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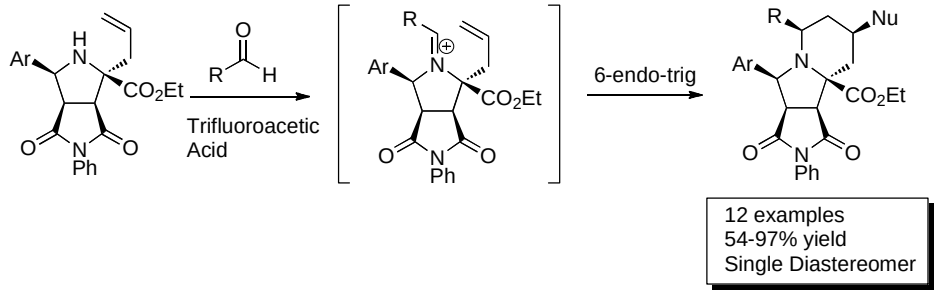
Construction of *N*-Heterocycles via Aza-Prins Cyclization and 1,3-Dipolar Cycloaddition

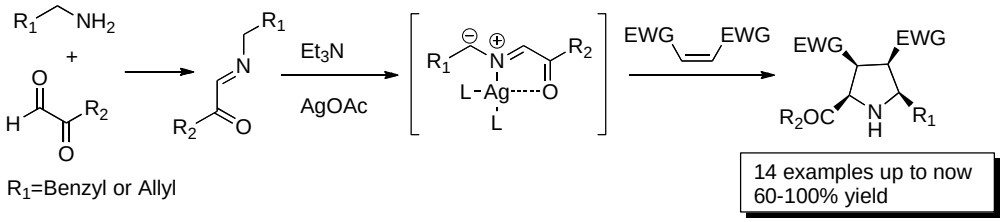
Among the methods to construct nitrogen-containing heterocyclic scaffolds, aza-Prins cyclizations and 1,3-dipolar cycloadditions have emerged as two powerful strategies. Our recent work, reported herein, involves the facile synthesis of indolizidines through aza-Prins cyclizations of 2-allyl prolines, and a new way to generate azomethine ylides for further elaboration to pyrrolidine systems.

The indolizidine scaffold is prevalent in numerous structurally complex and biological active natural products. For this reason, numerous studies have been aimed toward developing efficient methods for their creation. We report a diastereoselective construction of indolizidines by treating 2-allyl prolines with aldehydes in aqueous media. Upon iminium ion formation, aza-Prins cyclization occurs readily with a variety of nucleophiles. Using our method, we have successfully prepared a series of highly functionalized, polycyclic indolizidine structures in good to excellent yields. Importantly, only one diastereomer is observed for each system (Scheme 1).



Scheme 1. The aza-Prins cyclization strategy toward indolizidine scaffolds.

A conceptually new route to azomethine ylide was also discovered recently in our lab that offers a valuable alternative to traditional methods relying on the condensation of amino acid esters with aldehydes. Our new strategy provides a shortcut to azomethine ylides that are not readily accessible by current methodologies. With α-keto aldehydes, benzyl amines and allyl amines were employed to form imines, which are readilty deprotonated to generate azomethine ylides at room temperature upon chelation with a metal (Scheme 2). The scope of this process has been investigated, including screening the amine, aldehyde and dipolarophile components. Excellent yields and high levels of diastereoselectivity have been obtained.



Scheme 2. A new route to azomethine ylide followed by 1,3-dipolar cycloaddition.