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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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One-Step Synthesis of Saturated Spirocyclic N-Heterocycles with Stannyl Amine Protocol (SnAP) Reagents and Ketones

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Supporting Information

ABSTRACT: The combination of cyclic ketones and stannyl amine protocol (SnAP) reagents affords saturated, spirocyclic N-heterocycles under operationally simple reaction conditions. The resulting, *N*-unprotected spirocyclic amines are in great demand as scaffolds for drug discovery and development. The union of SnAP reagents and acyclic trifluoromethylketones yields α-CF_3 morpholines and piperazines.

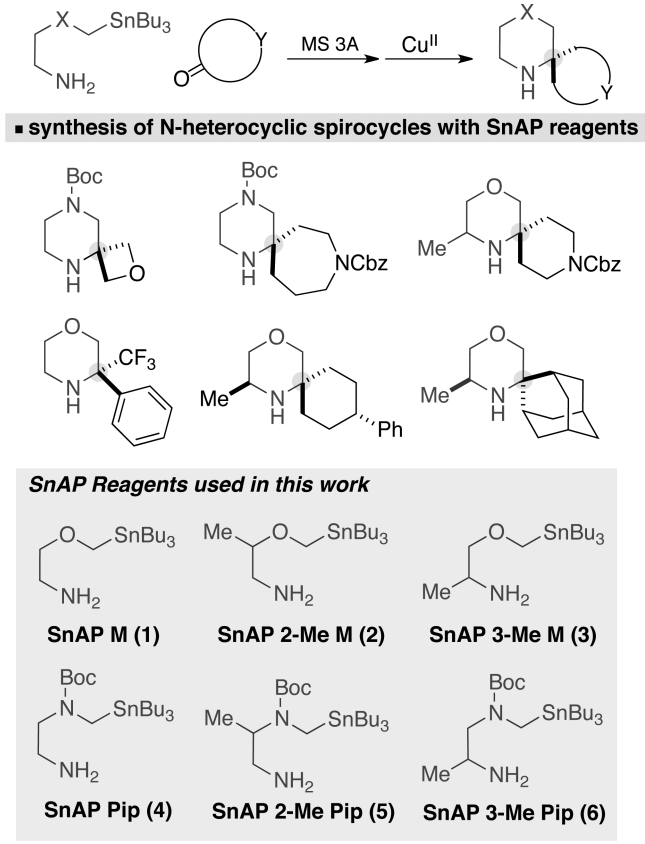
Saturated, spirocyclic N-heterocycles[1,2] are regarded as promising scaffolds for drug discovery[3] and development due to their rigid structures, decreased lipophilicities, and dramatically increased opportunities for fine-tuning the positioning of substituent groups. Despite their recognized advantages, relatively few multifunctional saturated spirocycles are actually available for use due to the lack of synthetic methods to form the spiro-ring junction. Current approaches include insertion of dichlorocarbene[4] to give spirolactams or spirolactones and cyclizations of linear precursors.[5] A major challenge in this area is the preparation of diverse spirocycles by the union of two discrete components.[6,7]

As part of our interest in devising reliable and general synthetic methodologies for the preparation of saturated N-heterocycles,[8] we recently disclosed SnAP reagents[9] for the construction of substituted thiomorpholines, morpholines, piperazines, diazepanes, and various medium-ring N-heterocycles from aldehydes. SnAP reagents provide direct routes into *N*-unsubstituted, fully saturated heterocycles under operationally simple protocols and with an outstanding substrate scope. Although we immediately recognized that the use of ketones as substrates would result in the facile formation of saturated spirocyclic compounds (Scheme 1), we approached the implementation of this synthetic route with trepidation, as the intermediate ketimines[10,11] are difficult to prepare and prone to enamine formation. We had also noted that some very sterically hindered aldehydes gave poor yields in the cyclization step,[9b] and few reports in the literature on intramolecular cyclizations onto ketimines showed a high preference on 5-*exo* over 6-*endo* ring closure.[12]

In this report we document the successful formation of saturated, spirocyclic N-heterocycles, with an emphasis on bi- and trifunctional derivatives that can serve as a valuable platform for further elaboration in drug development efforts. Key to our success was the identification of new conditions for the cyclizations with SnAP reagents on ketone substrates. Although this protocol is not yet suitable for some enolizable ketones, it offers direct access to many of the most interesting spirocyclic structures currently in demand. In many cases, spirocycles that were previously unknown or required lengthy routes[13] to prepare can now be formed in a single synthetic operation by combination of the appropriate SnAP reagent and ketone.

At the outset of our studies, the efficient formation of the requisite ketimines from ketone substrates and SnAP reagents required investigation and optimization. Although ketimine formation from certain nonenolizable ketones could be readily achieved, we chose to focus our efforts on cyclic ketones—particularly those bearing an additional functional group or substituent—as the resulting products have the greatest utility.

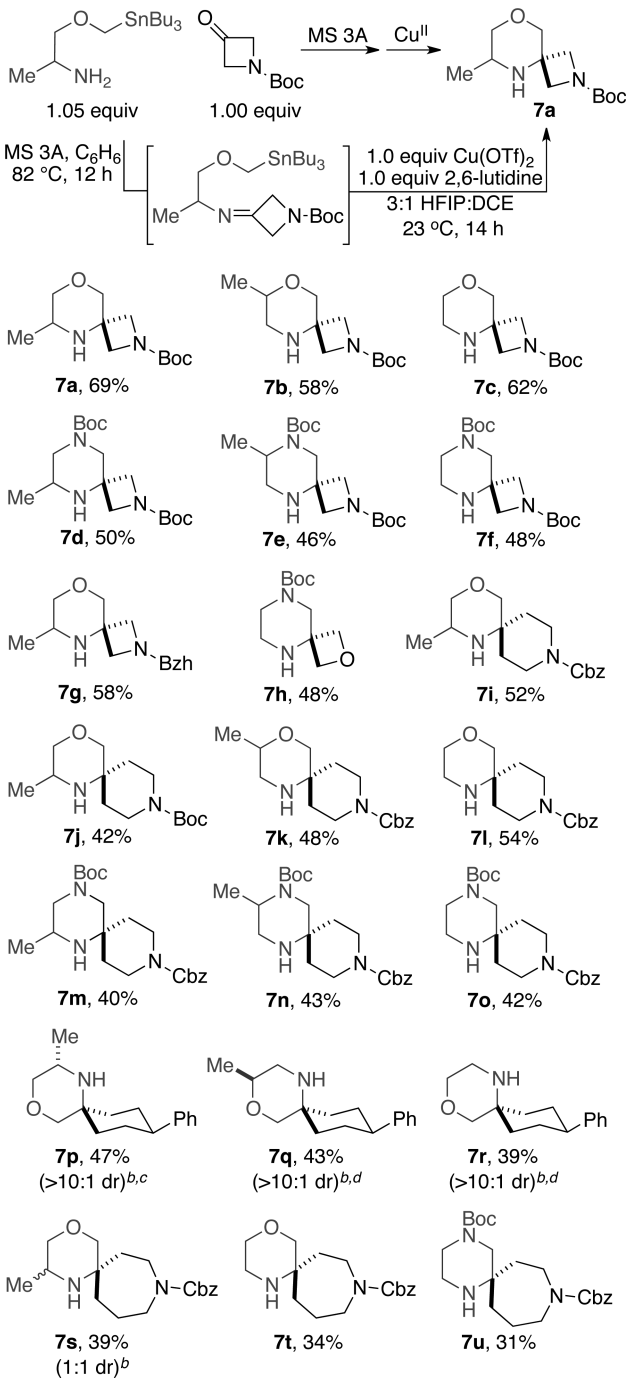
Scheme 1. One-Step Synthesis of Saturated, Spirocyclic N-Heterocycles with SnAP Reagents and Ketones



Received: November 1, 2014
Published: December 7, 2014

dx.doi.org/10.1021/ja511232b | J. Am. Chem. Soc. 2014, 136, 17726−17729

Scheme 2. One-Step Synthesis of Spirocycles from SnAP Reagents and Ketones[a]

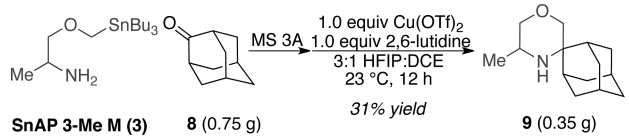


[a]Reaction conditions: ketimine (0.50 mmol), $Cu(OTf)_2$ (0.50 mmol), 2,6-lutidine (0.50 mmol), 3:1 HFIP/DCE, 14 h, 23 °C. Yield values refer to isolated yield after purification. [b] Determined by ^1H NMR. [c] Relative configuration determined by X-ray crystallography. [d] Assigned by analogy to **7p**. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. DCE = 1,2-dichloroethane. Bzh = benzhydryl. Boc = *tert*-butyloxycarbonyl.

We chose *N*-Cbz azetidinone and SnAP 3-Me-M **3** as our model substrates and developed conditions for ketimine formation by combining the SnAP reagent (1.0 equiv), the ketone (1.05 equiv), and MS 3A in refluxing benzene (82 °C) for 12 h. Under our standard conditions for cyclization (1.0 equiv $Cu(OTf)_2$, 1.0 equiv 2,6-lutidine, 3:1 HFIP/$ClCH_2CH_2Cl$ at 23 °C) we could detect the desired product formation. Upon further optimization, we found two parameters to be critical for spirocycle formation: (1) the use of an increased amount of HFIP and (2) the integrity of the intermediate ketimines. Under the optimized conditions, the spiro[3.5]-heterocycle **7a** could be obtained in 69% yield following aqueous workup and column chromatography. We speculated that a higher proportion of HFIP enhances the rate of cyclization.

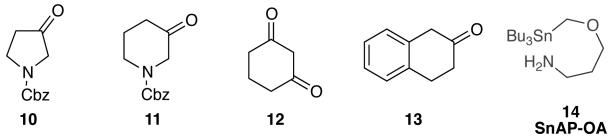
Encouraged by the successful results using four-membered ring ketones, we explored the synthesis of spiro[5.5]-heterocycles with other cyclic ketones. Under the established conditions, 4-, 6-, and 7-membered cyclic ketones all delivered the expected spirocycles in respectable yield (Scheme 2). A cyclohexanone bearing a 4-phenyl substitutent gave a single detectable diastereomer via addition to the equatorial face of the ketimine (**7p**–**r**). Substrate specific optimization is likely to be possible; for this study we used a single reaction protocol. The spirocycle formation can be easily used to produce meaningful quantities of the product, even with challenging substrates. For example, amantadine derivative **9** was prepared in one step (Scheme 3).

Scheme 3. Synthesis of Amantadine 9



Studies with 5-membered pyrolidinone **10** and 6-membered 3-piperidinone **11** showed that the integrity of the preformed ketimine was crucial for successful cyclization. With the ketimines derived from these substrates, which are prone to enamine formation, we observed large amounts of protodestannylation (Chart 1) along with small amounts of the

Chart 1. Poor Yielding Substrates for Spirocycle Formation Due to Enamine Formation or Protodestannylation



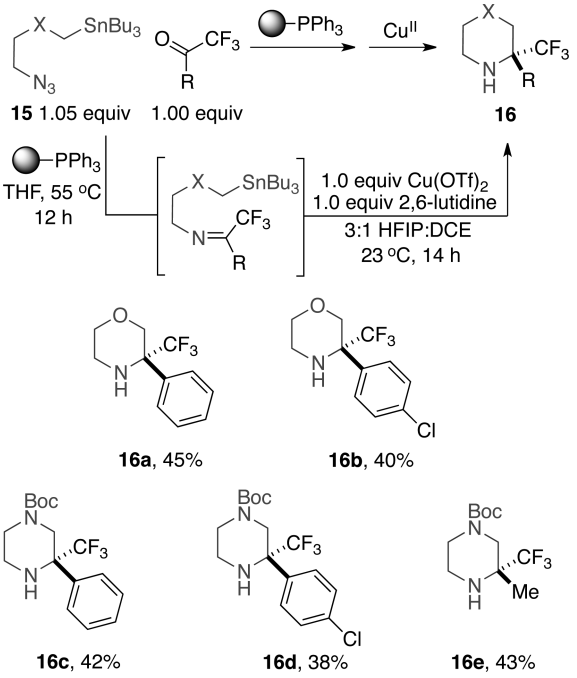
desired spirocycles. The stable vinylogous amide, derived from 1,3-cyclohexanedione **12**, gave only side products, and no spirocyclic product was observed. Likewise, only enamines were observed from ketone **13**. Attempts to use SnAP reagents that form larger rings, such as SnAP-OA **14**, also gave poor yields, as the slower rate of cyclization resulted in large amounts of protodestannylation. In general, we attribute the slightly diminished yields in SnAP reactions with ketone substrates, relative to aldehyde substrates, to the reduced rate of cyclization, leading to competing protodestannylation. Ongoing efforts to improve the stability of the intermediate radical or organocopper intermediate by changing the ligand will address these limitations in the future.

Direct condensations of *acyclic* ketones and SnAP reagents sometimes proved difficult. To overcome this, we devised azido SnAP reagent **15** to access the required ketimine by the combination of Staudinger and aza-Wittig reactions with

dx.doi.org/10.1021/ja511232b | J. Am. Chem. Soc. 2014, 136, 17726–17729

polymer-bound triarylphosphine.[14,15] When 2,2,2-trifluoroacetophenone was employed, we achieved full conversion of the ketone to the corresponding ketimines without any trace of triphenylphosphine oxide. Subsequent cyclization proceeded smoothly under the established reaction conditions to afford α-trifluoromethyl N-heterocycles **16a**–**16e** in acceptable yields (Scheme 4).[16]

Scheme 4. Azido SnAP Reagent for α-Trifluoromethyl N-Heterocycles Synthesis[a]



[a]Reaction conditions for ketimine formation: azido SnAP reagent (1.05 mmol), ketone (1.00 mmol), polymer-bound triphenyphosphine (1.10 mmol), THF (10 mL), 55 °C, 12 h. Conditions for cyclization: ketimine (1.0 mmol), $Cu(OTf)_2$ (1.0 mmol), 2,6-lutidine (1.0 mmol), 3:1 HFIP/DCE, 14 h, 23 °C. Yields refer to isolated yields after purification.

In summary, we have shown that the combination of cyclic ketones and SnAP reagents offers single step access to bi- and trifunctional spirocyclic N-heterocycles. It offers an easily recognized synthetic disconnection at the spirojunction, thereby enabling a cross-coupling approach to assemble spirocycles from equivalents of their respective monocyclic building blocks. This approach can also be used to prepare trifluoromethyl-substituted morpholines and piperazines from the corresponding ketones. Both of these scaffolds are desired frameworks for modern drug discovery, but their further exploration has been hampered by poor synthetic access and limited routes. SnAP reagents greatly expand the availability of saturated N-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data of all new compounds. 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

This work was supported by the European Research Council (ERC Starting Grant No. 306793 – CASAA and ERC Proof of Concept Grant No. 620214 – SnAP). We thank LOC MS Service (ETH Zürich) for analyses and Dr. Nils Trapp and Dr. Bernd Schweizer for the acquisition of X-ray structures. We are also grateful to Michael Lüscher, Kimberly Geoghegan, Sheng-Ying Hsieh, and Hidetoshi Noda for helpful discussions. SpiroChem AG is acknowledged for the generous gift of oxetan-3-one and 1-benzhydrylazetin-3-one.

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