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

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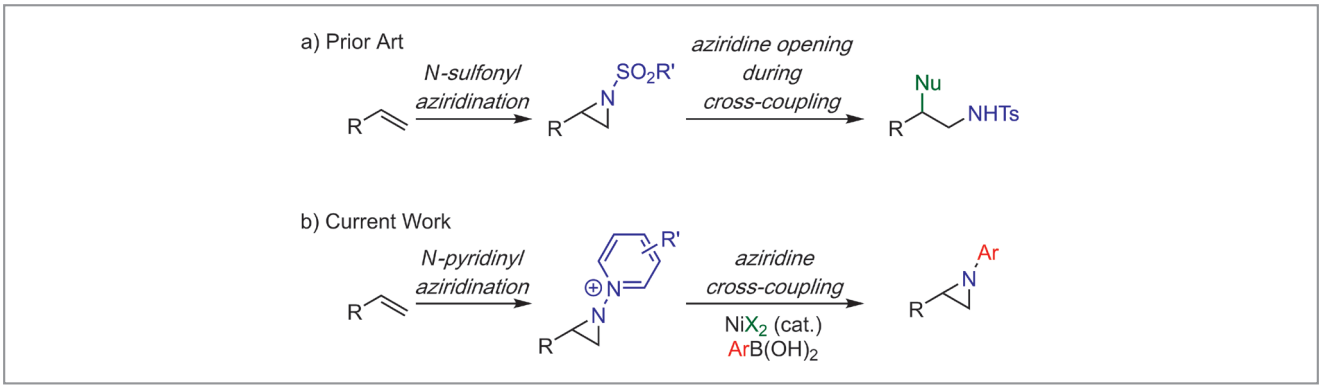
Nitrene transfer catalysis has been broadly investigated, because it provides the opportunity to efficiently install nitrogen-containing functional groups via C–H amination or olefin aziridination. Professor David Powers' group at Texas A&M University (USA) became involved in this area of science while studying the inorganic chemistry of metal nitrenes. Professor Powers told SYNFORM: "Over the past 5 years, our group has been developing new tools to study the chemical structures of transient nitrenes by *in crystallo* photochemistry (e.g., *J. Am. Chem. Soc.* **2020**, *142*, 19862–19867 and *J. Am. Chem. Soc.* **2019**, *141*, 16232–16236). During these studies we came to realize that while enormous progress has been made in nitrene transfer chemistry, significant limitations plagued most modern methods. Namely, reactions were either limited to intramolecular reactions or required the presence of strongly electron-withdrawing *N*-substituents, which resulted in *N*-protected products (Scheme 1a)." Professor Powers explained that the most common *N*-protecting groups are sulfonamides, phthalimides, and carbamates, but these nitrogen derivatives can be difficult to deprotect and derivatize in the downstream chemistry, which limits the utility of nitrene transfer catalysis in the synthesis of diverse *N*-functionalized products. The Powers group envisioned that *N*-aminopyridinium salts could expand the utility of formal nitrene transfer chemistry because these reagents are inherently bifunctional (Scheme 1b). Professor Powers said: "The *N*-amino group can engage as a nucleophilic moiety in an amination reaction and the N–N bond in the resulting aminopyridinium compound could be engaged as an electrophilic moiety."

Initially, the group's efforts to achieve olefin aziridination were predicated on synthesis of the iminoiodinane derived from *N*-aminopyridinium salts and iodosylbenzene, which they envisioned could be used in Rh- or Cu-catalyzed nitrene transfer reactions. "Despite many experiments, we were never able to isolate an *N*-aminopyridinium analogue of PhI=NTs," remarked Professor Powers. He continued: "We next sought to generate this intermediate *in situ* by combining iodosylbenzene and N-aminopyridinium salts in the presence of olefinic substrates and various transition-metal catalysts. Ultimately, these experiments revealed that efficient aziridination of styrenyl olefins could be achieved without metal catalysts but with the addition of a catalytic amount of iodide (Scheme 2)."

With access to *N*-pyridinium aziridines, the group was attracted to the potential to use these unique compounds as substrates in metal-catalyzed cross coupling to forge new C–N bonds. "This idea was based on 1) Prof. Mary Watson's beautiful C–C cross coupling using *N*-alkylpyridinium electrophiles (e.g., *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316), and 2) the potential that the low-lying LUMO of our substrates would enable cross coupling without aziridine ring opening, which




**Scheme 1** Olefin aziridination often requires strongly electron withdrawing *N*-substituents that can be challenging to remove and are not present in many synthetic targets of interest. We reasoned that development of aziridination using *N*-aminopyridinium reagents would provide the opportunity for facile *N*-derivatization by metal-catalyzed activation of the N–N bond.

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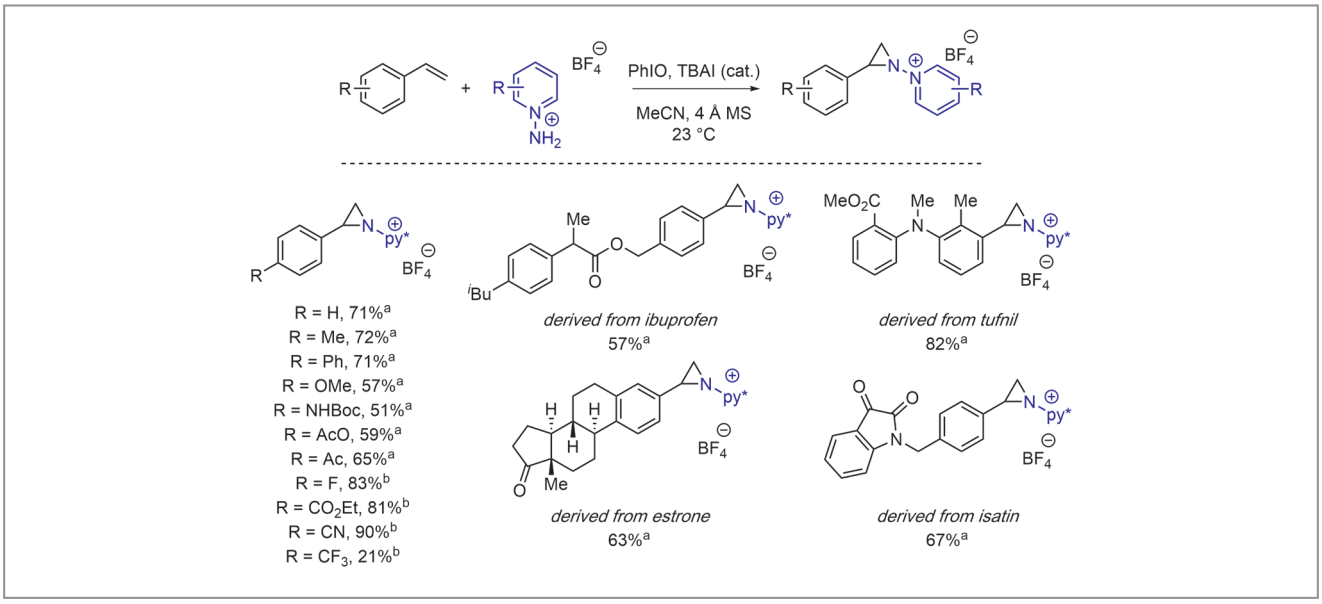



**Scheme 2** Optimized conditions for, and selected examples of, olefin aziridination using *N*-aminopyridinium reagents. [a] Conditions: styrene (1.0 equiv), 2,4,6-triphenyl-*N*-aminopyridinium tetrafluoroborate (1.0 equiv), iodosyl benzene (PhIO, 1.0 equiv), tetrabutylammonium iodide (TBAI, 5 mol%). [b] Conditions: styrene (1.0 equiv), 2,4,6-triphenyl-N-aminopyridinium tetrafluoroborate (1.6 equiv), PhIO (1.6 equiv), TBAI (20 mol%).

would contrast the cross-coupling reactions of other *N*-functionalized aziridines," said Professor Powers, who continued: "While we had initially developed the olefin aziridination chemistry using both *N*-aminopyridinium and the 2,4,6-triphenyl analogue, during our studies of Ni-catalyzed cross coupling, we found the triphenyl version was required for efficient cross coupling with arylboronic acid nucleophiles (Scheme 3, top; py* = 2,4,6-triphenylpyridinyl). While Pd catalysts were tried in the optimization, they turned out inactive in our cross-coupling. We rationalized that Ni is more compatible with single-electron processes than Pd, and cleavage of *N*-substituted pyridinium salts begins with a single-electron transfer to the pyridinium π*. This observation is in contrast to related Ni-catalyzed coupling that we developed in the context of C–H aminopyridylation, in which the unsubstituted pyridinium was a good substrate for coupling (*Angew. Chem. Int. Ed.* **2022**, *61*, e202200665)."

Professor Powers went on to list a few observations that were made during optimization of the aziridine cross-coupling chemistry:

1) The reaction proceeds in more reproducible yield when one equivalent of 2,4,6-collidine is added. The specific role of this additive is not known at this time.

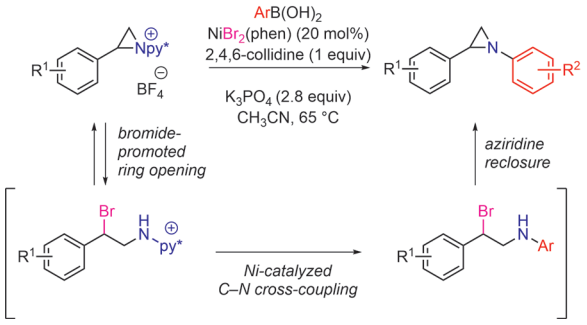
2) Separation of triphenylpyridine, which is a byproduct of C–N cross-coupling, from the *N*-aryl aziridine was challenging for some substrates and required purification by preparative HPLC.

3) The counter anions of the Ni catalyst were important for efficient catalysis, with bromide being particularly effective.

Professor Powers remarked: "Spectroscopic studies indicated that the bromide ion was opening the aziridines to generate 1,2-bromoamines. Further, exposure of these bromoamines to our cross-coupling conditions resulted in *N*-aryl aziridines. These observations led us to propose the reaction pathway illustrated in Scheme 3 in which reversible aziridine opening is promoted by the bromide counterion and cross-coupling is accomplished by the Ni ion. Further investigations are still needed in order to understand this unusual cross-coupling reaction."

Professor Powers concluded: "Access to *N*-pyridinium aziridines provides a number of exciting new directions to explore. Particular current interest is focused on using these species as precursors to *N*-centered aziridinyl radicals for use in synthesis. In addition, significant mechanistic work is underway to better understand the selective *N*-functionalization that we observe under Ni-catalyzed cross coupling, which contrasts ring opening chemistry that has been observed under similar conditions with *N*-tosylaziridines."




**Scheme 3** Top: Ni-catalyzed *N*-pyridinium aziridine cross coupling. Bottom: Proposed cross-coupling mechanism that proceeds through reversible aziridine opening and reclosure. The proposed mechanism suggests a bifunctional role for the $NiBr_2$ catalyst: the bromide ion is responsible for aziridine opening and the Ni ion is responsible for the C–N cross-coupling chemistry.

## About the authors

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**Hao Tan** was born in Shandong Province (P. R. of China). He completed his B.Sc. from Nankai University, Tianjin (P. R. of China). He joined the group of Dr. Powers at Texas A&M University (USA) in 2019. Currently he is working as a graduate student pursuing a Ph.D. in organic synthesis. His research interest focuses on the development of new amination chemistry based on installation of derivatization of *N*-aminopyridiniums.

**Samya Samanta** was born in West Bengal, India and completed his B.Sc. and M.Sc. degrees at the Indian Institute of Technology, Kharagpur (India) under the supervision of Prof. N. D. Pradeep Singh. In his Master's project, he worked on organophotoredox-mediated amide and benzothiazole synthesis. During his undergraduate studies, he also worked as an intern under Prof. David Berg at University of Victoria (Canada) on palladium- and platinum-based catalyst design for polymerization, and under Prof. Leong Weng Kee at Nanyang Technological University (Singapore) on osmium cluster complexes. Currently his research is on C–H amination chemistry under Prof. David C. Powers at Texas A&M University (USA).

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**David Powers** received a B.A. from Franklin and Marshall College (USA) and a Ph.D. from Harvard University (USA). He pursued postdoctoral training at the Massachusetts Institute of Technology (USA) and Harvard University. He joined the faculty at Texas A&M University (USA) in 2015 and was promoted to Associate Professor in 2021. His research group is interested in the chemistry of reactive intermediates, catalysis in confined environments, and novel methods in group-transfer catalysis.

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