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SnAP-eX Reagents for the Synthesis of Exocyclic 3-Amino- and 3-Alkoxy Pyrroldines and Piperidines From Aldehydes

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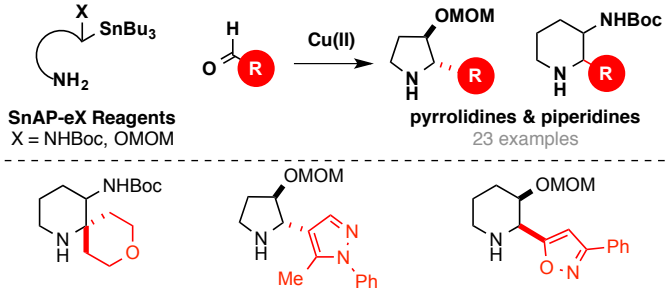
Supporting Information Placeholder



ABSTRACT: SnAP-eX (tin amine protocol, exocyclic heteroatoms) reagents allow the single-step transformation of aldehydes and ketones into 2,3-disubstituted pyrrolidines and piperidines containing exocyclic amine or alkoxy groups. These saturated N-heterocycles are of importance in modern drug discovery approaches and are prepared in moderate yields using an operationally simple protocol that is compatible with a range of functional groups and heterocyclic aldehydes.

Saturated N-heterocycles are key elements of pharmacologically active small molecules and natural products.[1] With the goal of developing predictable cross-coupling approaches towards these scaffolds, we recently introduced SnAP (tin amine protocol) reagents for the simple conversion of widely available aldehydes and ketones into functionalized, unprotected N-heterocycles (Figure 1).[2] Thiomorpholines,[3] morpholines,[3b,4] piperazines,[3b,4] diazepanes,[5] and other medium sized scaffolds and spirocyclic structures[4b,c] are readily produced using commercially available SnAP reagents with a mild and general reaction protocol.

Two of the most common saturated N-heterocycles used in drug discovery, substituted piperidines and pyrrolidines,[6] were not accessible using SnAP reagents, as a proximal heteroatom is needed to lower the oxidation potential of the C–Sn bond and stabilize the resulting radical.[7] We recognized that a limited, but important, class of these scaffolds could be prepared by SnAP reagents bearing a radical-stabilizing heteroatom that would end up exocyclic – rather than endocyclic – to the resulting saturated N-heterocycles. Towards this goal, we now document the synthesis and applications of SnAP-eX reagents for the preparation of substituted piperidines and pyrrolidines bearing an exocyclic N-Boc or O-MOM group (Figure 1).

Piperidines and pyrrolidines with exocyclic heteroatoms are found in many pharmaceuticals and make up the basic skeleton of various alkaloids.[8] For example, the non-peptidic NK-1 receptor antagonists (+)-CP-99,994, (+)-CP-122,721, or (+)-LP-733,060 all derive from 2-phenylpiperidin-3-ol.[9] Current synthetic approaches include intramolecular hydroamination,[10] hydrogenation of heteroaromatics,[11] C–H functionalizations,[12] intramolecular cyclizations,[13]

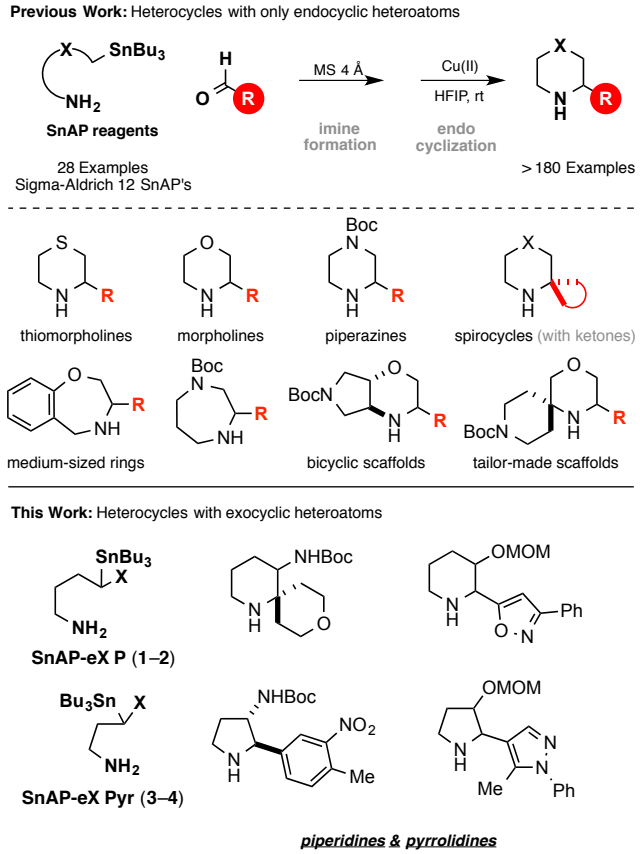


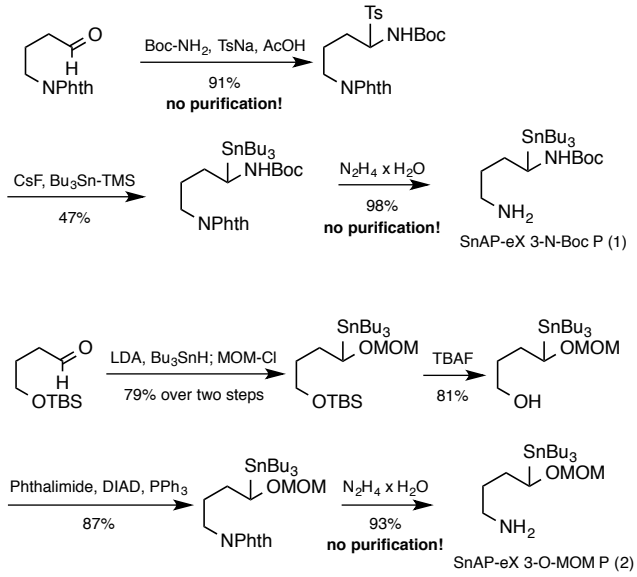
Figure 1. Synthesis of saturated N-heterocycles using SnAP reagents.

and annulations with sulfonium salts,[14] nitrones,[15] or cycloaddition partners.[16] While such approaches are suitable once a lead compound is identified, the substituent groups must be introduced at an early stage of the synthesis, making them less appealing in drug development and limiting their synthetic utility for library syntheses.

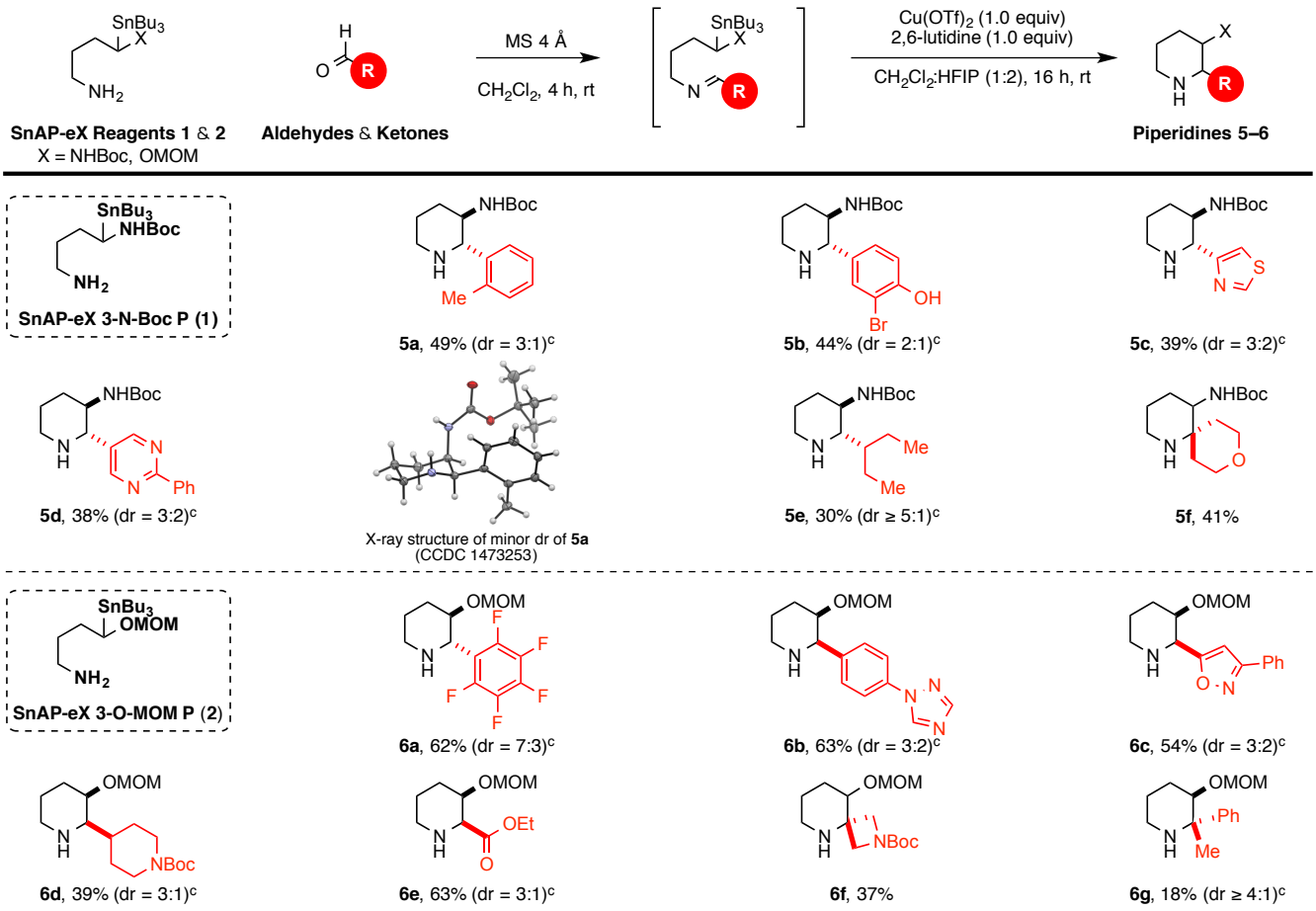
As a first test of using exocyclic heteroatoms, we designed and prepared SnAP-eX 3-N-Boc P (**1**) and SnAP-eX 3-O-MOM P (**2**) on a multigram scale by straightforward and efficient routes (Scheme 1, see Supporting Information for full synthetic details). Like other SnAP reagents, they can be stored for weeks without decomposition.[17]

SnAP-eX 3-N-Boc P (**1**) smoothly condensed with aldehydes to give imines that were cyclized to piperidines under our standard stoichiometric conditions for endocyclic SnAP reagents: 1.0 equiv $Cu(OTf)_2$ and 1.0 equiv 2,6-lutidine in CH_2Cl_2-HFIP (Scheme 2).[18] No special precautions were necessary for reaction set-up and all experiments were performed using identical reaction conditions without substrate-specific optimization. Aldehydes containing various functional groups, including aryl halides (**5b**), unprotected phenols (**5b**), heterocycles (**5c**, **5d**), or alkyl moieties (**5e**) were excellent substrates, leading to 3-amino-piperidines suitable for further elaboration. In preliminary studies, ketones were also suitable reactants, allowing the synthesis of functionalized spirocycles (**5f**, **6f**) that provide rigid, metabolically robust frameworks.[19]

Scheme 1. Synthesis of SnAP-eX reagents 1 and 2.



Scheme 2. Synthesis of 3-NHBoc- and 3-OMOM piperidines from SnAP-eX reagents.[a,b]



[a]Conditions: SnAP-eX 3-N-Boc P (**1**) or SnAP-eX 3-O-MOM P (**2**) (1.0 equiv, 0.5 mmol), aldehyde (1.0 equiv, 0.5 mmol), MS 4 A, CH_2Cl_2 (0.2 M), 2–6 h, rt; $Cu(OTf)_2$ (1.0 equiv, 0.5 mmol), 2,6-lutidine (1.0 equiv, 0.5 mmol), 1:2 CH_2Cl_2:HFIP (0.05 M), 16 h, rt; combined isolated yield of major and minor diastereomer; major diastereomer shown. [b]Ketimine formation using ketones: SnAP-eX **1** or

SnAP-eX **2** (1.0 equiv, 0.5 mmol), ketone (1.0 equiv, 0.5 mmol), MS 4 A, toluene (0.5 M), 12 h, 100°C. [c]Diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures.

The same conditions could also be used for the SnAP-eX 3-O-MOM P (**2**) reagent, with similar substrate scope and slightly better isolated yields. In all cases, we observed only modest diastereoselectivity. A slight preference for *trans*-products was observed in N-Boc series, while *cis*-products were usually favored with the O-MOM reagents. In any case, the effects were small and the diastereoselectivities were modest; improvements with different catalysts or conditions are ongoing.

The synthesis of pyrrolidines under similar conditions with SnAP-eX 3-N-Boc Pyr (**3**) or SnAP-eX 3-O-MOM Pyr (**4**) – prepared by analogous routes to their homologues – showed the same broad substrate scope and functional group tolerance (Figure 2).

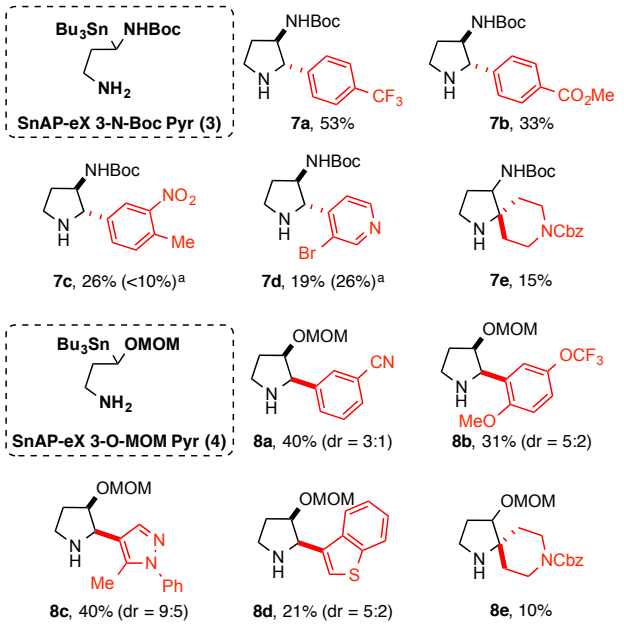


Figure 2. Synthesis of 3-amino-/3-alkoxy-pyrrolidines. All reactions were performed using 1.0 equiv of SnAP-eX **3** or SnAP-eX **4**, 1.0 equiv of aldehyde or ketone, 1.0 equiv of $Cu(OTf)_2$, 1.0 equiv of 2,6-lutidine in 1:2 CH_2Cl_2:HFIP (0.05 M) at rt for 16 h; combined isolated yield of major and minor diastereomer; major diastereomer shown. Diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. [a]0.5 equiv $(CF_3SO_3Cu)_2$ x $C_6H_5CH_3$ in 1:2 CH_2Cl_2:HFIP (0.05 M) at rt for 12 h; isolated yield.

Esters (**7b**), nitriles (**8a**), nitro groups (**7c**), and various heterocycles (**7d**, **8c**, **8d**) are viable substrates. Electron-rich aromatic and heteroaromatic or bulky aldehydes/ketones afforded higher amounts of protodestannylated side products (**7d**, **7e**, **8d**, **8e**), but some amounts of the desired products could be isolated. The formation of these products requires a disfavored 5-*endo*-trig cyclization,[20] which may be responsible for the lower isolated yields than those observed for the piperidine formations. In some cases, (i.e. **7d**) we found the use of alternative copper sources provided a small boost in isolated yield, suggesting that further substrate specific optimization will be possible. Despite the modest yields, SnAP-eX reagents provide a direct method for preparing *N*-unprotected 2,3-disubstituted pyrrolidines.

Support for *cis*/*trans* stereochemical assignment in 2,3-disubstituted piperidines was obtained by X-ray analysis of *cis*-**5a**, of the HCl salt of *cis*-**6a** and *trans*-**6a** as its *p*-nitrobenzoyl derivative **9** (Figure 3). *trans*-2,3-Disubstituted pyrrolidines were isolated using SnAP-eX **3,** while mixtures of separable diastereomers were obtained in the synthesis of 3-alkoxy-pyrrolidines using SnAP-eX **4**. In this case, the *cis*-configured diastereomer was usually the major component.[21] The relative configuration of pyrrolidines was established spectroscopically as the $J_{2,3}$ values of the diastereomers are significantly different and in agreement with reported data of related products.[21]

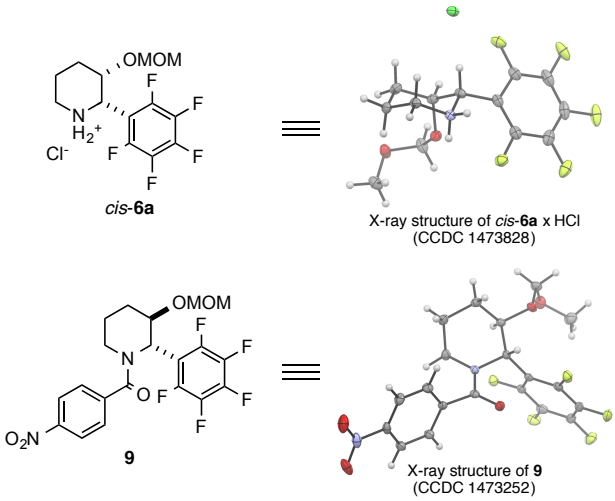
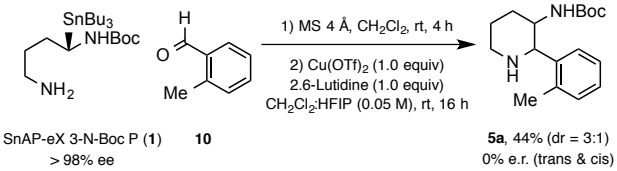


Figure 3. X-ray structures of *cis*-(±)-**6a** and *trans*-(±)-**9**.

The proposed mechanism of the SnAP chemistry involves oxidation of the C–Sn bond by Cu(II), leading to a heteroatom-stabilized carbon radical.[3,5] To date, all experiments are consistent with this proposed mechanism, but we cannot completely rule out a Sn to Cu transmetallation followed by nucleophilic addition to the imine. Examples of such transmetallations are known and have been reported to occur with stereoretention.[22] As a test for the proposed radical pathway, enantiomerically enriched SnAP-eX **1** was prepared. Using this reagent under the standard conditions, the piperidine product **5a** was formed as a racemate (Scheme 3). While still not conclusive, this observation further supports a free-radical mechanism for Cu-promoted SnAP chemistry.

Scheme 3. Racemization studies using enantiomerically enriched SnAP-eX 1.



In conclusion, SnAP-eX reagents enable systematic, flexible, and efficient access to diverse *N*-unprotected, saturated piperidines and pyrrolidines with the same remarkably broad scope of reaction partners that characterizes SnAP chemistry. The moderate yields of N-heterocycle formation using

SnAP-eX reagents **1**–**4** are attributed due to decreased reactivity of the secondary radicals and increased ring-strain in the formation of 5-membered rings. While this approach may not be suitable on large scale once a lead compound is identified, it is an appealing approach to library synthesis and structure-activity relationship studies as it offers a reliable and predictable route to important scaffolds for drug discovery and lead optimization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, spectral data for all new compounds, and X-ray crystallographic data for *cis*-(±)-**5a**, *cis*-(±)-**6a** and *trans*-(±)-**9** (PDF)

X-ray crystallographic data for *cis*-(±)-**5a** (CIF), *cis*-(±)-**6a** (CIF) and *trans*-(±)-**9** (CIF)

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Notes

The authors declare no competing financial interest.

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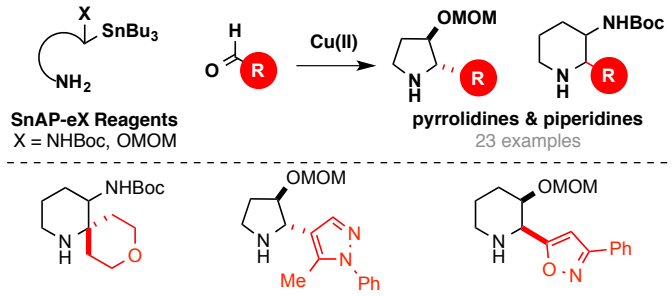

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