N-Aminopyridinium Reagents as Traceless Activating Groups in the Synthesis of *N*-Aryl Aziridines

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Abstract *N*-functionalized aziridines, which are both useful intermediates and are present in important synthetic targets, can be envisioned as arising from the direct addition of nitrenes (*i.e.*, NR fragments) to olefinic substrates. The exceptional reactivity of most nitrenes, in particular with respect to unimolecular decomposition reactions, prevents general application of nitrene-transfer chemistry to the synthesis of *N*-functionalized aziridines. Here we describe a strategy for the synthesis of *N*-aryl aziridines based on 1) olefin aziridination with *N*-aminopyridinium reagents to afford *N*-pyridinium aziridines followed by 2) Ni-catalyzed C–N cross-coupling of the *N*-pyridinium aziridines with aryl boronic acids. The *N*-pyridinium aziridine intermediates also participate in ring-opening chemistry with a variety of nucleophiles to afford 1,2-aminofunctionalization products. Preliminary mechanistic investigations indicate aziridine cross-coupling proceeds via a noncanonical mechanism involving initial aziridine opening promoted by the bromide counterion of the Ni catalyst, C–N cross-coupling, and finally aziridine reclosure. Together, these results provide new opportunities to achieve selective incorporation of generic aryl nitrene equivalents in organic molecules.

Aziridines, which are three-membered nitrogen-containing heterocycles, are attractive synthetic intermediates *en route* to 1,2-aminofunctionalization products and are present in various naturally occurring alkaloids and pharmacologically active compounds.[1] Retrosynthetically, aziridines can be envisioned as arising from the combination of a nitrene equivalent with an olefinic substrate. In practice, aziridination via nitrene transfer is severely limited by the promiscuous reactivity of unstabilized nitrenes:[2] For example, attempts to access *N*-phenylazidines from phenylnitrene (generated by thermolysis or photolysis of phenyl azide) result in polymeric tars instead of the desired aziridine.[3] Since Evans's report of Cu-catalyzed olefin aziridination,[4] myriad transition metal-catalyzed methods have been developed for nitrene transfer to olefins (Figure 1a).[5] Metal-catalyzed nitrene transfer catalysis typically requires electron-withdrawing groups, such as *N*-sulfonyl substituents, to activate the nitrogen equivalent for transfer;[6,7] there are limited reports of metal-catalyzed nitrene transfer from aryl azide precursors.[8] The resulting *N*-protected aziridines can be challenging to utilize in downstream *N*-functionalization chemistry. For example, exposure of *N*-sulfonyl aziridines to metal-catalyzed cross-coupling conditions typically results in aziridine opening, not *N*-functionalization.[9] N–H aziridines can be accessed by either deprotection of *N*-protected aziridines[10] or by direct synthesis of olefinic precursors (Figure 1b).[11] While derivitization of the N–H valence can provide access to some *N*-functionalization products, arylation of these compounds is not broadly developed.[12,13]

N-aminopyridinium reagents represent a burgeoning class of bifunctional reagents[14] which combine a nucleophilic *N*-amino group with a low-lying pyridinium-centered LUMO that enables access to N-centered radicals via reductive N–N cleavage (LUMO = lowest unoccupied molecular orbital).[15] In the context of amination chemistry, *N*-sulfonylaminopyridiniums have been utilized in photoredox-promoted olefin difunctionalization[16] and aromatic C–H amination reactions.[17,18]

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 pyrylium salts or by sulfonylation of *N*-aminopyridiniums.[19] Here, we describe the first example of olefin aziridination with *N*-aminopyridinium reagents (Figure 1c). Inspired by the Ni-catalyzed C–C coupling chemistry of *N*-alkylpyridinium electrophiles pioneered by Watson[20] and others,[21] we demonstrate that the resulting *N*-pyridinium aziridines are competent electrophiles for C–N bond-forming cross-coupling with aryl boronic acids to afford *N*-aryl aziridines. This two-step protocol provides access to the products of formal aryl nitrene transfer to olefinic substrates and stands in contrast to classical methods of aziridine functionalization which are based on *N*-centered nucleophilicity. Initial mechanistic experiments suggest that the cross-coupling proceeds via a non-canonical mechanism involving halide-promoted ring opening, C–N bond-forming cross coupling, and aziridine reclosure.

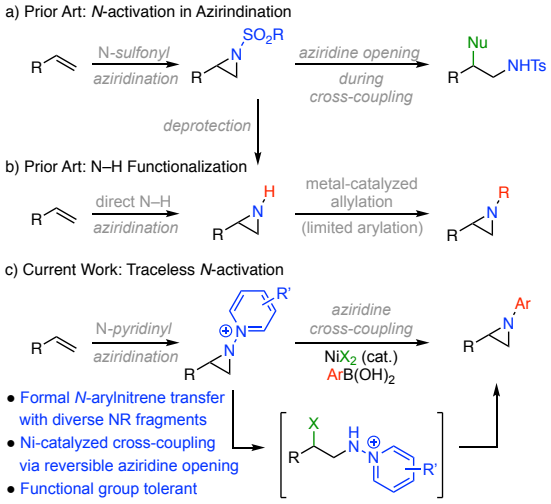

Figure 1. (a) Nitrene transfer to olefins provides access to aziridines but often requires the utilization of sulfonyl groups to activate the nitrogen. (b) N–H aziridines can be accessed directly from olefins and metal-catalyzed allylation methods enable functionalization of the N–H valence. (c) Here we advance *N*-pyridiniumaziridines as platforms for C–N cross coupling to provide access to *N*-substituted aziridines.

We began the development of a formal nitrene transfer sequence by developing robust conditions for olefin aziridination with *N*-aminopyridinium reagents as nitrogen sources. Combination of styrene and *N*-aminopyridinium triflate in the presence of iodobenzene diacetate ($PhI(OAc)_2$) and MgO resulted in 1-(2-phenylaziridin-1-yl)pyridin-1-ium in 64% yield. Aziridination could also be accomplished using *N*-amino-2,4,6-triphenylpyridinium tetrafluoroborate (**2**) as the nitrogen source under these conditions (42% yield of the corresponding pyridinium aziridine (**3a**)). During subsequent studies of C–N cross coupling (*vide infra*), the triphenyl derivative was found to be superior and thus we optimized the aziridination reaction with compound **2** as the pyridinium source. Examination of the impact of various catalysts, solvents, reaction temperatures, and additives (see Supporting Information Section C.1 for details) identified optimized aziridination conditions based on iodide catalysis in the presence of 4Å molecular sieves, which affords aziridine **3a** in 71% yield (Figure 2).

An array of 4-substituted vinyl arenes participate in aziridination with the optimized conditions: hydrocarbyl substituents (**3b** and **3c**), electron-donating alkoxy and Boc-protected amines (**3d** and **3e**), as well as various electron-withdrawing substituents (**3f**–**3k**) are all well tolerated. Both *meta*- and *ortho*-substituents (**3l**–**3p** and **3q**–**3s**, respectively) are compatible with the developed aziridination conditions and 2-vinylbenzothiophene undergoes aziridination to **3t** in 60% yield. For electron-neutral and -rich substrates, 5 mol% [TBA]I is utilized; for electron deficient substrates we increased the catalyst loading to 20 mol% to achieve efficient aziridination. Consistent with previous reports of iodide-catalyzed aziridination, functionalization of 1,2-disubstituted olefins is not stereospecific:[Error! Bookmark not defined.a] aziridination of *trans*-β-methylstyrene (*trans*-**1u**) affords a 45:55 *cis*:*trans* mixture of **3u**; aziridination of *cis*-**1u** affords a 35:65 *cis*:*trans* mixture of **3u**. The developed conditions are effective for the aziridination on more

complex substrates, including **3v**–**3z**, which are derived from pharmaceutically relevant isatin, estrone, ibuprofen, tufnil, and probenecid.

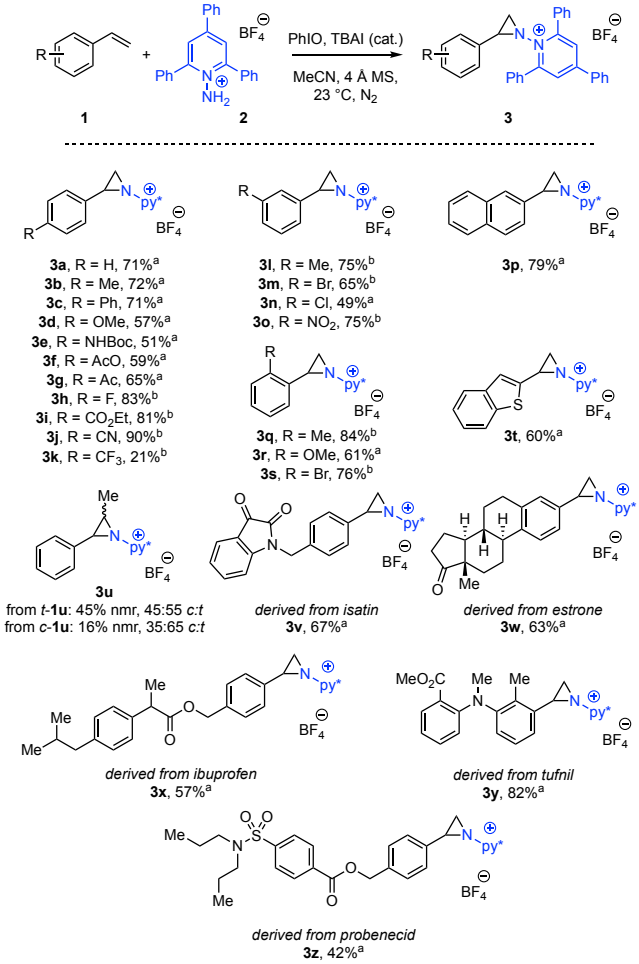

Figure 2. Iodide-catalyzed olefin aziridination. Condition a, **1** (1.0 equiv), **2** (1.0 equiv), PhIO (1.0 equiv), TBAI (5 mol%); condition b, **1** (1.0 equiv), **2** (1.6 equiv), PhIO (1.6 equiv), TBAI (20 mol%).

With conditions in hand to efficiently access *N*-pyridinium aziridines, we turned our attention to engaging these species as electrophiles in C–N coupling reactions. We envisioned a C–N cross coupling of *N*-pyridinium aziridines would 1) provide access to the products of formal nitrene transfer to olefins, 2) provide a rare example of an aziridine cross-coupling in which the aziridine ring remains intact, and 3) represent the first application of pyridinium electrophiles in C–N cross-coupling chemistry. We initiated our investigations by examining potential Ni-catalyzed cross

coupling of *N*-pyridinium aziridine electrophiles with appropriate organometallic nucleophiles (*i.e.*, Grignard reagents, organolithiums, organostannanes, and boronic acids). We identified that treatment of *N*-pyridinium aziridine **3a** with tolyl boroxine and $NiCl_2$(dme) in MeCN afforded *N*-arylaziridine **5b** in 36% yield. The coupling efficiency is extremely sensitive to the Ni(II) counter anion: Under identical conditions, $NiCl_2$ provided **5b** in 36% yield while $NiBr_2$ afforded **5b** in 60% yield. $Ni(OAc)_2$, $Ni(acac)_2$ and $NiSO_4$ salts were completely ineffective. Optimization of the cross-coupling reaction (see Supporting Information Section C.2 for details) ultimately identified the use of $NiBr_2$(phen) as catalyst in the presence of K_3PO_4 and 2,4,6-collidine provided *N*-tolylaziridine **5b** in 79% yield (Figure 3). The catalyst loading could be reduced to 10 mol% without significant loss of yield, but further reduction to 5 mol% resulted in substantial reduction in reaction efficiency.

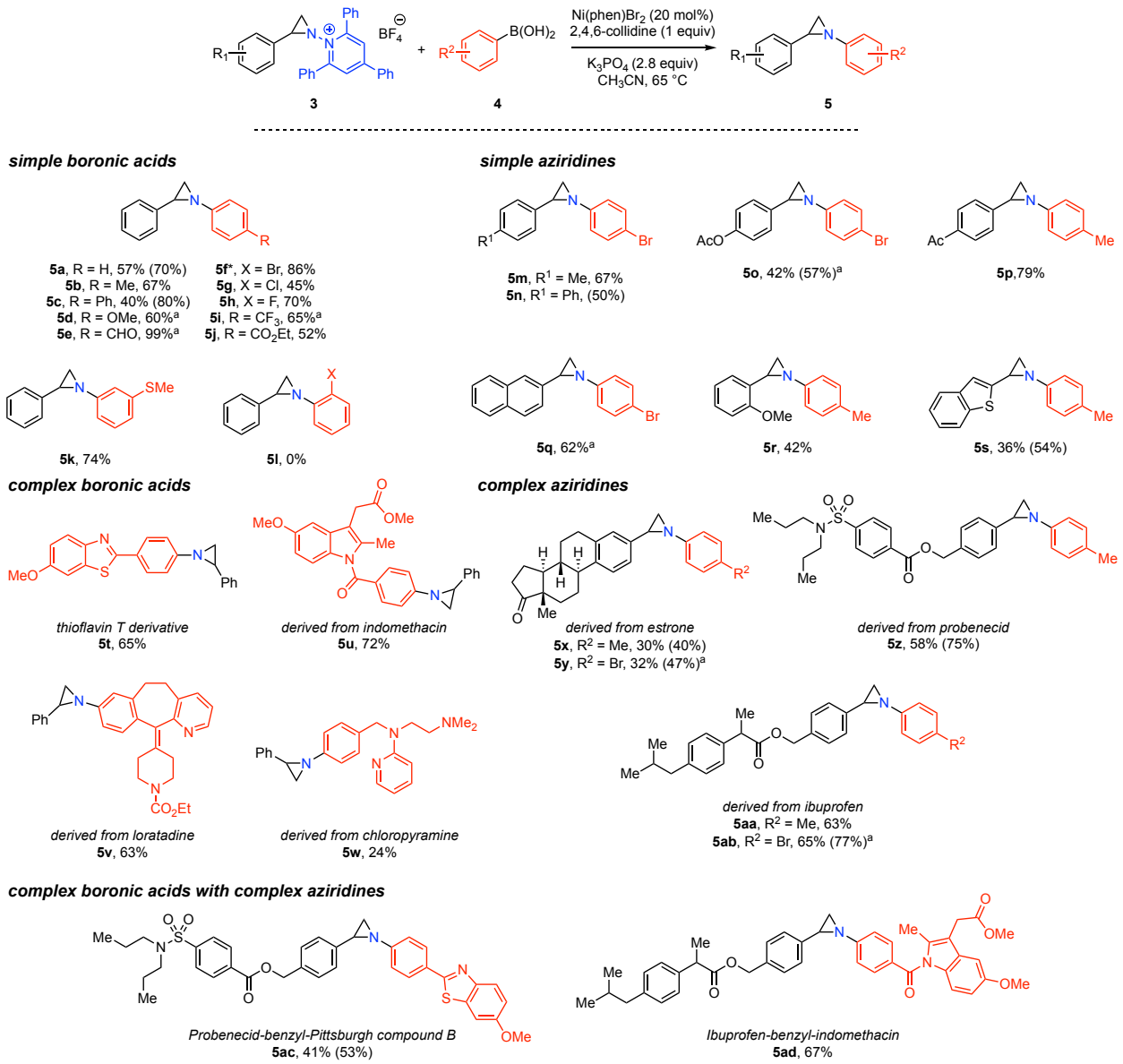

Figure 3. Ni-catalyzed cross-coupling of *N*-pyridinium aziridines with aryl boronic acids provides access to *N*-arylaziridines, which are the products of formal transfer of aryl nitrenes to olefins. [a]For these substrates, K_2CO_3 was used in place of K_3PO_4. Yields reported are based on isolated products (based on ^1H NMR integration).

The developed cross-coupling conditions enable cross-coupling with simple arylboronic acids substituted in the 4-position (**5a**–**5j**) and in the 3-position (**5k**), but substitution in the 2-position (**5l**) was not tolerated. Notably, electron-neutral and -rich aryl groups can be incorporated in the *N*-arylaziridine efficiently, which represent specific challenges in direct nitrene transfer strategies. Similarly, various substitutions of the pyridinium aziridine coupling partner were also tolerated

(**5m**–**5s**). The developed aziridination reaction was also compatible with both complex boronic acids, such as those derived from thioflavin T (**5t**), indomethacin (**5u**), loratadine (**5v**), and chloropyramine (**5w**), and with complex pyridinium aziridine partners, such as those derived from estrone (**5x**–**5y**), probenecid (**5z**), and ibuprofen (**5aa**–**5ab**). Finally, fragment coupling reactions in which both complex boronic acids and complex pyridinium aziridine partners could be directly linked via an aziridine ring were efficient (**5ac**–**5ad**).

In addition to direct C–N coupling with boronic acids, the developed *N*-pyridinium aziridines participate in ring-opening chemistry to access 1,2-difunctionalization products (Figure 4). Exposure of *N*-pyridinium aziridine **3a** to halide sources (*i.e.* [TBA]Br, [TBA]Cl, or pyridine·HF) or H_2O in the presence of $BF_3{\cdot}OEt_2$ resulted in opening of the aziridine to afford haloamine derivatives **6a**–**6c** or hydroxyamine **6d**. Attempts to isolate **6a** and **6b** resulted in low isolated yields due to aziridine reclosure to *N*-pyridinium aziridine **3a** (*vide infra*). A variety of other oxygen-, nitrogen-, and sulfur-based nucleophiles participate in aziridine opening to afford isolable aminopyridinium derivatives **6e**–**6j**. These ring-opened compounds could be isolated as analytically pure materials and participate in efficient Ni-catalyzed cross coupling to generate 1,2-aminofunctionalized compounds **7e**–**7j** (the products of *p*-tolylboronic acid coupling), respectively. The ring-opened product **6g** also participated in cross coupling with more complex boronic acids, as highlighted by the synthesis of **7k** and **7l**, which are derived from cross-coupling of ring-opened compounds with the boronic acid derived from indomethacin.

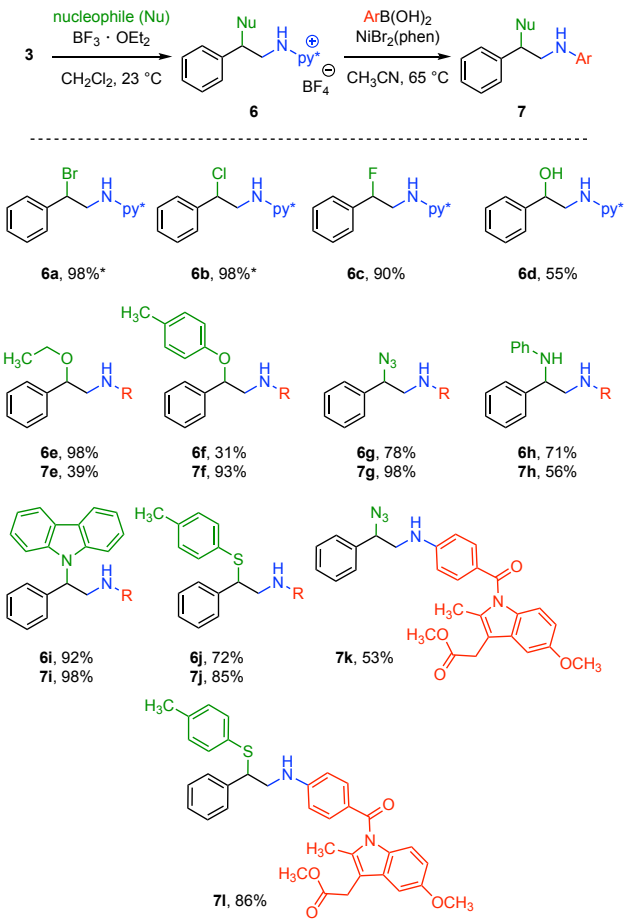

Figure 4. Nucleophilic opening of aziridine **3a** provides access to 1,2-aminofunctionalization products **6**. Ni-catalyzed cross-coupling of these ring-opened compounds provides opportunities to elaborate the resulting acyclic *N*-aminopyridinium derivatives to generate anilines **7**. *Yields determined by ^{1}H NMR due to instability of these compounds towards intramolecular elimination.

Metal-catalyzed cross-coupling of aziridine often results in ring opening products.[9] In contrast, we observed Ni-catalyzed C–N coupling to generate *N*-arylaziridines in which the aziridine ring is conserved in the product. To better understand this unusual reaction outcome, we were interested in evaluating the mechanism of C–N bond-forming chemistry that leaves the three-membered aziridine ring intact. These investigations were guided by 1) a desire to understand the bromide-specific activity noted in our original catalyst optimization studies and 2) the observation that while treatment of **3a** with [TBA]Br and $BF_3{\cdot}OEt_2$ resulted in ring opening, attempts to isolate the resulting benzyl bromide **6a** resulted in re-isolation of **3a**, which suggested that ring-opening with

bromide is reversible. This observation suggested the possibility that aziridine opening, followed by cross-coupling of an open-chain aminopyridinium intermediates, and finally aziridine reclosure may be operative (Figure 5a). Consistent with this hypothesis, treatment of aziridine **3a** with $NiBr_2$(dme) (with or without added phenanthroline) results in the observation of ring-opened compound **6a** by ^{1}H NMR (Figure 5b).[22] Further, exposure of a sample of compound **6a** to $Ni(OTf)_2$ or $Ni(BF_4)_2$ and *p*-ethoxylcarbonylphenylboronic acid results in the formation of *N*-arylaziridine **5j**, which demonstrates the viability of cross-coupling and aziridine reclosure (Figure 5c). The mechanistic scheme based on transient generation of open-chain intermediates rationalizes the particular activity of $NiBr_2$ as catalyst: $NiBr_2$ participates in efficient ring-opening chemistry and is an efficient catalyst for C–N coupling; $Ni(OAc)_2$ does not promote ring opening and is ineffective in C–N coupling.

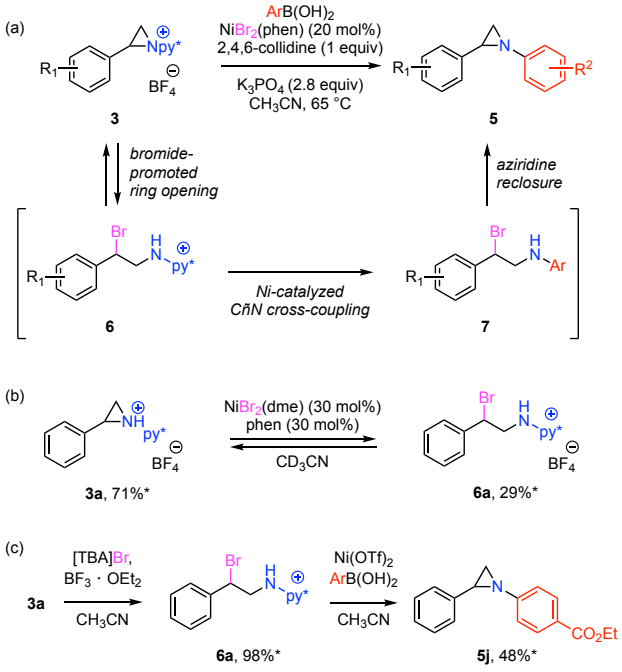

Figure 5. (a) Reversible halide-promoted aziridine opening, cross coupling, and aziridine reclosure are proposed to mediate C–N cross coupling of *N*-pyridinium aziridines. Consistent with this mechanism (b) $NiBr_2$ reacts with *N*-pyridinium aziridine **3a** to generate ring-opened **6a** and (c) exposure of ring-opened **6a** to $Ni(OTf)_2$ or $Ni(BF_4)_2$ affords arylated aziridine **5j**. *Yields determined by ^{1}H NMR spectroscopy.

In summary, we report a strategy for the synthesis of *N*-aryl aziridines, which are the formal products of aryl nitrene addition to olefins. This method overcomes the inherent instability of free nitrene fragments by harnessing *N*-pyridinium aziridine intermediates that participate in Ni-catalyzed C–N cross-coupling. By decoupling the aziridination from installation of the *N*-substituent, this strategy overcomes the common requirement for difficult-to-remove *N*-substituents in aziridination chemistry. The observed C–N cross-coupling chemistry contrasts the typical reactivity pattern of *N*-sulfonylaziridine cross-coupling, which typically participate in ring-opening C–N activation, by taking advantage of a unique reversible ring opening / reclosure mechanism. These studies not only provide strategies to access products of formal nitrene transfer to olefins but significantly expand the synthetic scope of nitrene transfer by demonstrating *N*-aminopyridinium to be a bifunctional amination reagent.

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