Lewis Acid Catalyzed Domino Generation/[2,3]-Sigmatropic Rearrangement of Ammonium Ylides to Access Chiral Azabicycles

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The *N*-fused azabicycle with a bridgehead quaternary center in fused 5/X (X = 5, 6, 7) rings is one of the most ubiquitous bicyclic structural frameworks. This motif is also the central structural unit found in a large number of therapeutics and natural products. Professor Min Zhang, from Chongqing University (P. R. of China), whose group has a long-standing interest in the total synthesis of complex natural products, explained that – from the chemistry viewpoint – the development of efficient reactions to construct such bicyclic ring systems remains a daunting challenge for organic chemists, presumably because of the problems associated with quaternary stereogenic center installment, as well as the inefficiency of bicyclic framework construction.[1] "Among the existing strategies to build this type of bicyclic skeleton, many are focused on the generation of the bridgehead quaternary stereogenic center and the bicyclic framework in multi-step ways, whereas efficient methods capable of combining these two events in one step are still very limited," said Professor Zhang.

[2,3]-Sigmatropic rearrangement of ammonium ylides is one of the most efficient approaches for synthesizing complex nitrogenous compounds.[2,3] During the rearrangement, a new stereogenic carbon center can be stereoselectively created by chiral induction of the neighboring chiral ammonium nitrogen atom through a concerted five-membered-ring transition state. "The most common way to generate the ammonium ylides for the rearrangement requires two separate steps: quaternization of a tertiary amine, then deprotonation of the resulting quaternary ammonium salt with a strong base.[2,3] The harsh reaction conditions needed for the preparation and deprotonation of the quaternary ammonium salts, as well as the problems associated with purification of ammonium salts, limit the application scope of this type of reaction," explained Professor Zhang.

Recently, a collaborative effort between the group of Professor Zhang and that of Professor Yu Lan uncovered a Lewis acid catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides, by which *N*-fused azabicyclic skeletons featuring various ring systems (5/X, X = 5, 6, 7) and bridgehead quaternary stereogenic centers were constructed simultaneously (Scheme 1). "The ammonium ylides were generated under mild reaction conditions by using a π-Lewis acid silver salt as the catalyst without a strong base, which is a requisite in traditional approaches to these compounds,[4]" said Prof. Zhang. He continued: "This protocol is compatible with racemization-prone substrates and consequently the chirality information originating from the chiral amino acids is efficiently transferred, furnishing a series of *N*-fused azabicycles in high enantiomeric purity (up to 99% ee)." Combined with density functional theory (DFT) calculations, the experimental results revealed that: 1) the reaction process involves four steps: tertiary amine quaternization, water-assisted protonation and deprotonation, and propargylic or allylic [2,3]-sigmatropic rearrangement; 2) protonation of the C–Ag bond largely increases the acidity of the C2-H and occurs prior to its deprotonation. "Both events were assisted by the residual water in the reaction system, which leads to the generation of ammonium ylides under mild conditions, without the involvement of strong bases, thus resulting in almost no chirality erosion," remarked Prof. Zhang. Following on the success of using a silver salt as the catalyst, and as an extension of this protocol, replacing the silver catalyst with a stoichiometric amount of I_2 generated the corresponding iodinated *N*-fused azabicycles with more handles for further synthetic elaboration.[5] Prof. Zhang concluded: "Considering the easy accessibility of the chiral precursors, this method represents a new mild way to generate ammonium ylides, and provides a new efficient method to construct *N*-fused azabicycles with a bridgehead quaternary center in various ring sizes."

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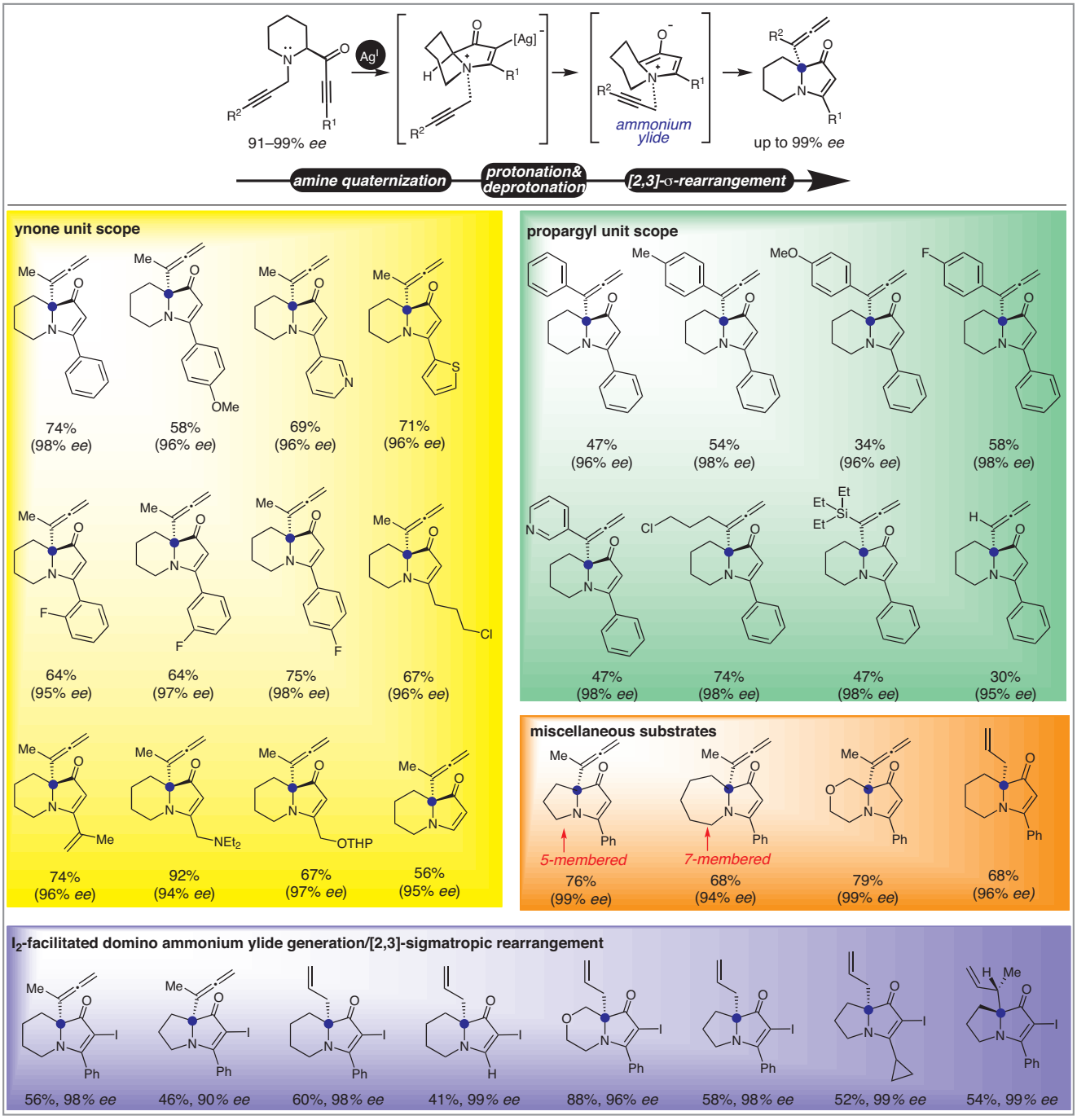

Scheme 1 π-Acid-catalyzed domino ammonium ylide generation/[2,3]-Stevens rearrangement

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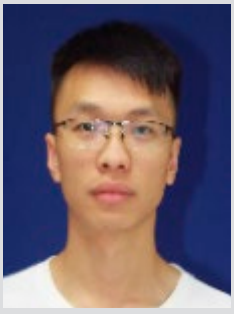

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