NH-Aziridines are NOT Just Secondary Amines: An Electrochemical Investigation and its Synthetic Implications

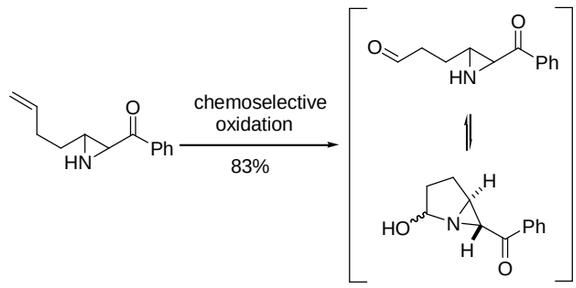
Andrei K. Yudin

Davenport Research Laboratories, Department of Chemistry, The University of Toronto, 80 St. George Street, Toronto, Canada, M5S 3H6

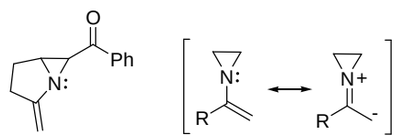
One of the long-standing goals of our research has been development of general solutions to the selective functionalization of small organic molecules with nitrogen-containing fragments. Our recent findings have led us to pose several fundamental questions that relate to the stereocontrolled synthesis of saturated nitrogen-containing heterocycles. Electroorganic synthesis has played a major role in this process from the standpoint of driving oxidation reactions on chemically inert electrodes. Electroanalytical tools have been utilized in order to explain AND predict chemical reactivity [1]. Specifically, we are interested in the asymmetric construction of quaternary and tertiary carbon centers next to nitrogen and applications of this methodology in target-oriented synthesis. The directions of our research are stereoselective metal-catalyzed amination of electron-deficient olefins followed by cycloamination, inter- and intramolecular reactions of functionalized aziridines, and asymmetric transformations of electrochemically-produced iminium ions.

Chemoselectivity in oxidation is the common ground of all areas of our research. Advances in this field are critical if we are ever to achieve synthetic efficiency similar to that displayed by Nature during production of secondary metabolites, many of which are important nitrogen-containing natural products. Typically, synthetic chemists tend to place heavy emphasis on temporarily masking the redox-sensitive groups using protecting group manipulations. In our view, finding cases where redox-sensitive functionalities can be chemoselectively generated in densely functionalized environments, is an important ***strategic*** goal of modern synthesis. In this regard, one of the significant recent observations in our lab (Scheme 1) suggests that N-unprotected aziridines withstand oxidative transformations of the nearby double bonds. We have observed a significant (0.8V) difference in the oxidation potential of cyclohexene imine compared to the value recorded for a typical secondary amine such as piperidine, known for its low stability towards oxidation [2]. We have shown that it is possible to transform a wide range of aziridine-containing precursors into the corresponding aldehydes via oxidative degradation of the nearby double bonds. Worthy of note, the observed oxidative stability is unprecedented among other amines. Based on the observed stability of aziridines coupled with the asymmetric aziridine ring formation/regioselective ring- opening sequence, we have defined strategies that allow rapid access to diversely functionalized heterocycles with complete stereocontrol. Unusual behavior of aziridines as iminium ion precursors (Scheme 2) has also been explored. Particularly instructive is the difference in behavior between highly constrained enamines A vs their counterparts B. Last, but not least, our electrochemical investigations have paved a way to novel amination protocols utilizing late transition metals [3]. These useful reactions are also due to high stability of aziridines towards oxidation. Additionally, these transformations should find wide applications in medicinal chemistry for the purposes of structure/activity relationships using bicyclic amine scaffolds. The unifying theme in all of these areas is chemoselectivity in oxidation. Each one of the processes we have tackled involves a redox challenge that must be met in a densely functionalized environment. Our ability to carry out such transformations with high efficiency should contribute to a growing armor of our redox-driven synthetic techniques. These and related topics will be discussed.

Scheme 1



Scheme 2



A **B**

References

1. Siu, T. and Yudin, A. K. *JACS* **2002**, *124*, 530.

2. Sasaki, M. and Yudin, A. K. *JACS* **2003**, *105*, 14242.

3. Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *JACS* **2004**, *126*, 5086.