzylaminopyridiniums (**2b**-**2e**) in 61-68% yield; in the case of the amination of 4-chloroethylbenzene (**1d**), the NIS-promoted condition proved superior and afforded **2d** in 78% yield (Table S1). Electron-rich substrates, such as 4-methylethylbenzene (**1f**), 3-methylethylbenzene (**1g**), 4-ethyl-1,1'-biphenyl (**1h**), and 2-ethylthiophene (**1i**) afford the corresponding *N*-benzylaminopyridinium **2f**-**2i** in moderate yields (44, 62, 59, and 58%, respectively). *Ortho*-substitution is tolerated as 1-ethylnaphthalene (**1j**) provided the

corresponding aminated product **2j** in 79% yield. Finally, the DDQ-promoted condition tolerates a boronic ester substituent (**2k**), which can be utilized as an additional handle for substrate functionalization via cross-coupling reactions. While the DDQ-promoted benzylic C–H amination method can be accomplished for gram-scale synthesis without any loss in the yield, it was inefficient to provide access to aminated products when applied to 1,1-diphenylmethane derivatives (**1l-1m**), and substrates with strongly electron withdrawing substituents (**1n-1o)**. In comparison, the NIS-promoted conditions afforded the *N*-benzylaminopyridinium derivatives of these substrates in greater efficiency. 1,1-Diphenylmethane derivatives (**2l** and **2m**) were accessed in 71%, and 69% yields, respectively. The electron-deficient substrates were also better tolerated under NIS promoted conditions to afford 17-51% yield of the corresponding aminated products (**2n-2o**). Reaction with acyl and phenyl protected phenols (**1p** and **1q**) under these conditions provided corresponding aminated products **2p** and **2q** in 68% and 56% yields, respectively. Similarly, protected amines, such as *N*-(4-ethylphenyl)acetamide (**1r**), afforded **2r** in 65% yield under the NIS-promoted conditions. In the context of more complex molecular settings, amination of isatin analogue **1s** proceed in 46% yield.

The products of benzylic C–H amination can be readily reduced to afford primary amines or derivatized for subsequent functionalization (Eqns. 1 and 2). Treatment of *N*-benzylaminopyridinium **2h** with Mg in MeOH result in reductive N–N cleavage to afford benzylamine, **3h**, in 89% yield.[16] Similarly, treatment of *N*-benzylaminopyridiniums with TsCl, 4-dimethylaminopyridine (DMAP, 10 mol%), and K_2CO_3 resulted in the sulfonylation of the N–H valence of **2a** to afford sulfonamide **4a** in 86% yield. These derivitizations can also be accomplished without purification of the intermediate *N*-benzylaminopyridinium **2** (see Supporting Information Section B.4).



Access to a large family of *N*-benzylaminopyridiniums provided the opportunity to investigate the reductive derivatization of the N–N bond as a strategy to rapidly build molecular complexity. In particular, we sought to generate electrophilic *N*-centered radical intermediates to engage with potential nucleophilic partners, such as olefins. To this end, photolysis (λ = 463 nm) of sulfonamide **4a** with $[Ir(ppy)_2(dtbbpy)][PF_6]$ (**6**, 1 mol%) in the presence of styrene resulted in the formation of tetrahydroisoquinoline **5a**, the product of anti-Markovnikov carboamination, as a 1.4:1 mixture of *cis*:*trans* diastereomers (71% yield). Similar attempts to promote the reductive activation of the N–N bond in **2a** were unsuccessful, presumably due to the relative instability of the incipient *N*-centered radical without resonance stabilization of the sulfonyl group (*vide infra*). Control reactions in the absence of light and/or photocatalyst did not yield any deaminative product. For details of the carboamination optimization, including the impact of solvent, photocatalyst, reaction stoichiometry, and reaction temperature, see the Supporting Information (Tables S2–S5).

The developed olefin carboamination reaction tolerates differently substituted halostyrenes to afford the corresponding tetrahydroisoquinolines (**7b**-**7e**) as diastereomeric mixtures in 68-78% yield. The relative stereochemistry of the tetrahydroisoquinoline products was assigned based on single-crystal X-ray diffraction analysis of chlorinated tetrahydroisoquinoline **7c** (for crystallographic details, see Figures S1-S2 and Tables S6-S7 in the Supporting Information). Electron-donating substituents such as 4- and 3-methylstyrenes (**5f** and **5g**) afforded tetrahydroisoquinolines **7f** and **7g** with *trans*- and *cis*-diastereomers being major products,

respectively. Deaminative carboamination of 4-acetoxystyrene (**5h**) provided tetrahydroisoquinoline **7h** in 76% yield with the trans diastereomer being major product. Tetrahydroisoquinolines **7i-7l**, derived from electron-deficient styrenes, were accessed in 47-61% yield with *cis* diastereoselectivity. Reaction with weakly withdrawing 4-phenyl substituted styrene **5m** afforded tetrahydroisoquinoline **7m** in 48% yield with a mixture of 1:2.2 *cis: trans* diastereoisomers. Deaminative carboamination of 4-(chloromethyl)styrene (**5n**) yielded **7n** in 76% yield with *cis* isomer as the major product. It should be noted that no significant side-reaction via hydrogen atom abstraction (HAA) at the benzylic position of **5n** was observed. Bulky olefinic substrate such as 2-vinylnaphthalene **5o** yielded **7o** in 53% yield with *trans* isomer as the major component. The reaction is also tolerant to substitution on the *N*-benzylaminopyridinium coupling partners. For example, coupling of **4j**, the *N*-benzylaminopyridinium derived from 1-ethylnaphthalene, with 4-fluorostyrene (**5b**) yielded the corresponding benzo-fused tetrahydroisoquinoline **7p** in 51% yield with a mixture of 1:1.5 *cis: trans* diastereomers. Introduction of 3-methyl substituted aminopyridinium (**4g**), with two non-equivalent *ortho* positions, to the deaminative functionalization reaction with 4-fluorostyrene (**5b**) led to a mixture of regioisomers in 69% yield. The *cis* diastereomer **7r** generated from cyclization at the sterically less hindered *ortho* position of **4g** was found to be the major component.

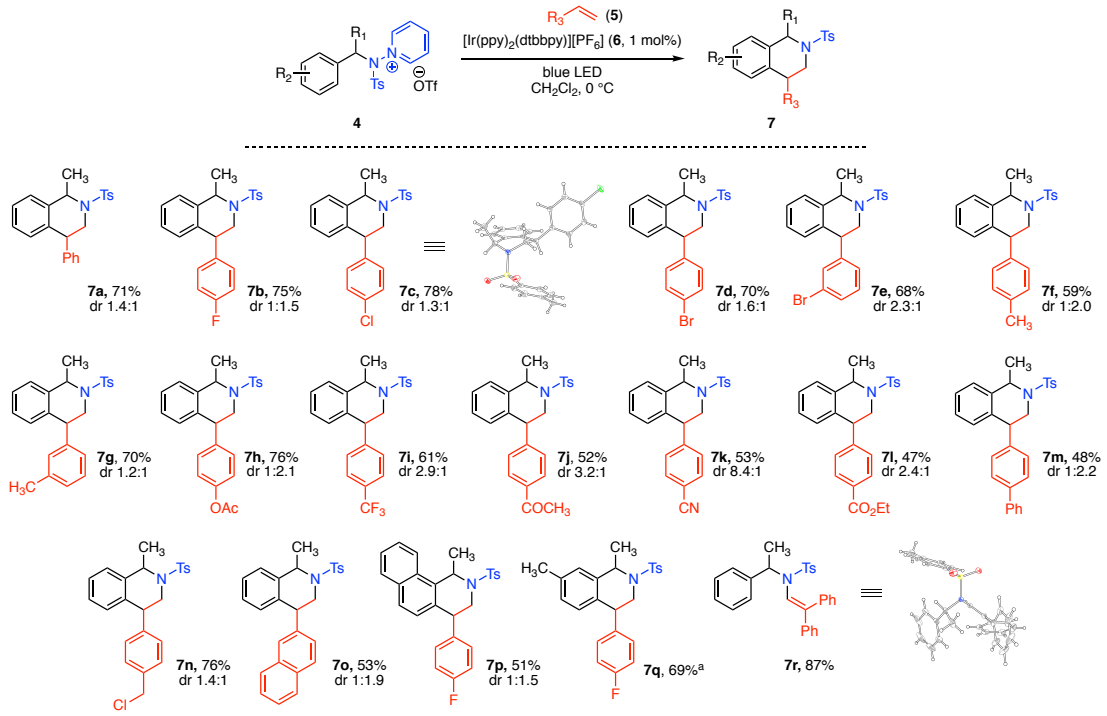
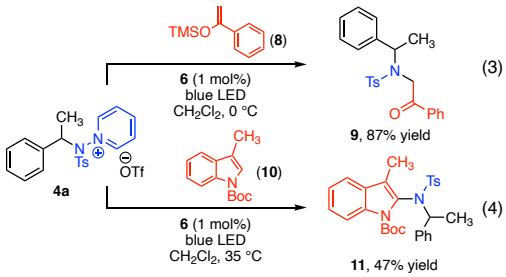


Figure 3. Photocatalytic carboamination promoted by deaminative functionalization of **4** in presence of olefins provides access to a family of 1,4-subsituted tetrahydroisoquinolines **7**. [a]Diastereomeric ratio was not obtained due to spectral overlap of regioisomers obtained from two inequivalent *ortho*-positions of 1-((4-methyl-*N*-(1-(*m*-tolyl)ethyl)phenyl)sulfonamido)pyridin-1-ium triflate (**4g**).

In addition to olefinic substrates, the electrophilic radicals generated by reductive activation of the N–N bonds in *N*-benzylaminopyridiniums engage in amination reactions with silyl enol ethers, such as **8**, to afford α-amino carbonyl derivative **9** in 87% yield (Eqn. 3) and by nucleophilic heterocycles, such as *tert*-butyl 3-methyl-1*H*-indole-1-carboxylate **10** to generate 2-aminated indole **11** in 47% yield (Eqn. 4). These examples highlight the diversity of deaminative functionalization reactions available to *N*-benzylaminopyridiniums.



Carboamination to access tetrahydroisoquinolines can be envisioned as arising from the mechanism illustrated in Figure 4a.[17] Electron transfer from an excited state of the Ir photocatalyst to the *N*-benzylaminopyridinium results in N–N cleavage to an amidyl radical (**12**), pyridine, and an Ir(IV) intermediate. Reaction of the generated amidyl radical **12** with olefin **5** generates benzylic radical **13**. Oxidation of **13** by Ir(IV) would afford cationic intermediate **14** and regenerate the photocatalyst. Electrophilic addition to the arene to the cation in **14** furnishes tetrahydroisoquinoline **7**. In support of this scheme, addition of *N*-tert-butyl-α-phenylnitrone (PBN) to the carboamination of **4a** resulted in observation of the PBN adduct of amidyl radical **12** by both X-band EPR spectroscopy and high-resolution APCI-MS (Figure 4b and S3).[11a,18] In addition, deaminative functionalization of **4a** in the presence of 1,1-diphenylethylene (**5r**) yielded the corresponding olefinic product **7r** in 87% yield as opposed to the expected tetrahydroisoquinoline (Figure 3). This divergent reactivity is presumably due to elimination from stabilized carbocation **14r** in preference to arene alkylation which would generate the corresponding tetrahydroisoquinoline.

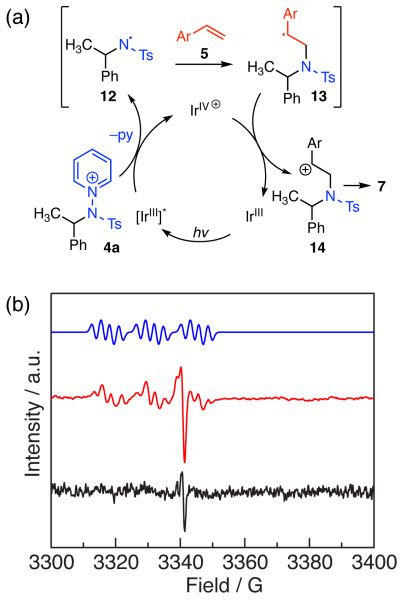


Figure 4. (a) Potential carboamination catalytic cycle. Electron transfer from the excited state of $[Ir(ppy)_2(dtbbpy)][PF_6]$ to **4a** results in reductive N–N cleavage to unveil amidyl radical **12** and Ir(IV). Addition to olefin **5** generates benzylic radical **13**. Oxidation by Ir(IV) generates a benzylic cation **14**, which alkylates the pendent arene to afford tetrahydroisolinolines **7**. (b) EPR spectra for photochemical deaminative functionalization of **4a** in presence of PBN was obtained in acetonitrile. The observed triplet of quartet in the photolyzed spectrum is attributed to PBN-trapped amidyl radical with $a_{N(PBN)} = 13.85$ G, $a_H = 3.20$ G, and $a_{N(amidyl)} = 2.52$ G; (—) without photolysis, (—) experimental spectrum with blue light irradiation, and (—) simulated spectrum.

In summary, here we have demonstrated the use of *N*-aminopyridinium reagents as bifunctional amine sources in C–H amination chemistry. The nucleophilicity of *N*-aminopyridinium allows these reagents to engage in C–H amination chemistry. Reductive N–N cleavage unveils electrophilic amidyl radical intermediates, enables the products of C–H amination to engage in olefin carboamination to afford tetrahydroisoquinoline products. The same amidyl radical intermediates also participate in the formal α-amination of ketones with silyl enol ethers and electrophilic addition to electron-rich heterocycles. The realization of C–H functionalization chemistry with *N*-aminopyridinium reagents both significantly expands the structural complexity that is available to this burgeoning class of bifunctional reagents and significantly expands the synthetic utility products accessible via C–H amination.

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