# Bespoke SnAP Reagents for the Synthesis of C-Substituted Spirocyclic and Bicyclic Saturated N-Heterocycles

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S *Supporting Information*

ABSTRACT: The precise placement of C-substituents on bicyclic and spirocyclic N-heterocycles is readily achieved by the combination of aldehydes and new SnAP reagents. The substituted SnAP reagents are readily prepared from simple starting materials and couple with a variety of aromatic and heteroaromatic aldehydes at room temperature under operationally simple conditions to deliver substituted morpholine and piperazine products.
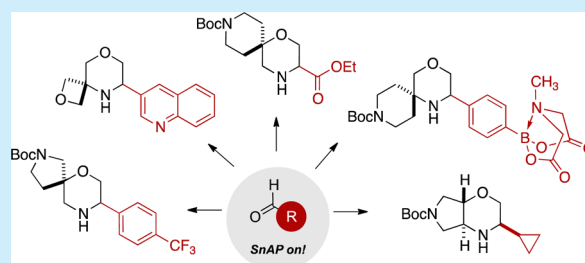
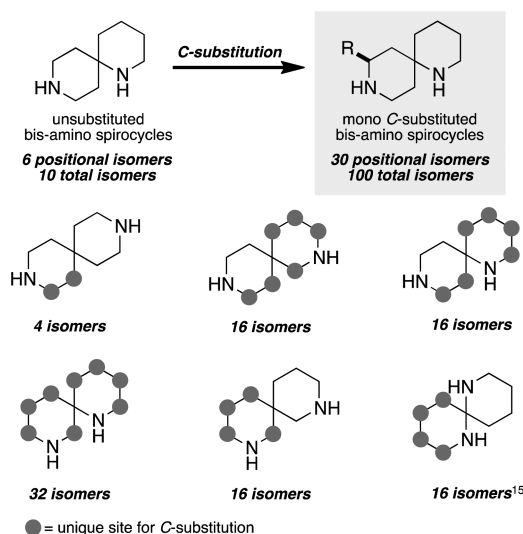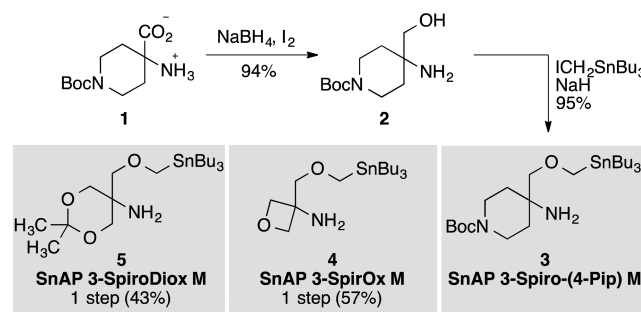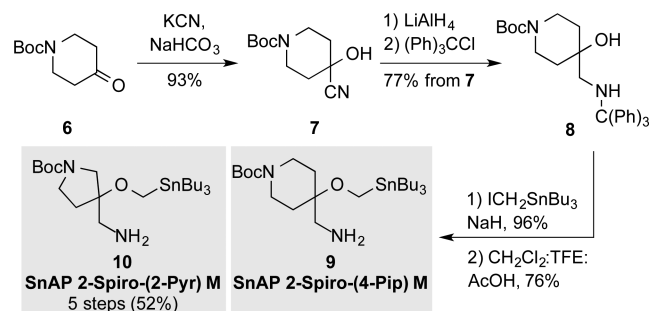Full exploration of chemical space in the design and development of small-molecule drugs[1] requires the rapid assembly of suitable frameworks from readily available components. In recent years, medicinal chemists have recognized the distinct advantages of saturated N-heterocycles,[2] which were represented in 42% of all small-molecule new molecular entities introduced between 2009 and 2013. Looking forward, considerable attention is focused on spirocyclic and bicyclic scaffolds,[3] as these constructs provide even greater opportunities for the fine-tuning of substituent groups while still providing a rigid, metabolically robust framework with low molecular weight.[4]

At the present time, the use of spirocyclic and bicyclic scaffolds[5,13,14] is largely limited to the derivatization of a few commercially available examples, typically by amide formation or other C–N bond-forming reactions.[6] The true potential of spirocycles for precise positioning of substituents on a rigid scaffold requires a means of incorporating substituent groups onto one of the carbon atoms (Figure 1). The introduction of a single C-substituent dramatically increases the number of

Figure 1. Unsubstituted and substituted bis-amino spirocycles.

Scheme 1. Synthesis of SnAP Reagents 3−5

Scheme 2. Synthesis of SnAP Reagents 9 and 10

Scheme 3. Synthesis of Spirocyclic Morpholines from SnAP Reagents[a]
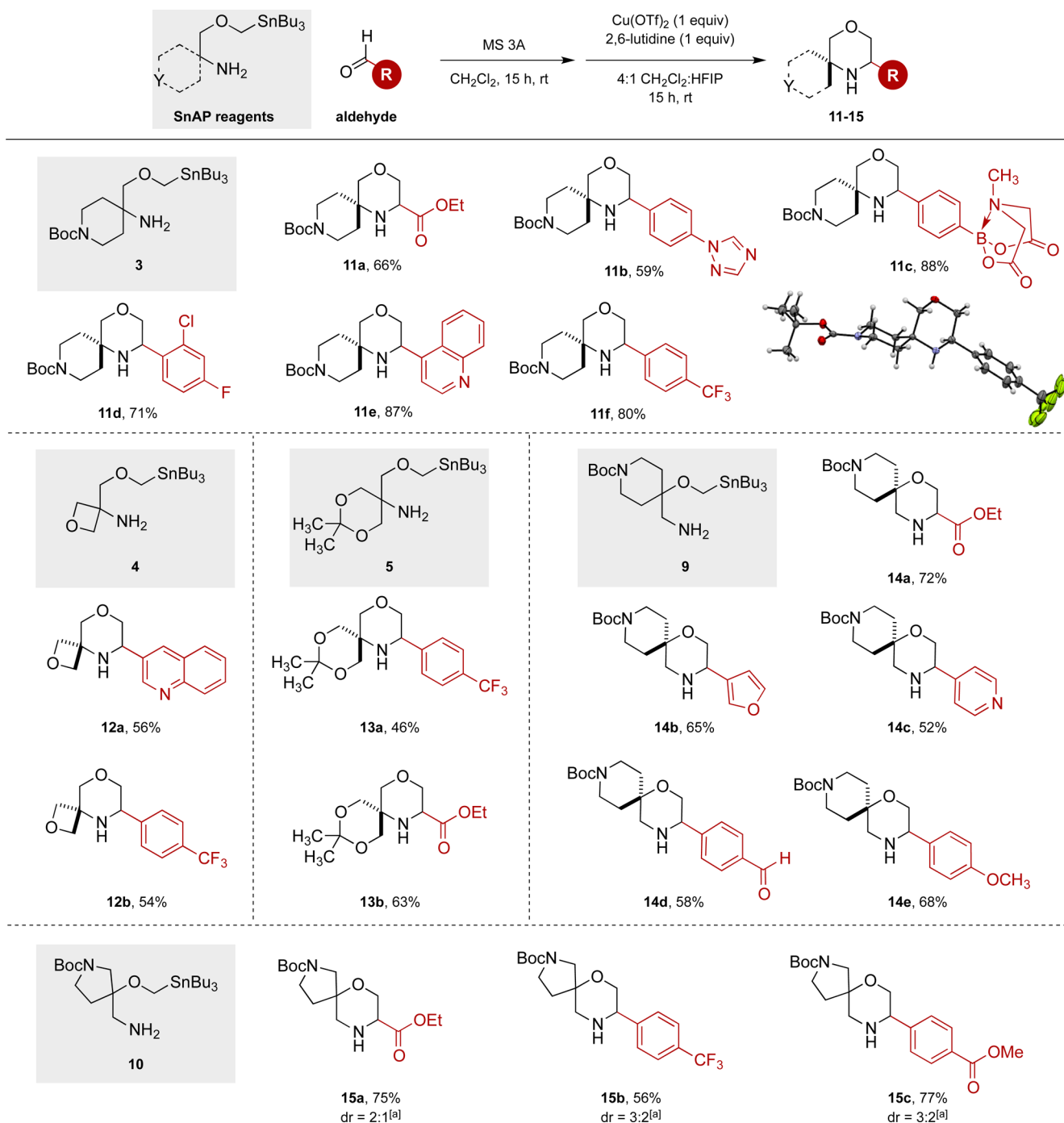
[a]All reactions were performed using 1 equiv of SnAP reagent, 1 equiv of Cu(OTf)$_2$, 1 equiv of 2,6-lutidine in 4:1 CH$_2$Cl$_2$/HFIP at rt for 15 h. Yields shown are of isolated, analytically pure products following column chromatography. MS = molecular sieves. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [a] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of purified products.
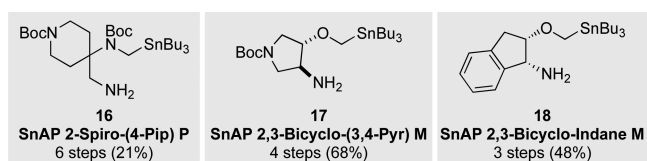

Figure 2. Additional custom SnAP reagents prepared by analogous methods (see Supporting Information for details).

potential structures, but the lack of effective synthetic methods has hampered the implementation of this seductive approach to drug development. Exciting methodologies for derivatizing saturated N-heterocycles by radical and C—H functionalization reactions promise to provide new entries,[7] but the current approaches have either not been extended to spirocyclic systems or require the use of N-substituents that limit the utility of the resulting products.[8]

As part of our efforts to provide a cross-coupling approach to the rapid construction of substituted, saturated N-heterocycles,
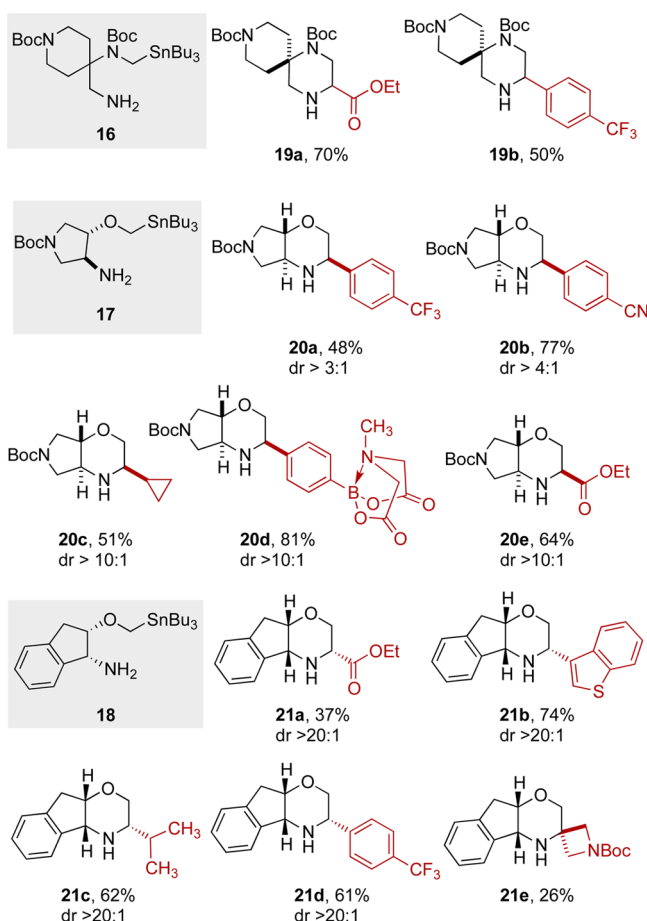
Figure 3. Synthesis of piperazines and bicyclic compounds. All reactions were performed using 1 equiv of SnAP reagent, 1 equiv of Cu(OTf)$_2$, 1 equiv of 2,6-lutidine in 4:1 CH$_2$Cl$_2$/HFIP at rt for 15 h. Yields shown are of isolated, analytically pure products following column chromatography. The dr was determined by ^{1}H NMR analysis of unpurified reaction mixtures.

we have introduced SnAP (stannyl (Sn) amine protocol) reagents for the one-step conversion of aldehydes and ketones into N-unsubstituted thiomorpholines,[9] morpholines, piperazines,[10] diazepanes,[11] and related heterocycles—including unsubstituted spirocycles.[12−14] These SnAP reagents serve as cross-coupling surrogates for the parent N-heterocycles and can be easily prepared in a few steps; several are commercially available. We envisaged the preparation of more elaborate SnAP reagents that could be used as cross-coupling partners with aldehydes to form C-substituted bicyclic and spirocyclic structures. In this communication, we report eight such SnAP reagents and their application to the one-step preparation of substituted bicyclic and spirocyclic morpholines and piperazines.

At the outset of our studies, we identified two initial targets, SnAP reagent **3** and its regioisomer **9**, which would form two distinct spirocyclic morpholines joined to a N-Boc-protected piperidine. Our first customized SnAP reagent **3** was derived from amino alcohol **2**, which could be prepared from the commercially available amino acid **1** (Scheme 1). Alkylation of the amino alcohol (ICH$_2$SnBu$_3$/NaH) afforded SnAP 2-spiro-(4-piperidine) morpholine (**3**) in 95% isolated yield. The alkylation reaction was successfully carried out in the presence of an unprotected primary amine. Two other structurally related SnAP reagents, SnAP 3-SpirOx M (SnAP 3-spiro-oxetane

morpholine) (**4**) and SnAP 2-spiro-(4-piperdine) morpholine (**5**), both containing a cyclic moiety on the 3-position of the SnAP skeleton, were prepared via the corresponding amino alcohols.[16]

The regioisomeric SnAP reagent **9**, SnAP 2-spiro-(4-piperdine) morpholine, could be accessed from N-Boc piperidone **6** (Scheme 2). Cyanohydrin formation (93% yield) followed by nitrile reduction and trityl protection of the resulting primary amine afforded compound **8** (77% isolated yield from cyanohydrin **7**). Alkylation using our standard conditions provided N-trityl-protected SnAP **9** in 96% yield. In this synthetic route, amine protection was necessary as N-alkylation is a competitive reaction. Deprotection was effected using a mixture of CH$_2$Cl$_2$/TFE/AcOH to provide SnAP reagent **9** in 76% yield. The identical synthetic route was applied to the synthesis of the five-membered ring SnAP 2-Spiro-(2-Pyr) M (**10**), starting from N-Boc pyrrolidinone (5 steps, 52% yield).

With the new SnAP reagents in hand, we examined their use in the formation of C-substituted spirocycles with a range of aldehydes. Pleasingly, the standard conditions used for SnAP cyclization (1 equiv of Cu(OTf)$_2$, 1 equiv of 2,6-lutidine, CH$_2$Cl$_2$/HFIP) gave the desired spirocyclic morpholine products in moderate to excellent yields (Scheme 3). No special precautions were necessary for the reaction setup, and all experiments were performed using identical reaction conditions without substrate-specific optimization. Aldehydes containing functional groups including esters (**11a**, **13b**, **14a**, **15a**, and **15c**), aldehydes (**14d**), and aryl halides (**11d**) enable the production of scaffolds suitable for further elaboration. The tolerance of aryl MIDA ester (**20d**) is noteworthy, as these substrates could potentially undergo oxidation in the presence of copper. When SnAP reagent **10** was employed, the resulting products were isolated as a mixture of diastereomers.[17] SnAP reagents **3**, **9**, and **10** contain a Boc-protected nitrogen atom within the appended ring, providing an additional exit vector for subsequent modification.[5b,18] The ability to construct regioisomeric products, such as **11a** and **14a**, where the piperidine ring has been shifted along the ethylene backbone demonstrates the suitability of these reagents for structure−activity relationship studies since they readily enable the subtle modification of the substituent spatial arrangements.[6a,b]

Oxetanes have become a popular functional group for drug discovery and have proven useful as surrogates for carbonyl and gem-dimethyl groups.[19] SnAP 3-SpirOx M (**4**) allows rapid access to oxetane-containing compounds (**12a,b**) in good yields. The protected diol in SnAP reagent **5** offers access, in good yield, to morpholines **13a** and **13b**, which are poised for further elaboration.

Similar approaches were used for the preparation of piperazine-forming SnAP reagent **16** and bicyclo-forming reagents **17** and **18** (Figure 2). These custom SnAP reagents were coupled with aldehyde partners to give spirocyclic piperazines (**19a,b**) and bicyclic morpholines (**20** and **21**) (Figure 3). When SnAP reagent **17** was employed, the diastereomeric ratio of the resulting products varied depending on the aldehyde used; in all cases, the major isomer could be identified as the structures shown in Figure 3 based on X-ray crystallographic analysis of compound **20a**. Diastereomerically pure bicycles (**21a−d**, dr >20:1) could be obtained using enantiomerically pure SnAP reagent **18**. A ketone was also a viable substrate and provided tetracycle **21e**, albeit in somewhat diminished yield.

In summary, we have demonstrated that bespoke SnAP reagents are readily prepared and suitable for the synthesis of substituted bicyclic and spirocyclic morpholines and piperazines. Despite the more elaborate SnAP reagents, the key cyclization occurs under the same standard, operationally simple conditions previously established for monosubstituted N-heterocycles. This work demonstrates the remarkably broad substrate scope of SnAP chemistry, with respect not only to the aldehyde but also to more elaborate SnAP reagents themselves. Although our strategy does not provide access to all possible classes of bicyclic N-heterocycles or all positional and structural isomers of C-substituted bicyclic and spirocyclic N-heterocycles, it offers a reliable and predictable route to a significant proportion of the scaffolds currently in demand for modern drug development.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, NMR spectra, X-ray analysis, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(20) CCDC number 1042707 (**11f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.