Catalytic One-Step Synthesis of Unprotected Piperazines, Morpholines and Thiomorpholines using SnAP Reagents

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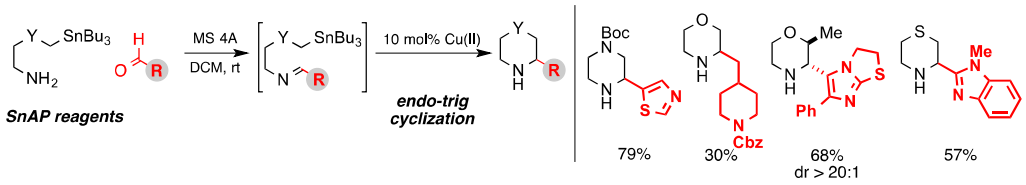
Saturated N-heterocycles have long been considered as privileged elements for the preparation of bioactive small molecules. Increasing recognition of problems associated with aromatic pharmacophores, such as poor solubility, bioavailability, or pharmacokinetics have further enhanced their importance in drug development.[1] Despite this, their synthesis often have considerable limitations, including harsh reaction conditions, restricted substrate scope, long synthetic routes, and intractable protecting groups. To directly access a variety of saturated N-heterocycles in a single synthetic operation, we have recently introduced SnAP (Stannyl Amine Protocol) reagents, which convert aldehydes and ketones into (thio)morpholines, piperazines, diazepanes, spiro- and other N-heterocycles.[2–6]

The major limitation using the SnAP reagents is the need for stoichiometric copper reagents. We have now identified new ligands and conditions that render the reaction catalytic in copper and expanded the substrate scope including □-bis(substituted) SnAP reagents. These studies, including approaches towards an enantioselective process and insights into the unique reaction mechanism, will be discussed.



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