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SnAP Reagents for the One-Step Synthesis of Medium Ring Saturated N-Heterocycles from Aldehydes

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Abstract

Saturated N-heterocycles are increasingly interesting scaffolds for the synthesis of bioactive molecules. Reliable and predictable synthetic methods for the preparation of these compounds, especially medium-sized rings, are limited. We describe the development of SnAP reagents for the transformation of aldehydes into 7, 8 and 9-membered saturated N-heterocycles. This process occurs under mild, room temperature conditions and offers exceptional substrate scope and functional group tolerance. Air- and moisture-stable SnAP reagents are prepared on multigram scale from inexpensive starting materials by simple reaction sequences. These new reagents and processes allow widely available aryl, heteroaryl and aliphatic aldehydes to be converted to diverse N-heterocycles including diazepanes, oxazepanes, diazocanes, oxazocanes, and hexahydrobenzoxazonines by a single synthetic operation.

Cross-coupling reactions for the elaboration of heteroaromatics have revolutionized organic synthesis and influenced enormously the synthesis of biologically active small molecules.[1–3] Recently, well-recognized limitations in the solubility, pharmacokinetics, bioavailability, and IP positions of heteroaromatics have led many scientists to favor saturated N-heterocycles in their drug development efforts.[4–8] The shift towards saturated compounds, which may contain chiral centers and be derived from larger rings or spirocyclic structures, raises synthetic challenges that are not addressed by the convenience and predictability of conventional metal-catalyzed cross coupling reactions.

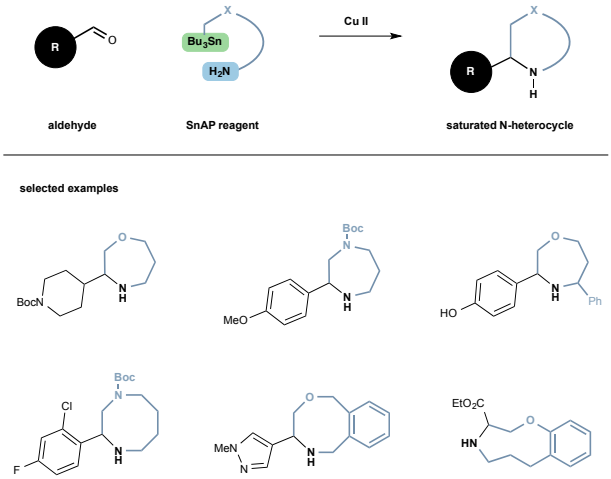


Figure 1 | SnAP reagent concept. The simple transformation of readily available aldehydes into substituted saturated medium ring N-heterocycles using SnAP reagents (SnAP = Tin(Sn) Amino Protocol). This approach provides a convenient alternative to metal-catalyzed cross-coupling reactions and affords unprotected saturated heterocycles in one step. Selected compounds are representative of the broad aldehyde scope and exemplify the one step synthesis of diazepanes, oxazepanes, benzoxazocanes, and other medium ring saturated N-heterocycles difficult to access by existing methods. Boc = *tert*-butoxycarbonyl.

In seeking to provide alternatives to cross-coupling of saturated N-heterocycles, we have recently introduced SnAP reagents for the synthesis of thiomorpholines from aldehydes.[9] This process employs widely available aliphatic, aryl, and heteroaryl aldehydes as cross-coupling substrates and operates under mild conditions. It affords directly *N*-unprotected products, has

outstanding substrate scope, and offers an easily recognized retrosynthetic disconnection for the preparation of mono-, di-, and trisubstituted thiomorpholines. Preliminary mechanistic studies invoked oxidative generation of a sulfur-stabilized primary carbon-centered radical followed by 6-*endo*-trig cyclization with an unactivated imine to form the stable aminyl radical. This surprisingly facile cyclization mode, which is favored over the expected 5-*exo*-trig cyclization, encouraged us to explore the development of SnAP reagents for the preparation of even more challenging saturated N-heterocycles derived from 7, 8, or 9-membered ring scaffolds with other heteroatoms such as oxygen and nitrogen to stabilize the initially formed primary carbon-centered radical (Fig. 1).

In this report we disclose new SnAP reagents for the synthesis of 7, 8, and 9-membered ring saturated N-heterocycles including oxazepanes, tetrahydrobenzoxazepines, diazepanes, tetrahydrobenzodiazepines, oxazocanes and others. These studies demonstrate, for the first time, that a sulfur-stabilized radical is not necessary for the success of the SnAP reagents for N-heterocycle synthesis. Despite the well-known challenges of forming larger rings,[10] this radical-based process provides a convenient, user-friendly entry into these relatively unexplored scaffolds for drug discovery and development. It also further confirms the exceptional substrate scope of the reaction, which accepts aryl, heteroaryl, aliphatic, halogenated, and glyoxylate aldehyde substrates.

Results

The requisite SnAP reagents suitable for the synthesis of 7, 8, and 9-membered saturated N-heterocycles including diazepanes, oxazepanes, and others were prepared on a multigram scale from inexpensive starting materials, by straightforward and efficient routes (Fig. 2; see Supplementary Information for detailed synthetic procedures). The SnAP reagents are easily handled, air- and moisture-stable liquids that can be stored for several weeks without decomposition.

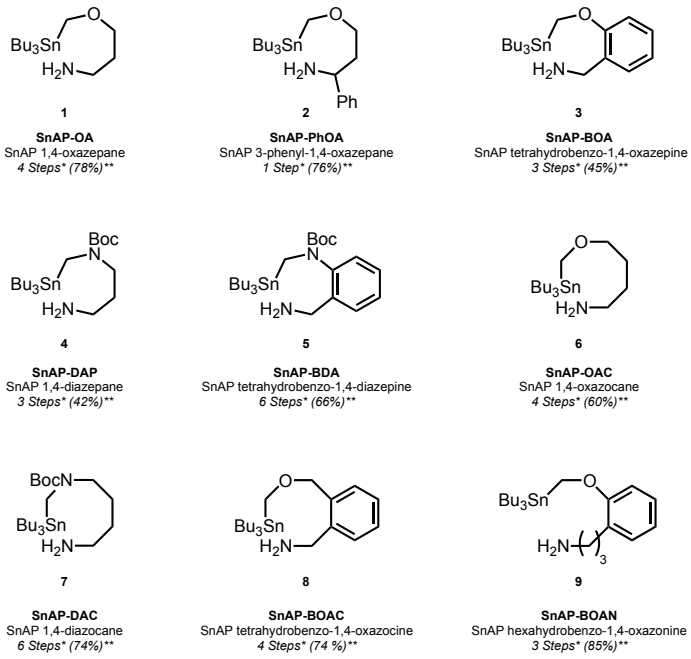


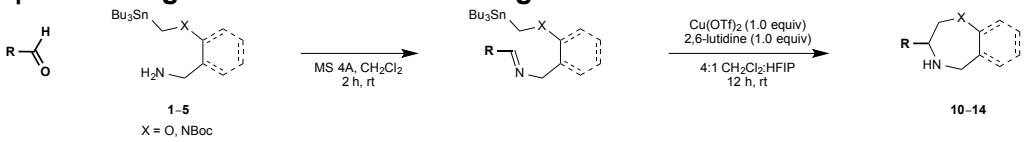
Figure 2 | SnAP reagents for 7, 8 and 9-membered ring synthesis. Stable and easily handled SnAP reagents prepared in short reaction sequences. * Steps from commercially available materials. ** Overall yield from commercially available starting materials. Boc = *tert*-butoxycarbonyl.

With these new SnAP reagents in hand, we explored the transformation of various aldehydes into substituted 7, 8 and 9-membered N-heterocycles. For the purposes of evaluation, we used a single reaction protocol for all of the SnAP reagents and aldehyde substrates. We anticipate that substrate specific optimization of the results will be possible if higher yields or faster reaction times are necessary. An advantage of this method for N-heterocycle synthesis is the operationally simple reaction protocol: combination of the SnAP reagent with the aldehyde gives the corresponding imine, which is cyclized with stoichiometric $Cu(OTf)_2$ and 2,6-lutidine in 4:1 CH_2Cl_2:HFIP at rt for 12 h. The imines were isolated by filtration and evaporation to ensure full conversion before subjection to the cyclization. Alternatively, the imine formation reaction can be diluted with additional CH_2Cl_2 and transferred to the copper/ligand mixture by a syringe equipped with an HPLC filter (**10a**, Table 1).

Synthesis of saturated 7-membered rings

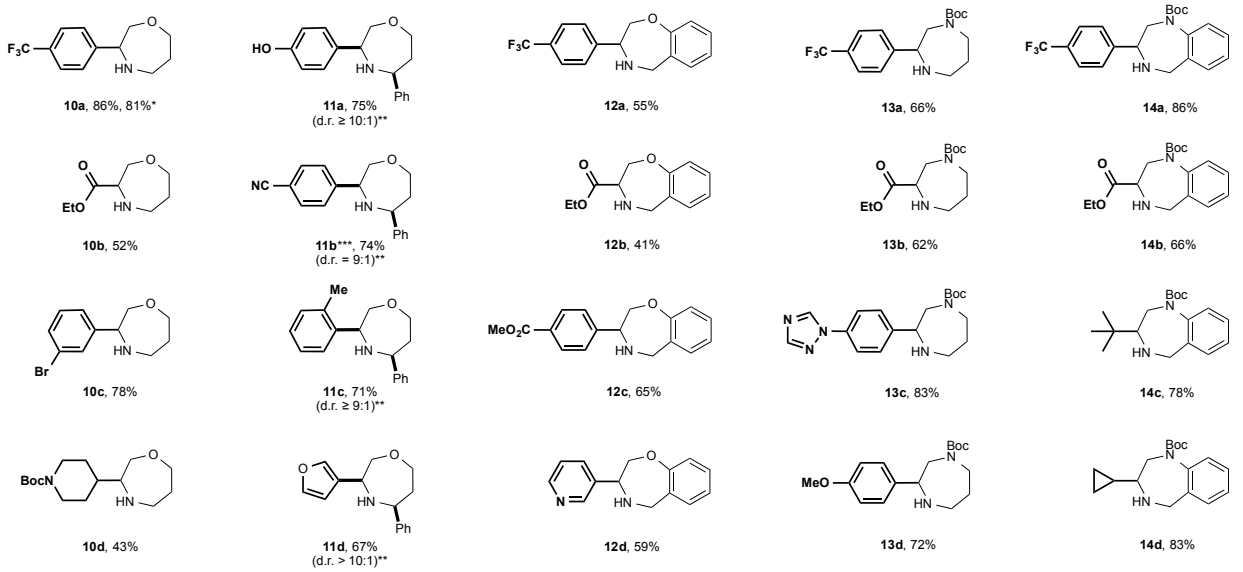
We first targeted the synthesis of oxazepanes, diazepanes and their derivatives, as these structures are both attractive scaffolds for medicinal chemistry and difficult to prepare by convenient, predictable synthetic methods. The transformation of aldehydes to these substituted 7-membered N-heterocycles using SnAP reagents **1**–**5** was examined using a series of aryl, heteroaryl, and aliphatic aldehydes (Table 1). The reaction proceeded well with both electron-rich and electron-poor aryl and heteroaryl aldehydes to give moderate to good yields of 7-*endo* products. Similar results were obtained with either the oxygen or nitrogen based SnAP reagents **1**–**5**. Imines prepared from aliphatic aldehydes including piperidine-4-carboxaldehyde (**10d**), cyclopropanecarboxaldehyde (**14d**) and bulky pivaldehyde (**14c**) all afforded the products in good yields. Sterically demanding o-tolualdehyde (**11c**) was incorporated in good yield and functional groups suitable for further elaboration of the products including esters, organohalides, nitriles, protected amines and even unprotected phenols (**11a**) were easily tolerated under the reaction conditions. The primary side products observed in these reactions were the protodestannylated imines, which we believed were formed by competing H-atom transfer from HFIP. Benzannulated and disubstituted products were accomplished using SnAP reagents **2**–**3**, **5**. Diminished formation of destannylated products and generally higher yields were observed for the synthesis of the 5-phenyl-1,4-oxazepanes (**11a**–**11d**) and the tetrahydrobenzodiazepines (**14a**–**14d**) using SnAP **2** and **5**, presumably due to faster rate of cyclization of the pre-aligned reacting groups. The *cis* relative stereochemistry observed for the synthesis of the disubstituted oxazepanes (**11a**–**11d**) was confirmed by X-ray crystallographic analysis of **11b** (Table 1; see Supplementary Information).

Table 1 | SnAP reagents for 7-membered rings



1–**5**
X = O, NBoc

10–**14**



10a, 86%, 81%*
11a, 75% (d.r. ≥ 10:1)**
12a, 55%
13a, 66%
14a, 86%
10b, 52%
11b***, 74% (d.r. = 9:1)**
12b, 41%
13b, 62%
14b, 66%
10c, 78%
11c, 71% (d.r. ≥ 9:1)**
12c, 65%
13c, 83%
14c, 78%
10d, 43%
11d, 67% (d.r. > 10:1)**
12d, 59%
13d, 72%
14d, 83%

Reaction conditions for imine formation: SnAP reagent (0.50 mmol), aldehyde (0.50 mmol), MS 4A, CH_2Cl_2 (2.5 mL), 2 h, rt. Reaction conditions for cyclization: imine (0.50 mmol), $Cu(OTf)_2$ (0.50 mmol), 2,6-lutidine (0.50 mmol), 4:1 CH_2Cl_2:HFIP (10 mL), 12 h, rt. Yield values refer to isolated yields after purification. * The imine formation step was diluted with CH_2Cl_2 to 0.0625 M and transferred to the cyclization reaction by syringe equipped with a filter. ** Diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. *** Relative stereochemistry was confirmed by X-ray analysis of (±)-**11b** (see Supplementary Information); others assigned by analogy. Boc = *tert*-butoxycarbonyl, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Gram-scale synthesis using SnAP reagents

A larger scale synthesis using SnAP-OA **1** (5 g) was performed using standard laboratory techniques to demonstrate the ease and scalability of our protocol and avoidance of chromatographic purification. (Fig. 3; see Supplementary Information). All reagents were used as purchased and HCl salt formation of the crude product as the sole purification technique afforded the desired product 75% yield and >98% purity (cf. Table 1, entry **10a**, 86% yield).

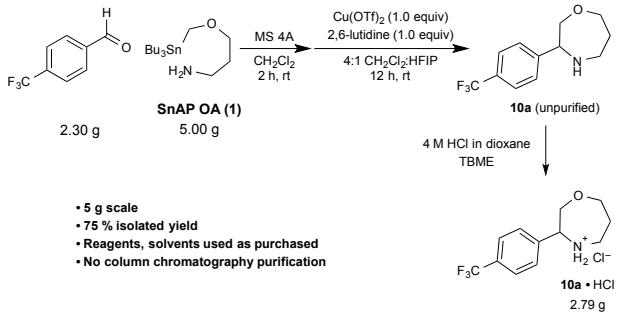


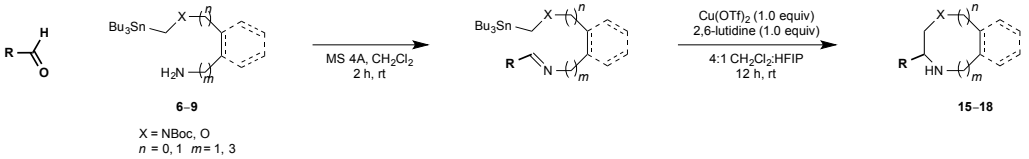
Figure 3 | Gram-scale synthesis of substituted 1,4-oxazepane. Condensation of **SnAP OA** (13.2 mmol) and *p*-trifluoromethylbenzaldehyde (13.2 mmol) afforded the corresponding imine, which was cyclized under standard protocol conditions: stoichiometric $Cu(OTf)_2$ and 2,6-lutidine in CH_2Cl_2:HFIP 4:1 at rt for 12h. The product obtained after work-up was purified by HCl salt formation to afford the desired product in 75% yield and >98% purity. Reagents and solvents are used as purchased. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Synthesis of saturated 8 and 9-membered rings

Encouraged by the successful synthesis of 7-membered ring N-heterocyles, we explored the use of SnAP reagents for the preparation of 8 and 9-membered N-heterocycles. Substituted diazocanes, oxazocanes and their benzannulated derivatives are currently little known heterocycles, perhaps due to the difficulty of preparing such molecules. The aldehyde scope was similar to that of the 7-membered ring synthesis, including aryl, heteroaryl and aliphatic aldehydes (Table 2). As anticipated, the cyclization yields were somewhat lower, with protodestannylation of the imine again as the major side product. In these cases, the electronics of the aldehyde had a strong influence on the cyclization. Electron-rich aldehydes such as *para*-anisaldehyde afforded mostly the protodestannylated imine. Higher dilution (0.02 M), the addition of $CaSO_4$ to scavenge water, or heat (60 °C in 1,2-dichloroethane) did not help to improve the ratio of product and protodestannylated side product. Introducing an aromatic ring into the tether, such as in SnAP-BOAC **8**, facilitated the cyclization and the corresponding saturated N-heterocycles were isolated in good yields with a broad substrate scope including electron-rich aldehyde (**17e**); only a small amount of the protodestannylated imine was observed. Although the yields of these substituted 8-membered ring heterocycles are modest under the current conditions, the facile synthesis of the starting materials and the lack of

convenient entry into these structures with other methods makes the use of SnAP reagents an attractive approach.

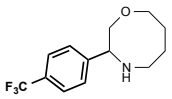
Table 2 | SnAP reagents for 8 and 9-membered rings



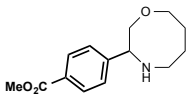
6–**9**

X = NBoc, O
n = 0, 1 *m* = 1, 3

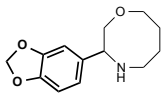
15–**18**



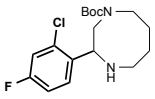
15a, 46%



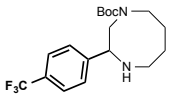
15b, 38%



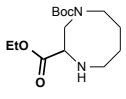
15c, 20%



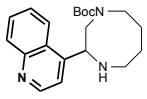
16a, 45%



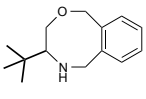
16b, 34%



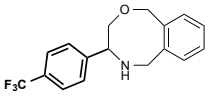
16c, 52%



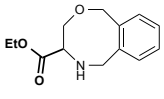
16d, 39%



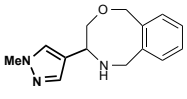
17a, 79%



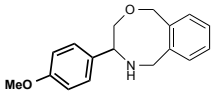
17b, 72%



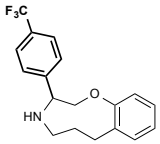
17c, 68%



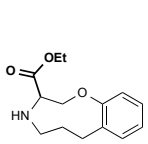
17d, 51%



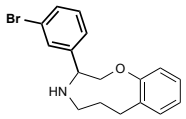
17e, 42%



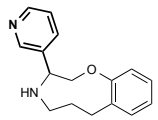
18a, 29%



18b, 41%



18c, 35%



18d, 22%

Reaction conditions for imine formation: SnAP reagent (0.50 mmol), aldehyde (0.50 mmol), MS 4A, CH_2Cl_2 (2.5 mL), 2 h, rt
Reaction conditions for cyclization: imine (0.50 mmol), $Cu(OTf)_2$ (0.50 mmol), 2,6-lutidine (0.50 mmol), 4:1 CH_2Cl_2:HFIP (10 mL), 12 h, rt
Yield values refer to isolated yields after purification. Boc = *tert*-butoxycarbonyl, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

We also evaluated the formation of 9-membered ring products with SnAP reagents and chose SnAP-BOAN **9** for initial attempts. The desired heterocyclic compounds were isolated in low to moderate yields but with a broad substrate scope with respect to the aldehydes (**18a**–**18d**). Further efforts to improve the efficiency of these challenging cyclizations by variation of the ligand and oxidant are currently ongoing. It is remarkable, however, that this process can easily access 8 and 9-membered rings, even in cases where the SnAP reagents contain no backbone elements that favor cyclization.

Discussion

Due to the increasing interest in saturated N-heterocycles, many efforts have been made to identify new synthetic methods for their preparation. To date, the majority of these methods focus on elaboration of preformed 5 and/or 6-membered saturated N-heterocycles.[11–15] Directed lithiation followed by transmetallation and metal-catalyzed cross-coupling is successful on pyrrolidine and piperidine substrates but has not proven useful for the elaboration of larger rings or those containing additional heteroatoms.[16–17] Only a few examples of the synthesis of saturated larger rings with a broad substrate scope have been reported, of which the ring-closing metathesis (RCM) is the most powerful.[18–19] C–H functionalization of *N*-benzyl protected cyclic amines via the formation of α-amino radicals has been applied to a single example of the arylation of *N*-benzyl azepane, as reported by Ito and Nakamura.[20–21] Wolfe et al. reported a promising alkene aminoarylation for the preparation of 2-carboaryl 1,4-tetrahydrobenzodiazepines.[22] Currently, most preparations of diazepanes and related structures are multi-step sequences proceeding with the intermediacy of lactams or by RCM, via products that must be reduced later.[23]

The use of SnAP reagents addresses the current difficulties in preparing saturated N-heterocycles, including more exotic substitution patterns and ring sizes, by providing a simple, predictable reaction from aldehydes, one of the most widely available starting materials. It also offers the unprecedented advantage of directly delivering *N*-unprotected products, obviating the need to cleave the often difficult to remove aryl or benzylic protecting groups used in C–H functionalization approaches to substituted N-heterocyles. Our investigation to date implicated a radical-based process initiated by Cu-mediated oxidation of the carbon–tin bond to form a heteroatom stabilized primary radical.[9] This mechanistic postulate provides an explanation for the remarkably broad substrate scope, which conveniently allows the formation of saturated N-heterocycles bearing aryl, heteroaryl, aliphatic, and carboxylate groups. Although radical cyclizations onto alkenyls typically proceed via *exo*-bond formation, the SnAP reagents as aza analogues always prefer formation of the *endo* products. This is presumably due to the

formation of a stable nitrogen radical, which is reduced by a copper (I) species and the thermodynamic preference of forming a stronger C–C bond over a C–N bond (Fig. 4). Additional, kinetic factors as orbital overlap of the SOMO with the LUMO (π^*) of the imine that has the higher coefficient on the carbon or polarization effects – the nucleophilic radical adds to the electrophilic imine carbon - may also contribute to this high regioselectivity.[24–27] Ring opening of possible *endo* radicals and reclosure to the *endo* products are inherently unlikely and radicals of this type, being both benzylic and in α-position to an amine are prone to dimerize due to their high stability.[24, 26–28] The presence of *exo* products has never been detected, regardless of the choice of aldehyde or SnAP reagent; the sole identifiable side products are those arising from protodestannylation indicating that the *endo* closure is a remarkably facile process.

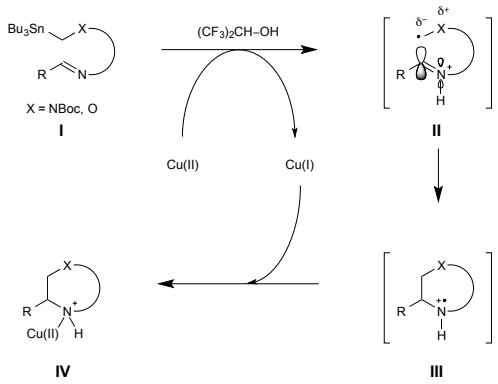


Figure 4 | Proposed mechanism for copper-mediated cyclization. Protonation of the iminotributylstannane **I** by the HFIP cosolvent is followed by oxidation with $Cu(OTf)_2$ to generate Cu(I) and the α-heteroatom-stabilized radical cation **II** (this heteroatom stabilized radical was trapped with TEMPO and the adduct characterized in prior work[9]). The polarized nucleophilic radical adds to the internal imine in *endo*-fashion to generate the cyclic radical cation **III**, which is reduced by Cu(I) to afford a Cu(II) product complex **IV**.

This report documents SnAP reagents for the synthesis of unsubstituted 7, 8, and 9-membered saturated N-heterocycles. Our experience indicates that more elaborate reagents containing additional substitution patterns and chiral centers can also be employed, leading to more complex products and often with excellent diastereoselectivity. The same principles can also be applied to SnAP reagents that lead to the formation of more common, but still extremely

valuable and difficult to prepare, targets including morpholines and piperazines. We anticipate further innovations in the design of new SnAP reagents as well as alternatives to the tin and copper metals used in the current process. In the meantime, SnAP reagents provide the first general approach to the synthesis of a wide range of saturated N-heterocycles.

In summary, we have developed SnAP reagents for cross-coupling with aldehydes to afford *N*-unprotected substituted, saturated medium-sized heterocycles. The cyclization takes place under mild conditions mediated by copper. The process accepts a broad substrate scope of electronically and sterically diverse aryl, heteroaryl, glyoxylic, and aliphatic aldehydes and tolerates functional groups including esters, protected amines, organohalides, ethers, nitriles, free hydroxyl groups, and various heterocycles. The results from the present study demonstrate that this cross-coupling of bench-stable SnAP reagents with readily available aldehydes represents a valuable entry for the synthesis of saturated medium-sized heterocycles.

Methods

General procedure for the synthesis of the N-heterocycles using SnAP reagents

To a solution of the amino tributylstannane – SnAP reagent (0.50 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL) was added the corresponding aldehyde (0.50 mmol, 1.00 equiv) and MS 4A (ca. 50 mg) under an inert atmosphere at rt. The reaction mixture was stirred for 2 h and filtered through a layer of Celite (ca. 0.3 cm), rinsing with CH_2Cl_2. The filtrate was concentrated under reduced pressure to afford the imine.

Separately, to a solution of 2,6-lutidine (0.50 mmol, 1.00 equiv) in HFIP (2.0 mL) in a dry Schlenk flask was added anhydrous $Cu(OTf)_2$ (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h during which a homogeneous suspension forms. A solution of the imine (0.50 mmol, 1.00 equiv) in dry CH_2Cl_2 (8.0 mL) was added in one portion and the resulting mixture was allowed to stir at rt for 12 h (unoptimized reaction time). The reaction was quenched at rt with a mixture of sat aq $NaHCO_3$ (4 mL) and 10% aq NH_4OH (2 mL). The mixture was stirred vigorously for 15 min, the

layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with H_2O (3 x 5 mL) and brine (10 mL), dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel using a precolumn of KF (ca. 3 cm).

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Author contributions

C.V.V. and M.U.L. performed the experiments, compound characterization and data analysis. All authors contributed in experiment design, discussions and wrote the manuscripts.

Additional information

Supplementary information and chemical compound information are available online in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to J.W.B.

Competing financial interests

The authors declare no competing financial interests.