Diversification of Amidyl Radical Intermediates Derived from C–H Aminopyridylation

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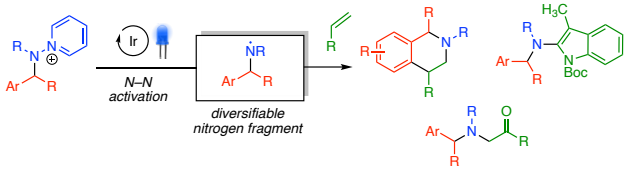
Supporting Information Placeholder

ABSTRACT: C–H amination chemistry promises to streamline access to nitrogen-containing fine chemicals. The typical need for *N*-activating substituents — such of *N*-sulfonyl groups, which are challenging to remove and difficult to engage in synthetic elaboration — limits synthetic utility. Here, we demonstrate that *N*-benzylaminopyridinium species, generated by C–H aminopyridylation, provide a platform for synthetic elaboration via reductive N–N bond activation to unveil electrophilic *N*-centered radicals. These reactive intermediates can be trapped either via anti-Markovnikov olefin carboamination to provide access to tetrahydroisoquinolines, which are important heterocycles in molecular therapeutics, or via aza-Rubottom chemistry with silyl enol ethers to provide α-amino ketones. This approach broadens the synthetic utility of *N*-alkylaminopyridinium intermediates and demonstrates a new approach to C–H amination with synthetically addressable, bifunctional reagents.



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] A variety of C–H amination methods, based on either nitrene or nitrogen-centered radical intermediates, have been advanced to install *N*-containing functional groups without the need for substrate prefunctionalization (Figure 1a).[3,4] In practice, electron-withdrawing groups, such as *N*-sulfonyl substituents, are typically required to activate aminating reagents for C–H functionalization and methods to elaborate the resulting sulfonamides to more complex nitrogen-containing molecules are limited.[5,6]

We recently introduced *N*-aminopyridinium salts as bifunctional reagents in C–H amination chemistry.[7] The combination of a nucleophilic *N*-amino group and a reductively activatable N–N bond[8] provided a platform to couple C–H amination with C–N cross coupling to achieve formal nitrene transfer to benzylic C–H bonds. Here, we demonstrate that reductive activation of the same N–N bonds allows derivatization of the products of C–H amination via electrophilic *N*-centered radicals (Figure 1b).[9] We highlight the amination/derivatization sequence in (1) the synthesis of tetrahydroisoquinolines, which are important heterocycles in medicinal chemistry and can be challenging to prepare by existing methods,[10] and (2) the synthesis of α-aminoketones via formal aza-Rubottom chemistry.[11] These protocols enable conversion of benzylic C–H bonds to an array of nitrogen-containing products and significantly expand the utility of *N*-aminopyridiniums as lynchpins of molecular synthesis.

During our initial studies of C–H aminopyridylation, we developed conditions that promoted selective benzylic C–H

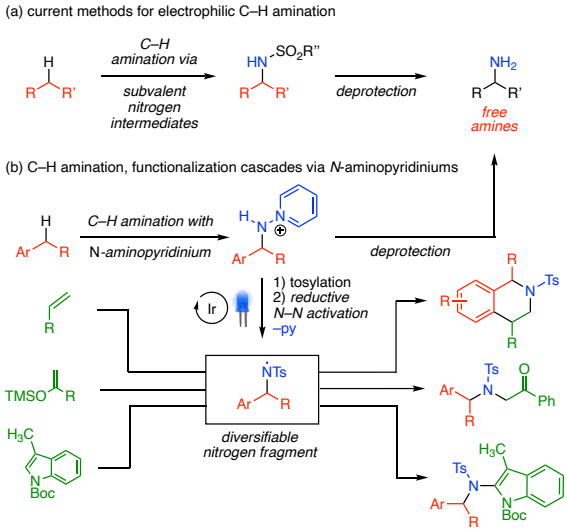


Figure 1. (a) Direct C–H amination via nitrene transfer or radical-mediated processes typically requires activation of the amine fragment with electron withdrawing substituents, which can be removed to ultimately generate free amines. (b) Here, we demonstrate C–H amination with *N*-aminopyridinium which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

functionalization of a variety of ethyl and alkylbenzene derivatives.[7] We envisioned that oxidative quenching of the excited state of an appropriate photoredox mediator would promote reductive cleavage of the N–N bond of these compounds to release pyridine and unveil an electrophilic aminyl radical. The generated aminyl radical could be engaged with exogenous substrate, such as an olefin, with the potential for additional C–C bond formation through cyclization in the presence of pendant phenyl moiety (*vide infra*). Initial attempts to photolyze a solution of **1a** in the presence of aryl olefins and a variety

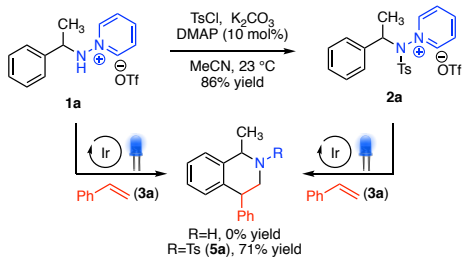


Figure 2. Visible-light promoted functionalization of *N*-benzylaminopyridiunium **2a** in presence of styrene afforded carboamination product **5a** while analogous functionalization of N–H substrate **1a** was not productive. The dichotomous observations are presumably due to stabilization of incipient *N*-centered radical via tosyl substitution. Conditions: $[Ir(ppy)_2(dtbbpy)][PF_6]$ (**4**, 1 mol%), blue LED, CH_2Cl_2, 0 °C .

of photoredox mediators were unsuccessful. We observed complete recovery of starting materials with no desired N–N cleavage. We reasoned that the inability to achieve N–N cleavage may arise from the instability of the aminyl radicals that would result from reductive extrusion of pyridine from **1a** and hypothesized that the installation of a sulfonyl group would stabilize the incipient *N*-centered radical (Figure 2). Tosylation of **1a** by treatment with TsCl, K_2CO_3, and DMAP (10 mol%) afforded sulfonamide **2a**. Consistent with the hypothesis that tosylation would enable reductive activation of the *N*-benzylaminopyridinium: The cyclic voltammograms (CVs) of compound **1a** and **2a** reveal that onset potential for reduction for compound **1a** and **2a** are –1.31 V and –0.86V vs. $Ag/AgNO_3$, respectively (Figure S1).

Photolysis (λ = 463 nm) of sulfonamide **2a** with $[Ir(ppy)_2(dtbbpy)][PF_6]$ (**4**, 1 mol%) in the presence of styrene (**3a**) resulted in the evolution of tetrahydroisoquinoline **5a** in 71% yield (1.4:1 ratio of *cis:trans* diastereomers). Tetrahydroisoquinoline **5a** represents the product of anti-Markovnikov carbonamination of styrene. 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 S1–S4).

The developed carboamination chemistry tolerates substitution on both the aminopyridinium and styrene reaction partners. Reaction of 4-fluorostyrene with differently substituted aminopyridinium salts resulted in the formation of tetrahydroisoquinolines **5b-5d.** Reaction of differently substituted halostyrenes with **2a** affords the corresponding tetrahydroisoquinolines (**5e**-**5g**) 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 **5e** (for crystallographic details, see Figures S2-S3 and Tables S5-S6 in the Supporting Information). Electron-donating substituents such as 4- and 3-methylstyrenes afforded tetrahydroisoquinolines **5h** and **5i** with *trans*- and *cis*-diastereomers being major products, respectively. Deaminative carboamination of 4-acetoxystyrene provided tetrahydroisoquinoline **5j** in 76% yield with the trans diastereomer being major product. Tetrahydroisoquinolines **5k-5n**, derived from electron-deficient styrenes, were accessed in 47-61% yield with *cis* diastereoselectivity. Reaction with weakly withdrawing 4-vinyl-1,1'-biphenyl afforded tetrahydroisoquinoline **5o** in 48% yield with a mixture of 1:2.2 *cis: trans* diastereoisomers. Deaminative carboamination of 4-(chloromethyl)styrene yielded **5p** 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 4-(chloromethyl)styrene was observed. Bulky olefinic substrate such as 2-vinylnaphthalene yielded **5q** 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 **2d**, the *N*-

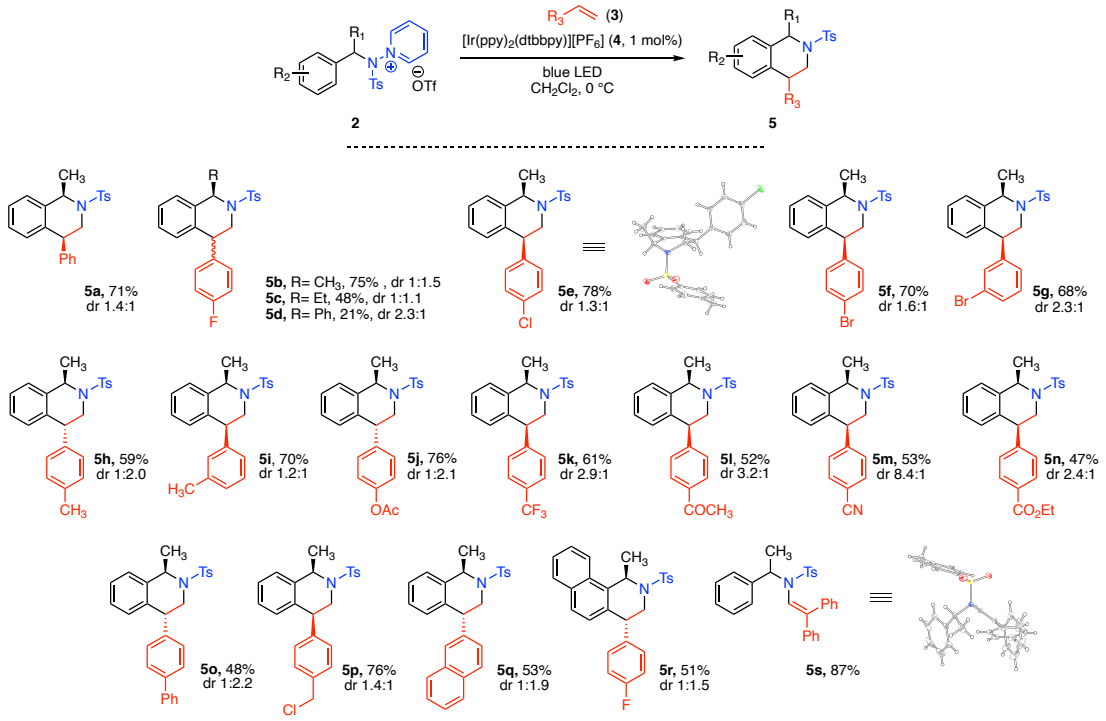


Figure 3. Photocatalytic carboamination promoted by deaminative functionalization of **2** in presence of olefins provides access to a family of 1,4-subsituted tetrahydroisoquinolines **5**. Conditions: **2** (1.0 equiv), **3** (1.6 equiv), CH_2Cl_2, 0 °C, 16 h. dr *cis:trans*

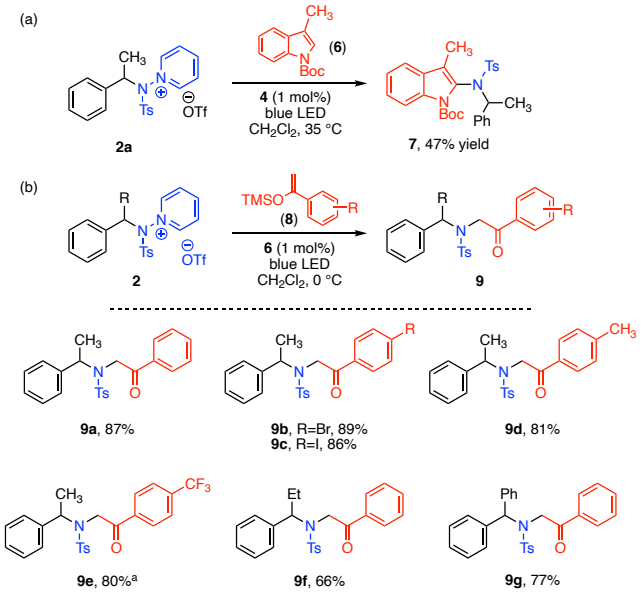


Figure 4. Functionalization of *N*-benzylpyridiunium **4** with (a) nucleophilic heterocycles (conditions: **2a** (1.0 equiv), **6** (3.0 equiv), CH_2Cl_2, 35 °C, 16 h), and (b) silyl enol ethers (conditions: **2a** (1.0 equiv), **8** (2.0 equiv), CH_2Cl_2, 0 °C, 16 h). [a] 4 equivalents of **8e** were used; with 2 equivalents the yield of **9e** was 61%.

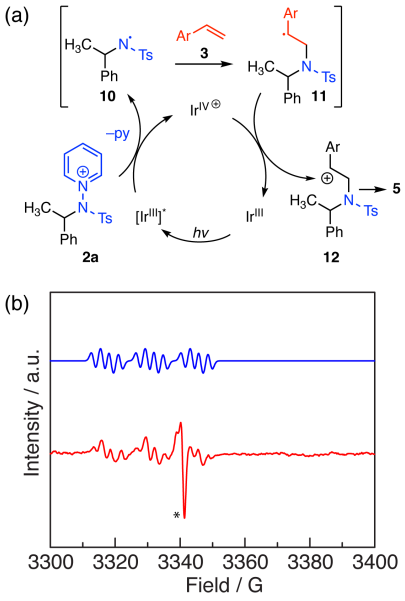


Figure 5. (a) Potential carboamination catalytic cycle. Electron transfer from the excited state of $[Ir(ppy)_2(dtbbpy)][PF_6]$ to **2a** results in reductive N–N cleavage to unveil amidyl radical **10** and Ir(IV). Addition to olefin **5** generates benzylic radical **11**. Oxidation by Ir(IV) generates a benzylic cation **12**, which alkylates the pendent arene to afford tetrahydroisolinolines **5**. (b) EPR spectra for photochemical deaminative functionalization of **2a** 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; (—) experimental spectrum with blue light irradiation, and (—) simulated spectrum.

benzylaminopyridinium derived from 1-ethylnaphthalene, with 4-fluorostyrene yielded the corresponding benzo-fused tetrahydroisoquinoline **5r** in 51% yield with a mixture of 1:1.5 *cis: trans* diastereomers. The diastereoselectivity does not appear to vary systematically with the electronic properties of the substituents on the olefin partners. Bulky substituents on the *N*-aminopyridinium partner give rise to preferential formation of the *trans* diastereomer (*i.e.*, **5r**). Reaction with non-aromatic olefins such as 1-octene or cyclohexene often resulted in the formation of imine from *in situ* generated *N*-centered radical **10**, presumably via HAA from aliphatic olefins (see the Supporting Information for additional details).

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 nucleophilic heterocycles, such as *N*-Boc-indole **6** to afford 2-aminated indole **7** in 47% yield (Figure 4a), and silyl enol ethers (**8**) to afford α-amino carbonyls **9** (Figure 4b). The amination of silyl enol ethers via *N*-aminopyridiniums,[12] which represents a formal aza-Rubottom reaction, tolerates both substitution of the nucleophilic partner **8** (*i.e.*, preparation of **9a**-**9e**) as well as variation of the benzylic substituents on the *N*-benzylpyridinium partner **2** (*i.e.*, preparation of **9f** and **9g**).

Reductive functionalization of *N*-benzylaminopyridiniums (**2**) can be envisioned as arising from the mechanism illustrated in Figure 5a (illustrated for olefin carboamination to generate tetrahydroisoquinolines).[13] Electron transfer from an excited state of the Ir photocatalyst to **2** results in N–N cleavage to an amidyl radical (**10**), pyridine, and an Ir(IV) intermediate. Reaction of the generated amidyl radical **10** with olefin **3** generates benzylic radical **11**. Oxidation of **11** by Ir(IV) would afford cationic intermediate **12** and regenerate the photocatalyst. Electrophilic addition to the arene to the cation in **12** furnishes tetrahydroisoquinoline **5**. In support of this scheme, addition of *N*-tert-butyl-α-phenylnitrone (PBN) to the carboamination of **2a** resulted in observation of the PBN adduct of amidyl radical **10** by both X-band EPR spectroscopy and high-resolution APCI-MS (Figure 5b and S4).[9i, 14] In addition, deaminative functionalization of **2a** in the presence of 1,1-diphenylethylene yielded the corresponding olefinic product **5s** in 87% yield as opposed to the expected tetrahydroisoquinoline (Figure 3), which is presumably due to elimination from stabilized carbocation **12s** in preference to arene alkylation to generate the corresponding tetrahydroisoquinoline. Similarly, the benzylic carbocation **12** can be trapped with water as nucleophile in a mixed solvent of acetone/water to form β-aminoalcohol (See supporting information page 35). The quantum yield for the deaminative olefin functionalization was found to be 15.8%, which is consistent with a non-radical chain pathway for the generation of tetrahydroisoquinolines (See supporting information Section F for additional details).

In summary, here we described utilization of benzyl C–H aminopyridylation products in olefin carboamination and formal aza-Rubottom oxidation of silyl enol ethers. The nucleophilicity of *N*-aminopyridinium allows these reagents to engage in C–H amination chemistry, and reductive N–N cleavage unveils electrophilic amidyl radical intermediates as diversifiable nitrogen synthons. 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.

ASSOCIATED CONTENT

Supporting Information

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

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The manuscript was written through contributions of all authors.
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Notes

The authors declare no competing financial interest.

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