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Recently, diversity-oriented synthesis (DOS) has become a major focus of contemporary biomedical research.¹ 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

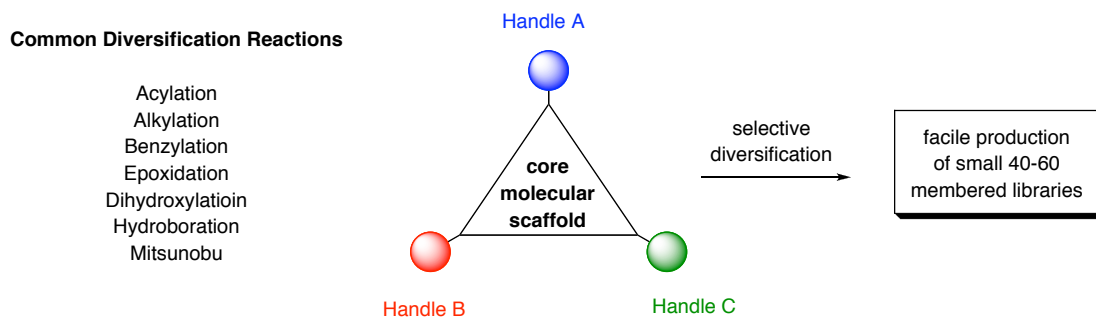


Figure 1. DOS approach towards exploration of chemical space.

This summer my research group will develop a new and novel methodology utilizing the reactivity of acyl iminium ions² to build a number of core scaffolds. We will be interested in developing our scaffolds utilizing multi-component reactions to maximize diversity of the core structure. We will further investigate this new methodology using “green chemistry conditions” further reduce waste generated from typical organic processes. Once the scaffold is in hand we will turn to the diversification of the core to generate a small 40-60-member library, which can be tested for biological testing.

¹ (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.

² (a) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

[3+2] additions

Tamura, O.; Mitsuya, T.; Huang, X.; Tsustume, Y.; Hattori, S.; Ishibashi, H. *J. Org. Chem.* **2005**, *26*, 10720-10725.

DOS papers (the first is a good overview)

(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.

N acyl iminium complexes

1) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

2) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497

[3+2] additions

Tamura, O.; Mitsuya, T.; Huang, X.; Tsustume, Y.; Hattori, S.; Ishibashi, H. *J. Org. Chem.* **2005**, *26*, 10720-10725.

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