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Forced Orthogonality in Chemical Synthesis

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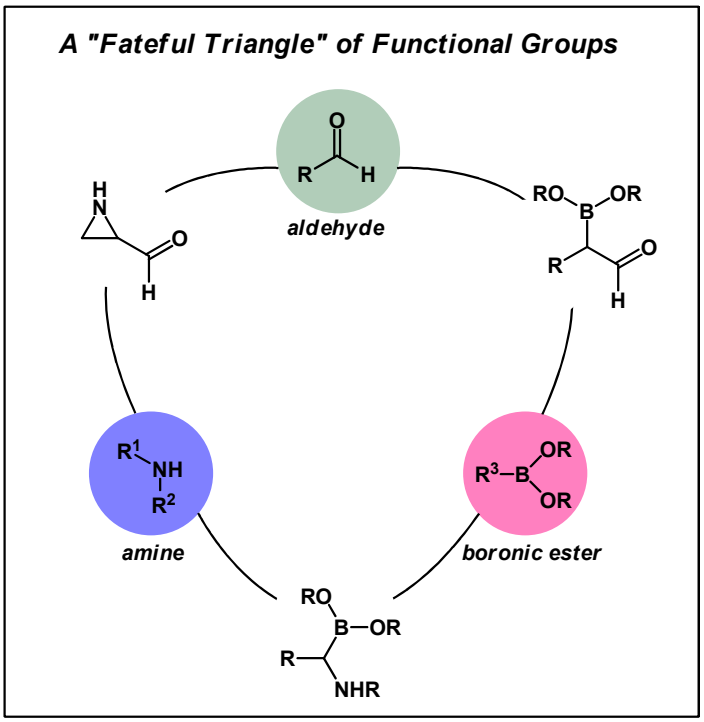
Over the past seven years, my lab has been exploring the use of amphoteric molecules in chemical synthesis. What started as a curiosity-driven project, has turned into a sustained exploration of a virtually untouched segment of chemistry characterized by molecules with unusual combinations of functional groups. The multifunctional nature arising from forced orthogonality enables amphoteric molecules to participate in reactions of high atom- and step- economy, thereby enabling efficient synthesis characterized by minimal reliance on protecting groups.



In this lecture, I will illuminate several classes of reagents developed in our lab. I will discuss the discovery of bench-stable aldehydes equipped with a C-B bond at the alpha position. These intriguing molecules have enabled the synthesis of a rich palette of other reagents that contain carbon-boron bonds at strategic positions. With the growing repertoire of boron-containing amphoteric molecules, we are in a good position to explore ideas that range from reaction discovery to the synthesis of boron-based biologically active compounds.

I will also present the evolution of peptide macrocyclization technology driven by amphoteric aziridine aldehydes. As part of this study, we are attempting to understand the conformational preferences of peptide macrocycles. As a result, we are moving closer to our ultimate goal of rationalizing the behavior of a wide range of substrate classes in our cyclization reactions, as well as understanding cellular activity of macrocycles. I will conclude my talk with a discussion of our integrative macrocyclization approaches and will present recent results of our protein crystallization efforts.