Aziridination of Internal Alkenes Using Primary Alkyl Amines in a Microflow Electrocell

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Aziridines are versatile synthetic intermediates en route to structurally diverse and complex nitrogen-containing molecules. In this issue of *Chem*, Noël and co-workers report the aziridination of internal alkenes with primary alkyl amines through novel electrochemical activation with hydrogen gas generated as the byproduct, assisted by a microflow electrocell.

Aziridines are important structural motifs that can be found in a variety of natural products and pharmacological molecules.[1] As a consequence of the high ring strain (28 kcal mol^{-1}), those three-membered heterocycles are amenable to selective ring-opening reactions with a wide range of nucleophiles to access diverse *N*-containing complex molecules.[2] However, the synthesis of aziridines is still far from trivial, even though a variety of methodologies have been developed to synthesize both racemic and chiral aziridines, which can generally be categorized into three main pathways: (1) addition of nitrenes to alkenes, (2) transferring of carbenes to the C=N bond of imines, and (3) intramolecular ring closure with an amino electrophile.[3] However, expensive transition-metal catalysts and excess oxidants are normally required,[4,5] and studies are largely limited to form aziridines bearing an electron-withdrawing *N*-protecting group,[5] which often cause unwanted aziridine opening in the subsequent deprotection step. The direct coupling between unprotected amines and readily available alkenes without the requirement of metal-based catalysts and stoichiometric oxidants therefore represents an ideal approach for aziridine generation and would be of great synthetic value.

The prevailing photocatalysis and electrochemistry have provided enormous opportunities to achieve oxidative coupling by releasing hydrogen gas without external chemical oxidants.[6] Compared with photoredox catalysis, which often relies on the formation of active open-shell species by single-electron transfer (SET), electrochemistry is capable of triggering consecutive SET to access reactive cation or anion intermediates. Sporadic examples of electrochemical aziridination have been developed to enable transition-metal-free and external oxidant-free synthesis, but applications are restricted to pre-functionalized amines, such as $PhtNH_2$.[7,8]

Continuous-flow microreactors offer a great platform for carrying out synthetic organic electrochemistry, bringing in merits such as significantly improved mass and heat transfer, rapid consumption of unstable intermediates,[9] streamlined multi-step synthesis, and easy scale-up.[10] Following their continuous interests in micro-flow electrochemical synthesis,[10] the Noël group reports, in this issue of *Chem*, an exciting breakthrough in this field in which they accomplished the aziridination of internal alkenes directly by using unprotected primary alkyl amines in a microflow electrocell setup under mild conditions without any external oxidants.[11] The generated aziridine products can be opened by various nucleophiles or the *in-situ*-generated hydrogen gas (Scheme 1A).

The authors first investigated and optimized the aziridination protocol in an electrochemical microflow reactor by using *trans*-anethole and cyclohexylamine as the substrates. They obtained 72% isolated yield of the aziridine product with only 5 min of the residence time compared to the 16 h reaction time needed in conventional batch reactors, and hydrogen gas was generated as the byproduct. The improved reactivity in a microflow electrochemical cell could be attributed to the high electrode surface-to-volume ratio, the short diffusion distance between two electrodes, reduced Ohmic drop, and less deposition of organic residue, which can cause passivation of the electrodes in batch reactors. The continuous-flow reactor allowed an easy scale-up of this transformation to a 10 mmol scale with 66% isolated yield (Scheme 1B). The reaction was compatible with a variety of primary alkyl amines (e.g., unactivated alkyl amines, benzylamines, propargylamines, and esters of amino acids) and aryl or heteroaryl substituted internal alkenes (both electron neutral and electron rich). Notably, ammonia can be applied in this protocol to achieve unprotected N–H aziridines. However, a portion of aziridine products were difficult to isolate probably because of the electron-rich nature toward excess amine or hexafluoroisopropanol (HFIP). Those compounds were isolated as the corresponding 1,2-amino thioethers after a subsequent ring opening by using 4-bromothiophenol as a nucleophile.

Remarkably, Noël and co-workers also attempted to utilize the hydrogen gas generated at the cathode to produce the hydroamination products in a streamlined fashion. The gas-liquid product

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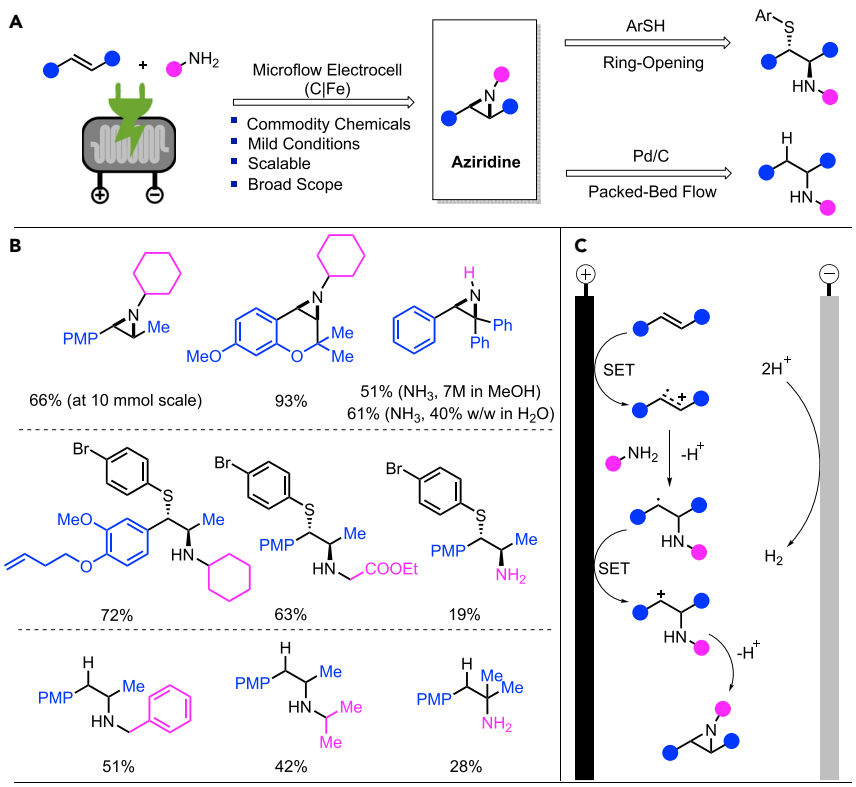

Scheme 1. The Electrochemical Flow Aziridination of Alkenes with Primary Amines
(A) Electrochemical flow synthesis of aziridines and subsequent ring opening.
(B) Selected examples of aziridines, ring-opening products, and hydroaminated products.
(C) Proposed reaction mechanism.

mixture from the micro-flow electrocell directly entered an integrated packed-bed reactor filled with Pd/C to deliver the corresponding hydroaminated products (Scheme 1B), enabling an atom-efficient electrochemical synthesis.

A plausible mechanism was proposed on the basis of cyclic voltammetry experiments, additive study, and density functional theory (DFT) calculations (Scheme 1C). First, the alkene undergoes single-electron oxidation to form a cation radical at the carbon anode. The alternative anodic oxidation of the amine coupling partner is unlikely due to the higher energy input requirement. The radical cation intermediate reacts with an amine to deliver an alkyl radical, which undergoes the second single-electron oxidation to generate a carbocation species. Finally, a rapid barrierless intramolecular ring closure followed by deprotonation yields the desired aziridine product.

Overall, a unique strategy for the synthesis of unprotected aziridines has been realized by Noël and co-workers via the use of micro-flow electrocell. The consecutive single-electron oxidation enabled the aziridine formation directly from simple alkenes and primary alkyl amines. The *in-situ*-generated hydrogen gas could be employed to open the aziridine ring through hydrogenation by streamlining the electro flow cell with a packed-bed flow reactor. This study represents an elegant example of achieving conventional inaccessible reactivity and will inspire new perspectives for the discover of uncharted chemical space though the use of electrochemical micro-flow technology.

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