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SnAP reagents for the one-step synthesis of medium-ring saturated N-heterocycles from aldehydes

Cam-Van T. Vo†, Michael U. Luescher† and Jeffrey W. Bode*

Interest in saturated N-heterocycles as scaffolds for the synthesis of bioactive molecules is increasing. Reliable and predictable synthetic methods for the preparation of these compounds, especially medium-sized rings, are limited. We describe the development of SnAP (Sn amino protocol) reagents for the transformation of aldehydes into seven-, eight- and nine-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 a 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 into 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 intellectual property positions of heteroaromatics have led many scientists to favour saturated N-heterocycles in their drug-development efforts[4–8]. The shift towards saturated compounds, which may contain chiral centres and be derived from larger rings or spirocyclic structures, raises synthetic challenges that are not addressed by the convenience and predictability of conventional metal-catalysed cross-coupling reactions.

In the search to provide alternatives to the cross-coupling of saturated N-heterocycles, recently we introduced SnAP (Sn amino protocol) 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 the oxidative generation of a sulfur-stabilized primary carbon-centred radical followed by 6-*endo*-trig cyclization with an unactivated imine to form the stable aminyl radical. This surprisingly facile cyclization mode, which is favoured over the expected 5-*exo*-trig cyclization, encouraged us to explore the development of SnAP reagents for the preparation of the even more challenging saturated N-heterocycles derived from seven-, eight- or nine-membered ring scaffolds with other heteroatoms, such as oxygen and nitrogen, to stabilize the initially formed primary carbon-centred radical (Fig. 1).

In this report we disclose new SnAP reagents for the synthesis of saturated N-heterocycles with seven-, eight- and nine-membered rings, 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 seven-, eight- and nine-membered saturated N-heterocycles, including

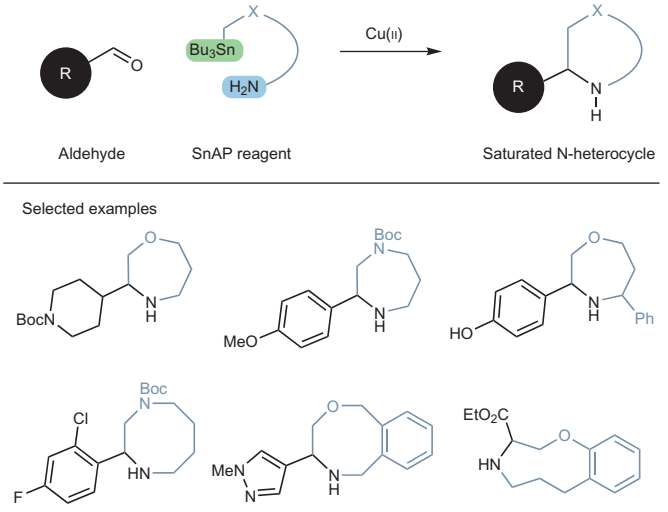

Figure 1 | The SnAP-reagent concept. The concept of the simple transformation of readily available aldehydes into substituted saturated medium-ring N-heterocycles using SnAP reagents is shown. This approach provides a convenient alternative to metal-catalysed cross-coupling reactions and affords unprotected saturated heterocycles in one step. The 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 that are difficult to access by existing methods. Boc, *tert*-butoxycarbonyl.

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diazepanes, oxazepanes and others, were prepared on a multigram scale from inexpensive starting materials by straightforward and efficient routes (Fig. 2; see the 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.

With these new SnAP reagents in hand, we explored the transformation of various aldehydes into substituted seven-, eight- and nine-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 $Cu(OTf)_2$ ($OTf = OSO_2CF_3$) and 2,6-lutidine in 4:1 CH_2Cl_2:HFIP (HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol) at room temperature (r.t.) for 12 hours. The imines were isolated by filtration and evaporation to ensure full conversion before being subjected to 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 a high-performance liquid chromatography filter (10a, Table 1).

Synthesis of saturated seven-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 into these substituted seven-membered N-heterocycles using SnAP reagents 1–5 was examined with 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 the piperidine-4-carboxaldehyde 10d, the cyclopropanecarboxaldehyde 14d and the bulky pivaldehyde 14c, all afforded the products in good yields. The sterically demanding *o*-tolualdehyde 11c was incorporated in good yield and functional groups suitable for further elaboration of the products, including esters, organohalides, nitriles and protected amines; 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 believe were formed by competing hydrogen-atom transfer from HFIP. Benzannulated and disubstituted products were accomplished using SnAP reagents 2, 3 and 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 reagents 2 and 5, presumably because of a faster rate of cyclization of the prealigned 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 the Supplementary Information).

Gram-scale synthesis using SnAP reagents. A larger-scale synthesis using SnAP 4-oxazepane 1 (5 g) was performed with standard laboratory techniques to demonstrate the ease and scalability of our protocol and the 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 in 75% yield with >98% purity (compare Table 1, entry 10a).

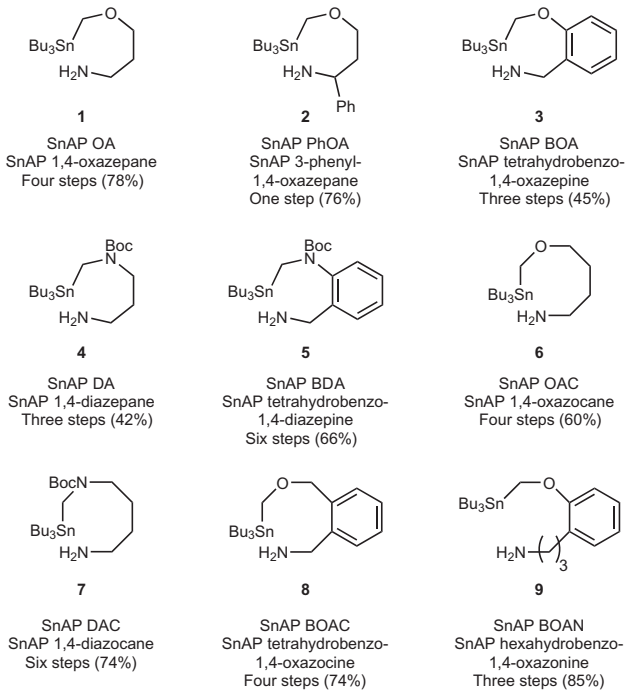
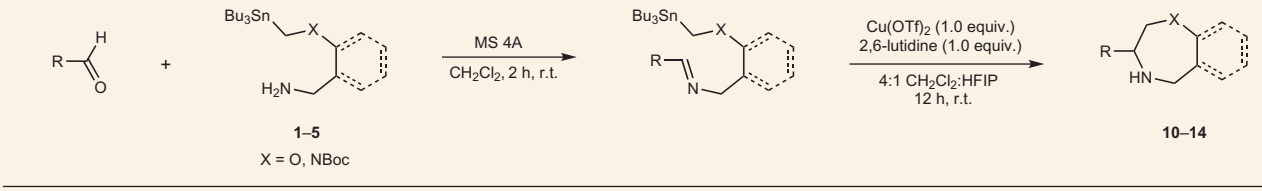


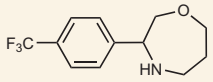
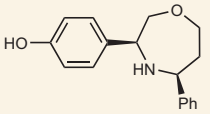
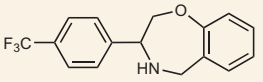
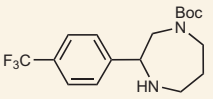
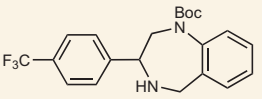
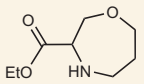
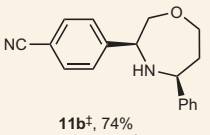
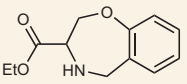
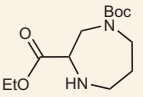
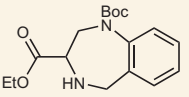
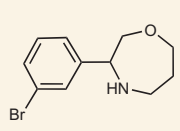
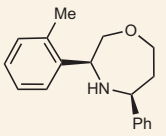
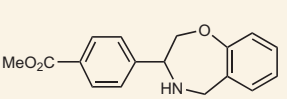
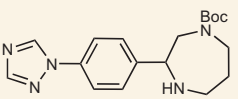
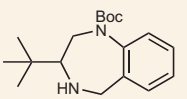
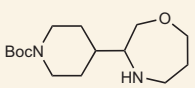
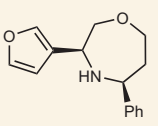
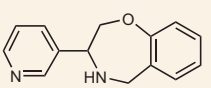
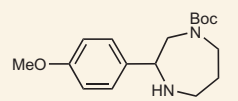
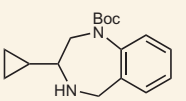
Figure 2 | SnAP reagents for seven-, eight- and nine-membered ring synthesis. Stable and easily handled SnAP reagents prepared in short reaction sequences. Steps are from commercially available materials. The overall yields are from commercially available starting materials.

Synthesis of saturated eight- and nine-membered rings. Encouraged by the successful synthesis of seven-membered ring N-heterocycles, we explored the use of SnAP reagents for the preparation of eight- and nine-membered N-heterocycles. Substituted diazocanes, oxazocanes and their benzannulated derivatives are currently little-known heterocycles, perhaps because of the difficulty in preparing such molecules. The aldehyde scope was similar to that of the synthesis of seven-membered rings, including aryl, heteroaryl and aliphatic aldehydes (Table 2). As anticipated, the cyclization yields were somewhat lower, with protodestannylation of the imine again the major side product. In these cases, the electronic properties 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 trace amounts of 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 tetrahydrobenzo-1,4-oxazocine (8), facilitated the cyclization and the corresponding saturated N-heterocycles were isolated in good yields with a broad substrate scope that included the electron-rich aldehyde 17e; only a small amount of the protodestannylated imine was observed. Although the yields of these substituted eight-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 make the use of SnAP reagents an attractive approach.

We also evaluated the formation of nine-membered ring products with SnAP reagents and chose SnAP hexahydrobenzo-1,4-oxazocine (9) for the 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

Table 1 | SnAP reagents for seven-membered rings.



				
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), two hours, r.t. 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 hours, r.t. 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 a syringe equipped with a filter.
†Diastereomeric ratio (d.r.) 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 were assigned by analogy.

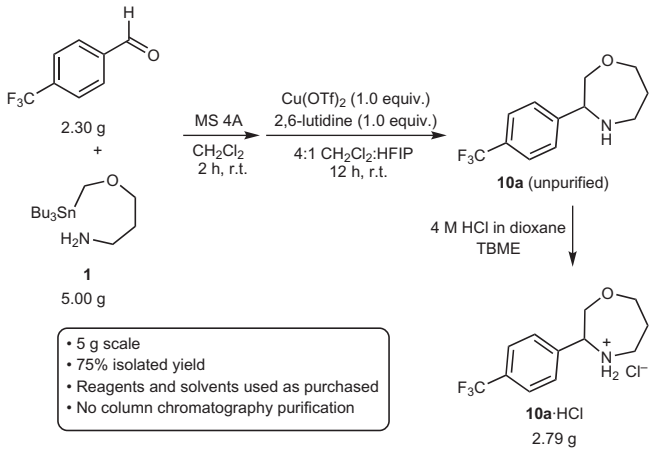


Figure 3 | Gram-scale synthesis of substituted 1,4-oxazepane. Condensation of SnAP OA (13.2 mmol) and *p*-trifluoromethylbenzaldehyde (13.2 mmol) afforded the corresponding imine, which was cyclized under standard protocol conditions: stoichiometric $Cu(OTf)_2$ and 2,6-lutidine in CH_2Cl_2:HFIP 4:1 at r.t. for 12 hours. 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 were used as purchased. TBME, *tert*-butyl methyl ether.

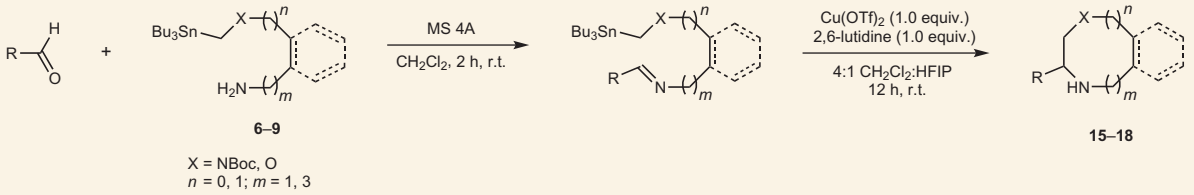
eight- and nine-membered rings, even in cases where the SnAP reagents contain no backbone elements that favour cyclization.

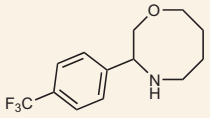
Discussion

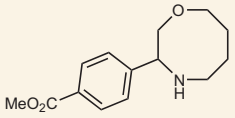
Owing to the increasing interest in saturated N-heterocycles, many efforts have been made to identify new synthetic methods for their preparation. To date, the majority of these methods have focused on elaboration of preformed five- and/or six-membered saturated N-heterocycles[11–15]. Directed lithiation followed by transmetalation and metal-catalysed cross-coupling is successful on pyrrolidine and piperidine substrates, but has not proved useful for the elaboration of larger rings or those that contain additional heteroatoms[16,17]. Only a few examples of the synthesis of saturated larger rings with a broad substrate scope are 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 multistep sequences that proceed with the intermediacy of lactams or by RCM, via products that must be reduced later[23].

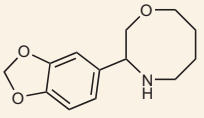
The use of SnAP reagents addresses the current difficulties in preparing saturated N-heterocycles, including more-exotic

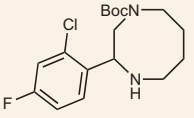
Table 2 | SnAP reagents for eight and nine-membered rings.

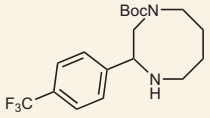


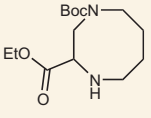

15a, 46%

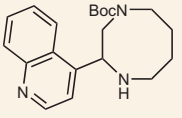

15b, 38%

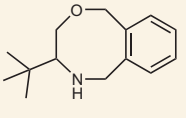

15c, 20%

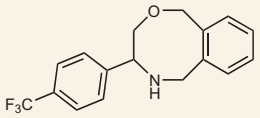

16a, 45%

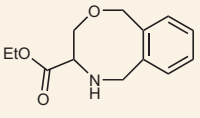

16b, 34%

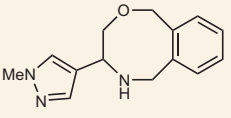

16c, 52%

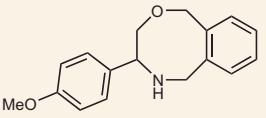

16d, 39%

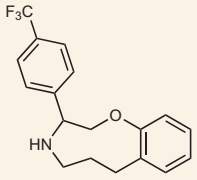

17a, 79%

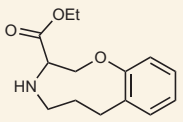

17b, 72%

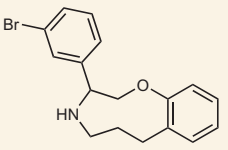

17c, 68%

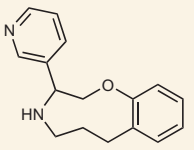

17d, 51%


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), two hours, r.t. 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 hours, r.t. Yield values refer to isolated yields after purification.

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 delivering N-unprotected products directly, which obviates 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 implicates a radical-based process initiated by copper-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 that bear 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 because of the formation of a stable nitrogen radical, which is reduced by a Cu(I) species and the thermodynamic preference to form a stronger C–C bond over a C–N bond (Fig. 4). Also, kinetic factors, such as orbital overlap of the singly occupied molecular orbital with the lowest occupied molecular orbital (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 contribute to this high regioselectivity[24–27]. Ring opening of possible *exo* radicals and reclosure to the *endo* products are inherently unlikely and radicals of this type, being both benzylic and in the α-position of an amine, are prone to dimerize because of their high stability[24,26–28]. The presence of *exo* products has not been detected, regardless of the choice of aldehyde or SnAP reagent; the sole identifiable side products are those that arise from protodestannylation, which indicates that the *endo* closure is a remarkably facile process.

This report documents SnAP reagents for the synthesis of unsubstituted seven-, eight- and nine-membered saturated N-heterocycles. Our experience indicates that more-elaborate reagents containing additional substitution patterns and chiral centres can also be employed, and lead to more-complex products, 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 and 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

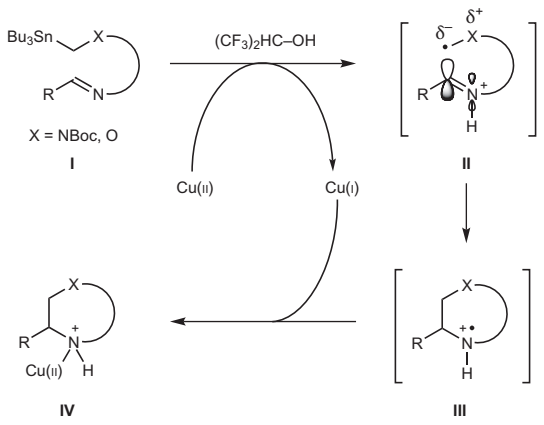


Figure 4 | Proposed mechanism for copper-mediated cyclization. Protonation of the iminotributylstannane **I** by the HFIP cosolvent is followed by oxidation with $Cu(OTf)_2$ to generate Cu(I) and the α-heteroatom-stabilized radical cation **II** (this heteroatom-stabilized radical was trapped with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and the adduct characterized in prior work[9]). The polarized nucleophilic radical adds to the internal imine in an *endo* fashion to generate the cyclic radical cation **III**, which is reduced by Cu(I) to afford a Cu(II) product complex **IV**.

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 to the synthesis of saturated medium-sized heterocycles.

Methods

The general procedure for the synthesis of the N-heterocycles using SnAP reagents was as follows. To a solution of the aminotributylstannane–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 molecular sieve (MS) 4A (~50 mg) under an inert atmosphere at r.t. The reaction mixture was stirred for two hours and filtered through a layer of Celite (~0.3 cm), rinsing with CH_2Cl_2. The filtrate was concentrated under reduced pressure to afford the imine.

Separately, anhydrous $Cu(OTf)_2$ (0.50 mmol, 1.00 equiv.) was added to a solution of 2,6-lutidine (0.50 mmol, 1.00 equiv.) in HFIP (2.0 ml) in a dry Schlenk flask and stirred at r.t. for one hour, during which a homogeneous suspension formed. 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 r.t. for 12 hours (unoptimized reaction time). The reaction was quenched at r.t. with a mixture of saturated aqueous $NaHCO_3$ (4 ml) and 10% aqueous NH_4OH (2 ml). The mixture was stirred vigorously for 15 minutes, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layers were washed with H_2O (3 × 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 (~3 cm).

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References

1. Schröter, S., Stock, C. & Bach, T. Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles. *Tetrahedron* **61,** 2245–2267 (2005).
2. Slagt, V. F., de Vries, A. H. M., de Vries, J. G. & Kellogg, R. M. Practical aspects of carbon–carbon cross-coupling reactions using heteroarenes. *Org. Process Res. Dev.* **14,** 30–47 (2009).
3. Seregin, I. V. & Gevorgyan, V. Direct transition metal-catalyzed functionalization of heteroaromatic compounds. *Chem. Soc. Rev.* **36,** 1173–1193 (2007).
4. Ritchie, T. J. & Macdonald, S. J. F. The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design? *Drug Discov. Today* **14,** 1011–1020 (2009).
5. Ritchie, T. J., Macdonald, S. J. F., Young, R. J. & Pickett, S. D. The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types. *Drug Discov. Today* **16,** 164–171 (2011).
6. Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52,** 6752–6756 (2009).
7. Leeson, P. D., St-Gallay, S. A. & Wenlock, M. C. Impact of ion class and time on oral drug molecular properties. *Med. Chem. Comm.* **2,** 91–105 (2011).
8. Meanwell, N. A. Improving drug candidates by design: a focus on physicochemical properties as a means of improving compound disposition and safety. *Chem. Res. Toxicol.* **24,** 1420–1456 (2011).
9. Vo, C-V. T., Mikutis, G. & Bode, J. W. SnAP reagents for the transformation of aldehydes into substituted thiomorpholines—an alternative to cross-coupling with saturated heterocycles. *Angew. Chem. Int. Ed.* **52,** 1705–1708 (2013).
10. Galli, C. & Mandolini, L. The role of ring strain on the ease of ring closure of bifunctional chain molecules. *Eur. J. Org. Chem.* 3117–3125 (2000).
11. Mitchell, E. A., Peschiulli, A., Lefevre, N., Meerpoel, L. & Maes, B. U. W. Direct α-functionalization of saturated cyclic amines. *Chem. Eur. J.* **18,** 10092–10142 (2012).
12. Müller, T. E., Hultzsch, K. C., Yus, M., Foubelo, F. & Tada, M. Hydroamination: direct addition of amines to alkenes and alkynes. *Chem. Rev.* **108,** 3795–3892 (2008).
13. Hannedouche, J. & Schulz, E. Asymmetric hydroamination: a survey of the most recent developments. *Chem. Eur. J.* **19,** 4972–4985 (2013).
14. Schultz, D. R. & Wolfe, J. P. Recent developments in palladium-catalyzed alkene aminoarylation reactions for the synthesis of nitrogen heterocycles. *Synthesis* **44,** 351–361 (2012).
15. Zhou, Y-G. Asymmetric hydrogenation of heteroaromatic compounds. *Acc. Chem. Res.* **40,** 1357–1366 (2007).
16. Campos, K. R. Direct sp^3 C–H bond activation adjacent to nitrogen in heterocycles. *Chem. Soc. Rev.* **36,** 1069–1084 (2007).
17. Coldham, I. & Leonori, D. Synthesis of 2-arylpiperidines by palladium couplings of aryl bromides with organozinc species derived from deprotonation of *N*-Boc-piperidine. *Org. Lett.* **10,** 3923–3925 (2008).
18. Crestey, F. O., Witt, M., Jaroszewski, J. W. & Franzyk, H. Expedite protocol for construction of chiral regioselectively *N*-protected monosubstituted piperazine, 1,4-diazepane, and 1,4-diazocane building blocks. *J. Org. Chem.* **74,** 5652–5655 (2009).
19. Deiters, A. & Martin, S. F. Synthesis of oxygen- and nitrogen-containing heterocycles by ring-closing metathesis. *Chem. Rev.* **104,** 2199–2238 (2004).
20. Murakami, M., Hayashi, M. & Ito, Y. Generation of (α-aminoalkyl) samarium(III) by a new method of metalation and its carbon–carbon bond-forming reactions. *Appl. Organomet. Chem.* **9,** 385–397 (1995).
21. Yoshikai, N., Mieczkowski, A., Matsumoto, A., Ilies, L. & Nakamura, E. Iron-catalyzed C–C bond formation at α-position of aliphatic amines via C–H bond activation through 1,5-hydrogen transfer. *J. Am. Chem. Soc.* **132,** 5568–5569 (2010).
22. Neukom, J. D., Aquino, A. S. & Wolfe, J. P. Synthesis of saturated 1,4-benzodiazepines via Pd-catalyzed carboamination reactions. *Org. Lett.* **13,** 2196–2199 (2011).
23. Hoyt, S. B. *et al.* Discovery of a novel class of benzazepinone $Na_v1.7$ blockers: potential treatments for neuropathic pain. *Bioorg. Med. Chem. Lett.* **17,** 4630–4634 (2007).
24. Tomaszewski, M. J. & Warkentin, J. Rate constants for aryl radical cyclization to aldimines: synthesis of tetrahydroisoquinolines by fast 6-*endo* closures to carbon. *Tetrahedron Lett.* **33,** 2123–2126 (1992).
25. Bowman, W. R., Stephenson, P. T., Terrett, N. K. & Young, A. R. Radical cyclisations of imines and hydrazones. *Tetrahedron* **51,** 7959–7980 (1995).
26. Tomaszewski, M. J., Warkentin, J. & Werstiuk, N. H. Free-radical chemistry of imines. *Aust. J. Chem.* **48,** 291–321 (1995).
27. Friestad, G. K. Addition of carbon-centered radicals to imines and related compounds. *Tetrahedron* **57,** 5461–5496 (2001).
28. Kim, S., Yoon, K. S. & Kim, Y. S. Kinetic studies of intramolecular additions of alkyl radicals onto imines. *Tetrahedron* **53,** 73–80 (1997).

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Author contributions

C-V.T.V. and M.U.L. performed the experiments, compound characterization and data analysis. All authors contributed to experiment design, discussions and writing the manuscripts.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at 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.