

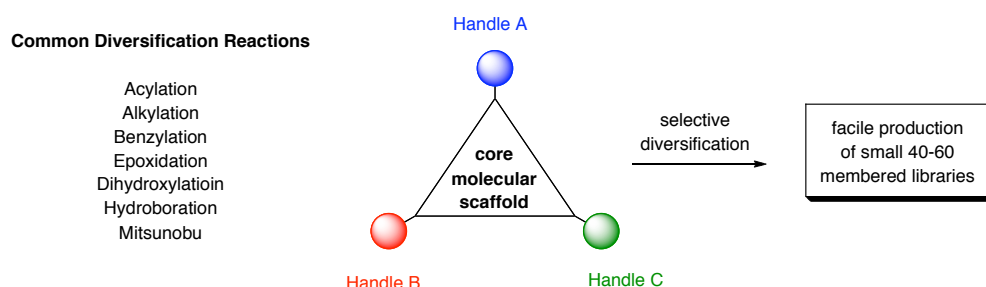
# Investigation of *N*-acyliminium ions in cycloaddition reactions

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Recently, diversity-oriented synthesis (DOS) has become a major focus of contemporary biomedical research.<sup>1</sup> DOS aims to populate and probe previously unexplored chemical space through the use of small molecules having diverse and complex structures. DOS is different from target-oriented synthesis (TOS), which aims to target certain regions of known bioactive chemical space (i.e. a natural product that exhibits interesting biological properties). Typically in TOS a synthetic chemist utilizes retro synthetic analysis to work backwards from complex targets towards commercially available starting materials. DOS, on the other hand, does the exact opposite by utilizing *Forward Synthetic Analysis*. In this strategy you start from a common core and build three-dimensional complexity to diversify the scaffold in attempt to fill new chemical space. DOS looks to find molecules that may have interesting biological properties in areas of chemical space that may not have been explored. As with any synthetic strategy there is a risk when incorporating this mode of thinking. With no biological target in mind it may be difficult to rationalize your target and develop new innovative chemistry (publishable chemistry). To circumvent this potential roadblock, it is of utmost importance to develop novel methodology in building the central scaffold or core structure.

The use of building blocks in organic synthesis have been important for the development of natural products. These advanced synthons can serve as important intermediates in complex multi-step syntheses, or for the construction of central core (scaffolds) armed for future diversification (Figure 1). Scaffolds that can be generated in a facile manner with multiple points of diversity or “handles” for subsequent manipulation is important when designing target molecules. A typical scaffold should have at least two to three points of manipulation so small libraries of 40-60 compounds can easily be produced from common diversification reactions.



**Figure 1.** DOS approach towards exploration of chemical space.

This summer my research students will continue to develop a new and novel methodology utilizing the reactivity of acyliminium ions<sup>2</sup> to build a number of innovative molecules. We will be interested in developing our scaffold utilizing a new multi-component reaction that we have begun to develop over the past 1.5 years. The primary goal in this project is to generate isoxazolidine scaffolds in a multi-component reaction. Initially the reaction will be conducted in a step-by-step manner but eventually the reaction will be run in a single pot in attempt to reduce or eliminate “organic waste” and make the reaction “greener”.

<sup>1</sup> (a) Burke, M. D.; Schreiber, S. L., *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L., *J. Am. Chem. Soc.* **2004**, *126*, 14095-14104.

<sup>2</sup> (a) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497