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Stannyl Amine Protocol (SnAP) Reagents

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Abstract: Saturated *N*-heterocycles are of growing interest in drug discovery due to their increased solubility, bioavailability, and pharmacokinetics over their aromatic counterparts. Recently, the use of Stannyl Amine Protocol (SnAP) reagents have shown a great promise for the direct synthesis of a broad range of saturated *N*-heterocycles.

Keywords : N-heterocycles, bioavailability, Pharmacokinetics, SnaP

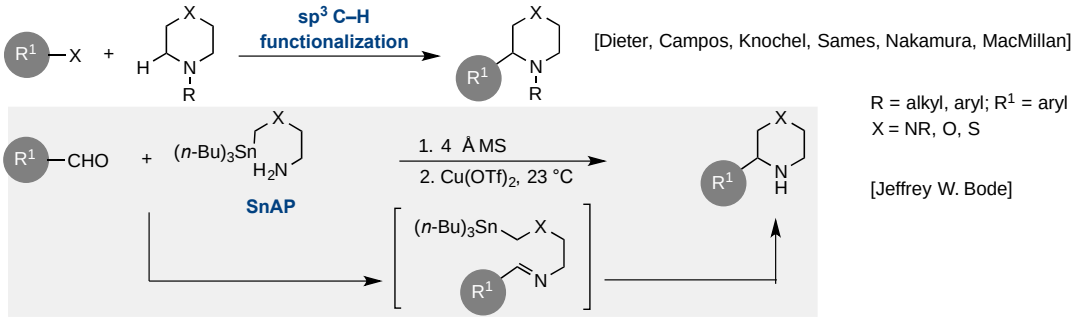
Introduction

Saturated *N*-heterocycles are prevalent in biologically active and medicinally significant molecules. It may contain chiral centers, spirocyclic structures shows the advantage in solubility, bioavailability, pharmacokinetics over their aromatic counterparts which became a considerable interest in drug development.[1] Efficient syntheses of these building blocks are of longstanding interest. Several advances have been made through the years; however they are limited by their lengthy synthetic routes, which impacts their commercial availability. Recently the research group led by Prof. Jeffrey W. Bode at ETH-Zürich reported Stannyl Amine Protocol (SnAP) reagents for the direct syntheses of a broad range of saturated N-heterocyles.

SnAP Reagents: Development

C–H functionalizations are known synthetic methods for the syntheses of saturated *N*-heterocycles but are limited by the requirement of *N*-protecting groups that need to be removed for further elaboration, harsh reaction conditions and narrow substrate scope.[2] Stannyl Amine Protocol (SnAP) reagents were first reported for the synthesis of saturated *N*-heterocycles in 2013.[3] The concept of SnAP reagents evolved from the idea that an aldehyde could couple intermolecularly with a tethered amine to form the imine followed by intramolecular cyclization to form the saturated *N*-heterocyclic ring. Inspired by the intermolecular addition of organostannanes to imine reported by the group of Kagoshima in the early 2000's,[4] Jeff W. Bode's

Scheme 1. **C–H Functionalization Methods and SnAP Reagents**

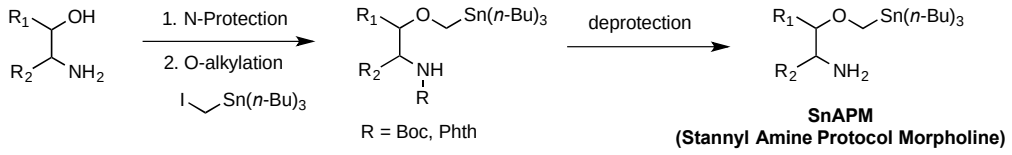


research group found that tributyl stannanes functional group serve as the ideal intramolecular coupling partners with the formed imine (Scheme 1).

SnAP Reagents: Synthesis

SnAP reagents can be prepared in a very straightforward and efficient way from commercially available starting materials. Currently, many SnAP reagents are commercially available from the chemical company Aldrich to synthesize saturated *N*-heterocycles including spirocyclic and bicyclic structural motifs. For example synthesis of SnAP Morpholine (M) started with *N*-protection of simple amino alcohols followed by O-alkylation with tributyl(iodomethyl)stannane and deprotection to yield SnAPM reagents (Scheme 2). SnAP reagents can be easily handled, and air -and moisture-stable and can be stored at -10 °C for months without much decomposition.

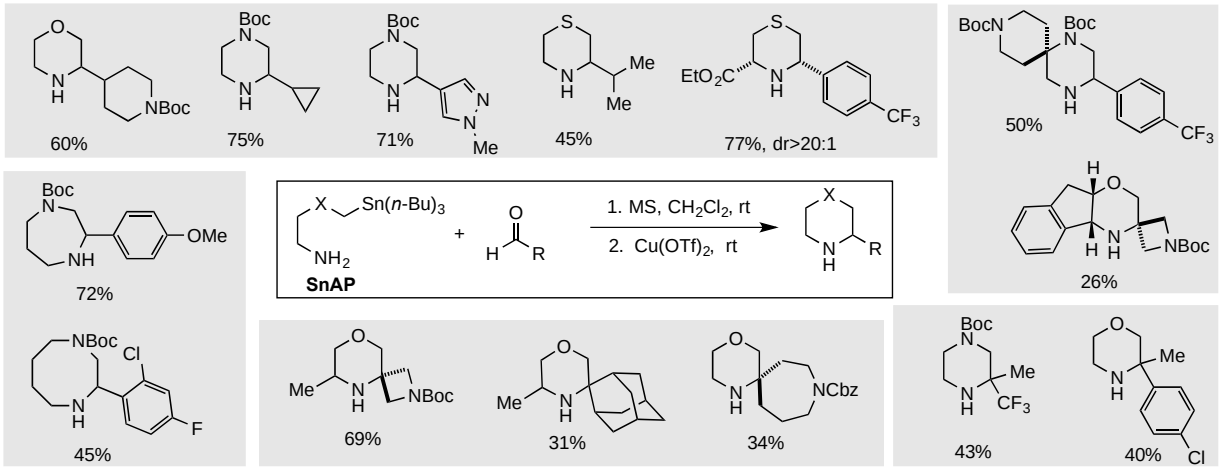
Scheme 2. **Example of the Synthesis of SnAP Reagent**



SnAP Reagents: Application

SnAP reagents can be coupled with a broad variety of aliphatic, aromatic, heteroaromatic, glyoxylic aldehydes and ketones in presence of stoichiometric $Cu(OTf)_2$ to synthesize various saturated *N*-heterocyles including thiomorpholines, morpholines, piperazines, diazepanes, ozazepanes, diazocanes, oxazocanes, other medium sized heterocycles, and spirocycles. [1b,1c,5]

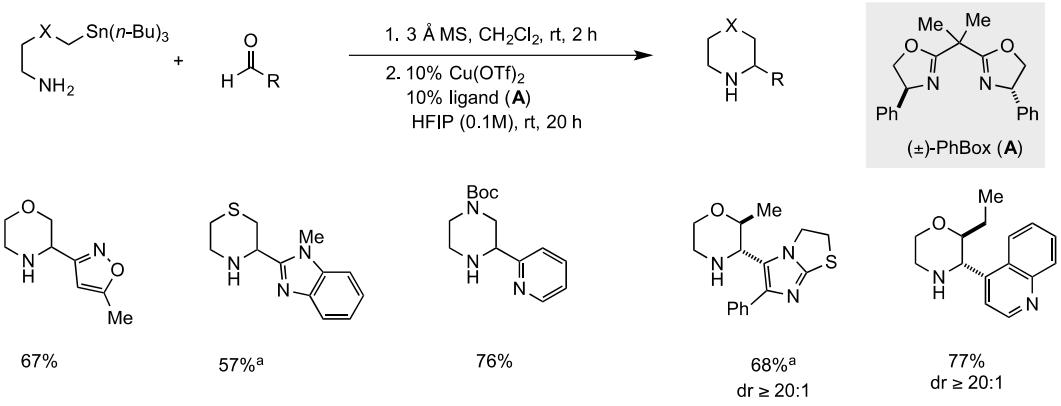
Scheme 3. **Application of SnAP reagents in the synthesis of Saturated *N*-Heterocycles**



SnAP Reagents: Catalytic Synthesis of Saturated *N*-Heterocycles

Recently, the Bode group reported ligand-accelerated SnAP reactions using a catalytic amount of $Cu(OTf)_2$ to synthesize a broad range of saturated N-heterocycles.[6] This catalytic method expanded the substrate scope to include 2-(pyridine)piperzine moieties which was difficult to access using stoichiometric $Cu(OTf)_2$.

Scheme 3. **Catalytic synthesis of Saturated *N*-Heterocycles**



[a] 20% $Cu(OTf)_2$, 20% **A** [b] HFIP = hexafluor-2-propanol

Conclusion:

Since the first report of Stannyl Amine Protocol (SnAP) reagents in 2013, numerous SnAP reagents have been reported in the last two years. SnAP reagents can be easily prepared (some of them are commercially available), are stable and allow for the direct synthesis of medium-sized saturated *N*-heterocycles, bicycles and spirocycles. Recently a catalytic SnAP reaction was reported with expanded substrate scope. Remaining limitations include the use of toxic organotin reagents and the synthesis of enantioriched *N*-heterocycles.

Acknowledgements

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