JOC The Journal of Organic Chemistry

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Synthesis of Saturated N-Heterocycles

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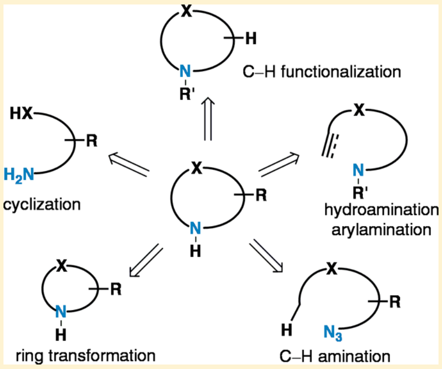
ABSTRACT: Saturated N-heterocycles are prevalent in biologically active molecules and are increasingly attractive scaffolds in the development of new pharmaceuticals. Unlike their aromatic counterparts, there are limited strategies for facile construction of substituted saturated N-heterocycles by convergent, predictable methods. In this Synopsis, we discuss recent advances in the synthesis of these compounds, focusing on approaches that offer generality and convenience from widely available building blocks.



The last three decades have witnessed the remarkable success of metal-catalyzed cross-coupling reactions in organic chemistry.[1] Over the years, extensive improvements have been made in the development of ligands, metals, reaction conditions, and building block availability, making this method one of the most useful tools to append aromatic rings into a molecule.[2] With this powerful tool, it is not surprising to observe an increase of aromatic ring count in the new bioactive small molecules.[3] However, limitations in solubility, pharmacokinetics, and bioavailability of high-aromatic-ring-count molecules are now well recognized, leading scientists to favor saturated building blocks, especially saturated N-heterocycles (Figure 1).[4] Unlike their aromatic counterparts, they cannot be easily prepared by cross-coupling reactions.[5,6] In this Synopsis, recent advances in the construction of saturated N-heterocycle synthesis, especially the facile synthesis of common 5–7-membered N-heterocycles, will be reviewed.

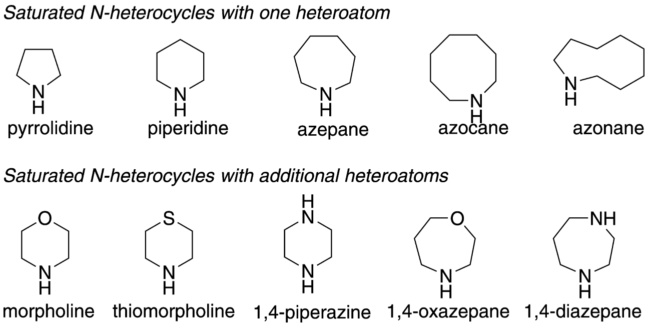


Figure 1. Saturated N-heterocycles.

■ SYNTHESIS OF SATURATED N-HETEROCYCLES CONTANING ONE HETEROATOM

Functionalization of Saturated N-Heterocycles. The most efficient construction of substituted saturated N-heterocycles would be direct sp^3 C−H functionalization. This transformation could allow access to a variety of N-heterocycles from the readily available unsubstituted starting materials. To date, most reports have focused on functionalization of the C−H bond adjacent to nitrogen.[7]

α-Lithiation with Diamine Ligands. In 1989, Beak and Lee reported the pioneering α-functionalization of N-heterocycles by lithiation.[8] This process involved α-deprotonation with an alkyllithium/diamine complex to generate the dipole-stabilized carbanion, followed by the addition of electrophiles to provide α-substituted derivatives (Figure 2). An asymmetric version was later developed with the use of the chiral diamine (−)-sparteine.[9] Extensive work on ligand design and reaction condition optimization performed by O'Brien and others enabled access the opposite enantiomers of α-substituted N-heterocycles by using enantiomeric (+)-sparteine surrogates.[10] The chiral

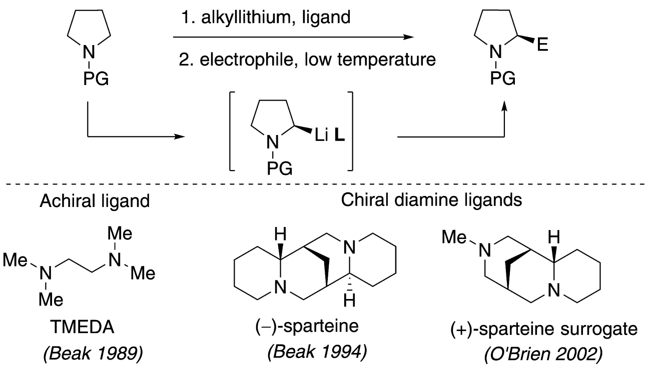


Figure 2. α-Lithiation with diamine ligands and addition to electrophiles.

Received: January 18, 2014
Published: March 11, 2014

dx.doi.org/10.1021/jo5001252 | J. Org. Chem. 2014, 79, 2809−2815

organolithium complex was configurationally stable at low temperature and added to the electrophile with the retention of stereochemistry. The method was successfully used in the asymmetric synthesis of more complex structures such as (−)-indolizidine 167B,[12] (+)-L-733,060.[11] Sparteine-mediated α-functionalization was most successful with *N*-Boc-pyrrolidine. Asymmetric functionalization of *N*-Boc-piperidine was computationally calculated to proceed with lower enantioselectivity and with a higher activation barrier compared to that of *N*-Boc-pyrrolidine.[13]

Because of the instability of lithium complex at higher temperatures (>−30 °C), the scope of the electrophiles was limited to more reactive examples, such as benzophenone, CO_2, Me_2SO_4, and TMSCl.[14] To expand the electrophile scope, transmetalation of the lithium complex to other metals such as copper and zinc was used to generate more stable organometallic complexes. Dieter et al. developed a method involving the transmetalation of the lithium complex to copper followed by trapping with less reactive electrophiles such as vinyl iodide, α,β-unsaturated ketones, and propargyl mesylates.[15] In 2006, Campos and co-workers successfully generated the configurationally stable organozinc via the transmetalation of the lithium complex to $ZnCl_2$, followed by Negishi coupling reaction to access a variety of enantioenriched 2-arylpyrrolidines.[16] They further utilized this method in the kilogram-scale synthesis of 2-arylpyrrolidines **1**, a precursor of glucokinase activator **2** in 64% yield and 91% ee (Figure 3).[17] The transformation was also applied for the preparation of 2-arylpiperidines[18] and recently for the selective β-arylation of piperidine.[19,20]

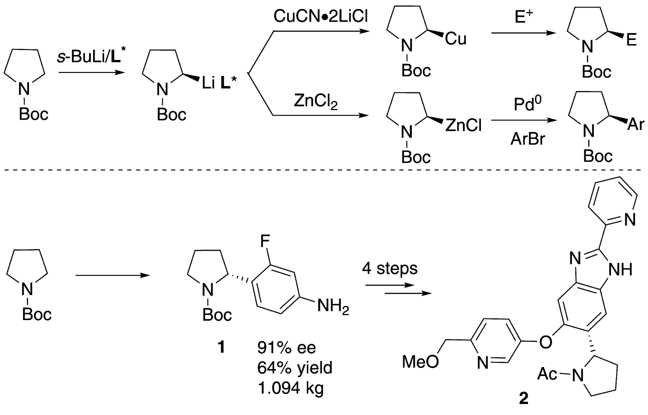


Figure 3. Lithiation, transmetalation, and cross-coupling.

Metal-Catalyzed C–H Functionalization. The major concerns in sp^3 C−H activation are reactivity and selectivity.[21] Cleavage of sp^3 C−H bonds is kinetically and thermodynamically unfavorable. Among C−H bonds in the cyclic amines, the bonds adjacent to heteroatoms are more reactive. With the appropriate directing groups, activation of the C−H bond next to heteroatoms could be achieved selectively. Murai and co-workers reported the reaction of *N*-2-pyridyl cyclic amines with alkenes in the presence of the low-valent metal $Ru_3(CO)_{12}$ to access α-alkylated saturated cyclic amines.[22] The reactions proceeded well with *N*-2-pyridylpyrrolidines and piperidines and a range of mono- and disubstituted alkenes. Based on the same concept, the research groups of Sames[23] and later Maes developed sp^3 C−H bond arylation of pyrrolidines and piperidines, using aryl boronate esters as coupling partners (Figure 4).[24] This approach was, however, not successful for larger ring N-heterocycles. Other limitations include the difficulty of removing the directing group and overarylation on unsubstituted N-protected cyclic amines.[25]

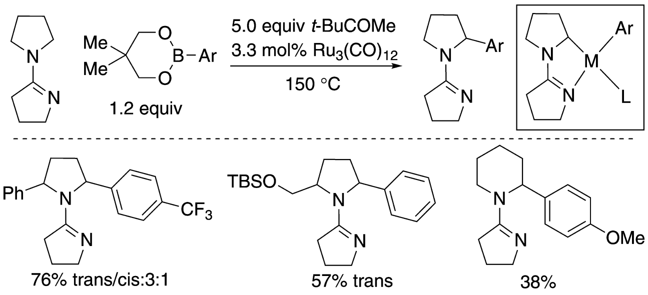


Figure 4. Directed C−H activation by Sames et al.

With the unique reactivity of tantalum−amidate complex for activating the C−H bonds adjacent to nitrogen, Schafer and co-workers recently developed a new route for the synthesis of α-substituted, unprotected piperidines, piperazines, and azepanes (Figure 5).[26] In this transformation, the Ta−amidate complex selectively activates sp^3 C−H bond by β-hydrogen abstraction forming tantallaaziridine complex **3**, which undergoes alkene insertion leading to the formation of the α-alkylated cyclic amine.

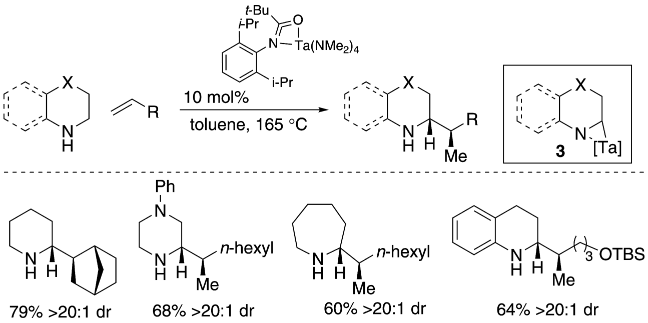


Figure 5. Direct C−H activation by Schafer et al.

Radical-Based C–H Functionalization. The pioneering work of Curran and Snieckus in 1990 on the formation of α-amino carbon-centered radicals via 1,5-hydrogen transfer inspired other research groups to develop radical-based α-functionalization of cyclic amines.[27] Nakamura and co-workers developed an iron-catalyzed C−C bond formation at the α-position of acyclic and cyclic amines with Grignard or zinc reagents.[28] The reactions proceeded under mild conditions in the presence of an iron catalyst to provide α-aryl pyrrolidines, piperidines, and azepanes. Other methods to generate α-amino radicals including BEt_3/O_2 (or air) or light in the presence of organic photosentitizer were developed by Yoshimitsu[29] and Hoffmann (Figure 6).[30] The later method allowed accessing a highly functionalized proline **4**, an important precursor in the total synthesis of (±)-kainic acid (**5**). In 2011, MacMillan reported the photoredox α-amino C−H arylation. The α-amino radical was generated under photoredox conditions and trapped with electron-deficient arenes or heteroarenes as radical coupling partners (Figure 7).[31]

Redox-Neutral C–H Functionalization. Another approach to the functionalization of saturated N-heterocycles is intramolecular redox-neutral C−H functionalization. The transformation is related to the generation of an electrophile/nucleophile pair via intramolecular hydride shift or iminium

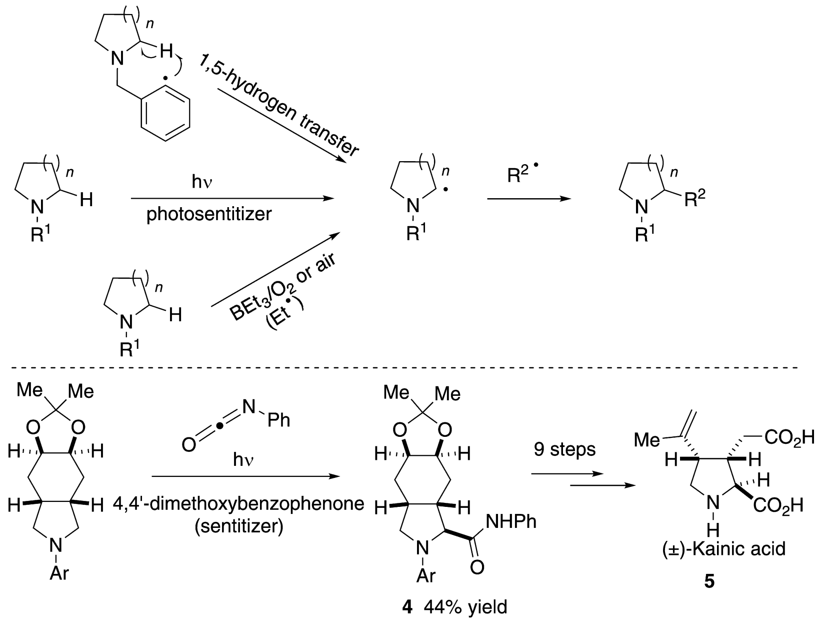


Figure 6. Radical-based C−H functionalization.

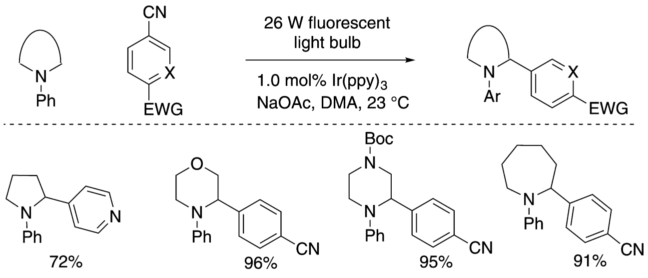


Figure 7. Photoredox C−H functionalization by MacMillan et al.

isomerization. In 2012, Maulide and co-workers reported the functionalization at α-position of acyclic and cyclic amines with Grignard reagents (Figure 8).[32] A variety of commercially available Grignard reagents (alkyl, aryl, alkenyl, and allylic) and alkynyl trifluoroborates were employed to form α-substituted pyrrolidines. This procedure was sensitive to the nature of amines; it worked well with pyrrolidines but poorly with others. N-Phenyl carboxaldehyde is critical for the reaction success. It serves as a hydride acceptor and directs the addition of Grignard reagents at the α-position.

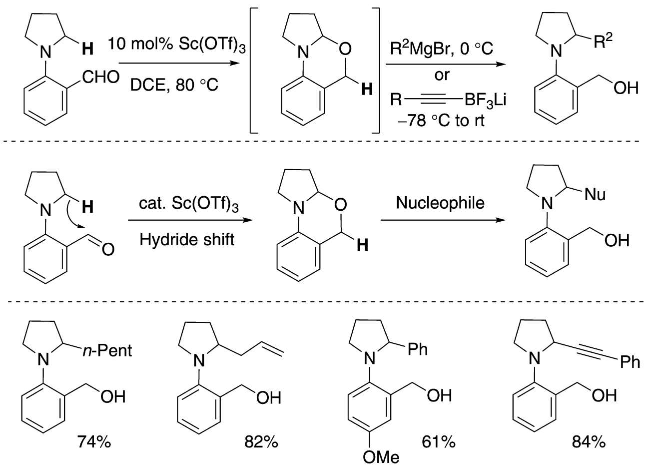


Figure 8. Redox C−H functionalization via 1,5-hydride shift by Maulide et al.[32]

The redox-neutral C−H functionalization and N-alkylation of cyclic amines has been recently developed by Seidel and co-workers (Figure 9). Cyclic iminium ions were generated by the acid-catalyzed iminium isomerization[33] and trapped by various nucleophiles. Relatively bulky and/or electron-deficient aryl aldehydes were used to prevent the addition of nucleophiles to the acyclic iminium ions. α-Cyanation,[34] α-alkynylation[35] α-phosphonation,[36] and α-arylation[37] were developed with trimethylsilyl cyanide, copper acetylides, phosphites, and electron-rich arenes as nucleophiles. The reactions worked well with pyrrolidine and larger ring sizes (piperidine and azepane). With more challenging substrates, such as morpholine, the regioselectivity eroded and the adduct of nucleophile and acyclic iminium ion was generated as the major product.

Direct functionalization of saturated N-heterocycles is conceptually ideal but is not yet a general approach. Lithiation, followed by the addition of an electrophile or metal-catalyzed cross-coupling reaction, is currently the most reliable method but still suffers from laborious conditions and is largely restricted to the construction of α-functionalized pyrrolidines and piperidines. Other classes of saturated N-heterocycles with different ring sizes or additional heteroatoms are not accommodated.

Metal-Mediated Hydroamination and Arylamination. The concept of transforming an acyclic amine into a cyclic amine in an atom-economic fashion has motivated many researchers. Intramolecular hydroamination or arylamination of an alkene or alkyne with pendant amine functional group delivers α-substituted cyclic amine. Palladium-catalyzed alkene arylamination and hydroamination have emerged as useful methods to prepare α-substituted pyrrolidines and other N-heterocycles (Figure 10). Readers can find the updated and detailed reviews in recent publications.[38]

Schafer and co-workers reported an asymmetric synthesis of substituted morpholines and piperazines (Figure 11).[39] A titanium−amidate complex catalyzed the regioselective hydroamination with oxygen- and nitrogen-containing aminoalkynes,

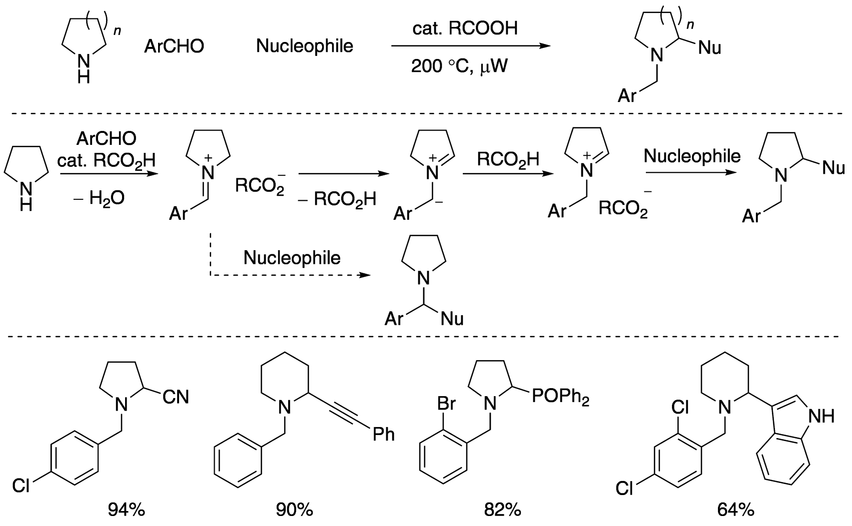


Figure 9. Redox C−H functionalization via iminium isomerization by Seidel et al.[33−37]

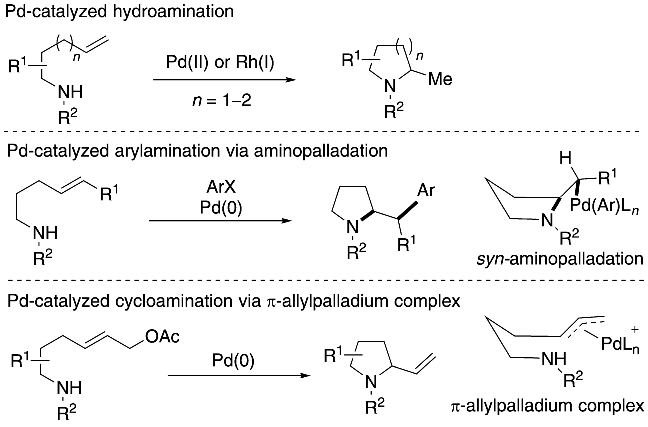


Figure 10. Palladium-catalyzed alkene arylamination and hydroamination.

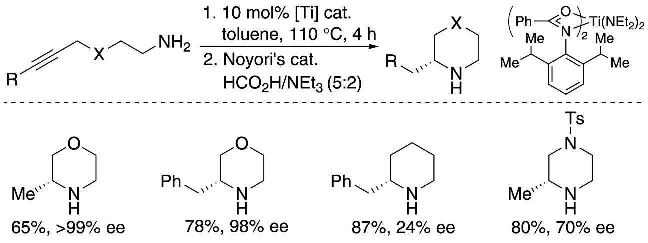


Figure 11. Hydroamination and reduction by Schafer et al.[39]

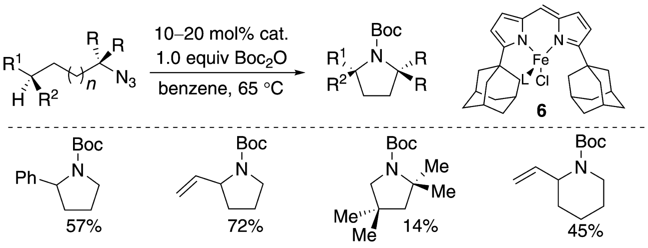


Figure 12. C−H amination by Betley and Hennessey.[40]

followed by enantioselective reduction using Noyori−Ikariya catalyst to generate substituted morpholines and piperazines in high yield and with good enantioselectivity.

In 2013, Betley and Hennessey reported the iron-catalyzed sp^3 C−H bond amination of organoazides for the synthesis of N-heterocycles (Figure 12).[40] Inspired by the heme-iron activity in Nature, they developed the iron dipyrrinato catalyst **6**, which mimics the electronic structure of the well-known cytochrome P450 reactive iron-oxo intermediate.[41] In this transformation, the Fe(II) catalyst reduces the azide to generate an Fe(III) radical imido, which either undergoes direct C−H insertion or hydrogen abstraction and radical rebound to afford the Fe(III) product. Catalyst turnover was achieved by in situ *N*-Boc protection. Like other sp^3 C−H bond functionalization methods, selectivity is a concern. More activated C−H bonds at benzylic, allylic, or tertiary carbon positions react preferentially. Ring size also plays an important role in the cyclization. In many cases, it is not simple to rationalize the dominant factor in determining the product outcome.

■ SYNTHESIS OF SATURATED N-HETEROCYCLES WITH ADDITIONAL HETEROATOMS

Cyclization. While direct functionalization and hydro/carboamination are often used for the preparation of N-heterocycles with one heteroatom, cyclization is more commonly used for constructing cyclic amines with additional heteroatoms. Nucleophilic substitution of amino alcohols/thiols/amines with dihalo derivatives is frequently employed for preparing morpholines, thiomorpholines, or piperazines.[42] The intrinsic limitation of this approach is low yield due to the competing elimination reactions. A multiple-step synthesis such as alkylation followed by lactamization and reduction,[43] reductive amination,[44] or ring-closing metathesis followed by reduction could finally deliver the desired products.[45] In addition to the lengthy synthesis, the complexity of the final products in these procedures is derived from the initial starting materials

Nucleophilic Substitution. To minimize the side reactions caused by strongly basic conditions of substitution reactions, Aggarwal and co-workers developed a softer electrophile, a vinyl sulfonium salt, instead of dihalo compounds to provide a range of *N*-protected mono-/disubstituted morpholines, thiomorpholines, and piperazines in good yields (Figure 13).[46] The vinyl selenium salt was also used for the same purpose.[47] The removal of the protecting group on nitrogen, *N*-tosyl in most cases, was unfortunately problematic.

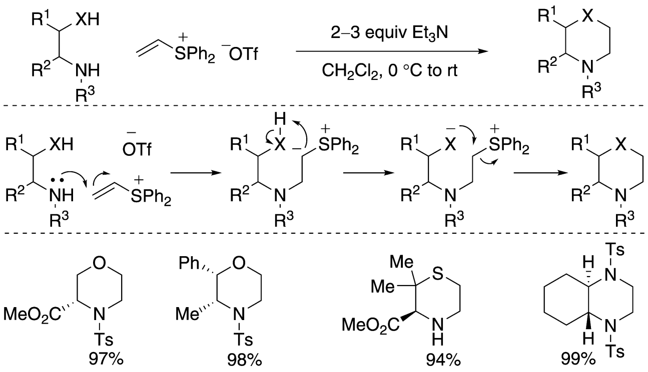


Figure 13. Vinyl sulfonium salts for N-heterocycle synthesis by Aggarwal et al.[46]

Ring Transformations. Ring transformations have not been often employed for the preparation of substituted N-heterocycles. In most cases, the substituents on N-heterocycles are set prior to the ring transformation. The synthesis of substituted morpholines, thiomorpholines, and piperazines via the Lewis acid catalyzed ring expansion of 3-oxetanone-derived spirocycles was recently reported by Carreira and co-workers (Figure 14).[48]

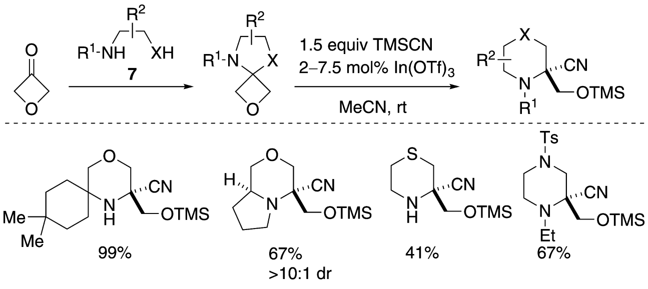


Figure 14. Ring expansion of 3-oxetanone by Carreira et al.[48]

The elegance of the transformation lies in that changing heteroatom-substituted amino compound **7** will lead to the formation of different substituted N-heterocycles.

SnAP Reagents: Conversion of Aldehydes into Saturated N-Heterocycles. *(SnAP = Tin (Sn) Amine Protocol).* In 2013, our group introduced SnAP reagents for the conversion of aldehydes into N-unprotected 3-thiomorpholines.[49] The transformation involves an intramolecular C–C bond-forming radical addition of an imine bearing a pendant organostannane (Figure 15).

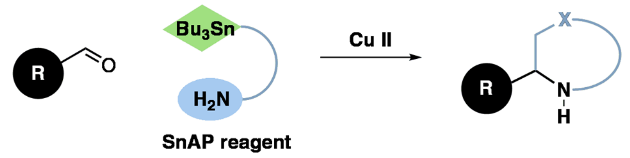


Figure 15. SnAP reagent concept.

Aminotributylstannane **8** (SnAP TM) was condensed with aldehyde to afford the corresponding imine, which was cyclized with a stoichiometric amount of $Cu(OTf)_2$ to provide *N*-unprotected 3-thiomorpholine. The reaction accepted an outstanding scope of aldehydes including aryl, heteroaryl, and alkyl aldehydes (Figure 16).

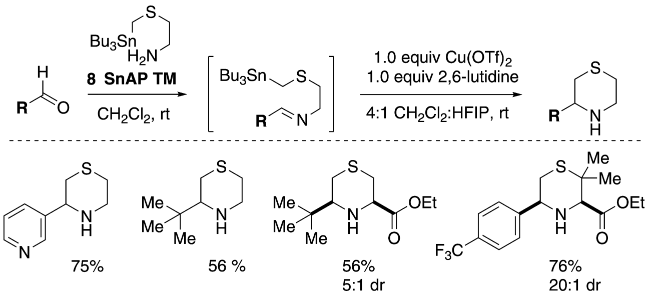
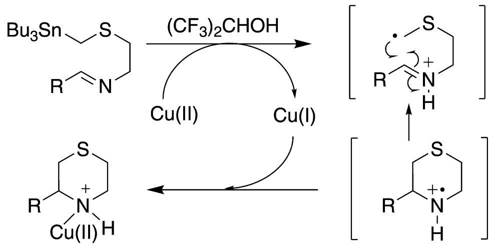


Figure 16. One-step synthesis of 3-thiomorpholines.

Scheme 1. Proposed Mechanism



Preliminary mechanistic studies invoked a copper-mediated oxidation of the carbon–tin bond to generate the sulfur-stabilized carbon-centered radical followed by 6-*endo-trig* cyclization to deliver the product (Scheme 1).

The generation of the sulfur-stabilized carbon-centered radical followed by cyclization to form the stable aminyl radical was key to the successful thiomorpholine formation. Based on the assumptions that other heteroatoms such as oxygen and nitrogen could also stabilize the primary radical, a family of SnAP reagents to access other ring sizes and types of saturated N-heterocycles including morpholines, piperazines, diazepanes, and others has been developed (Figures 17 and 18).[50,51] The reactions were not sensitive to the heteroatom type and retained similar reactivity toward a wide range of aldehydes under a single reaction protocol. Air- and moisture-stable SnAP reagents were prepared on a multigram scale from inexpensive starting materials.

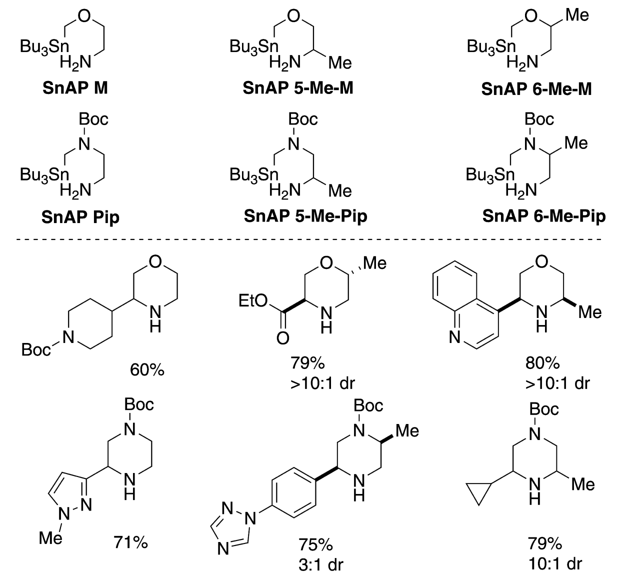


Figure 17. SnAP reagents for the synthesis of substituted morpholines and piperazines and selected examples prepared.

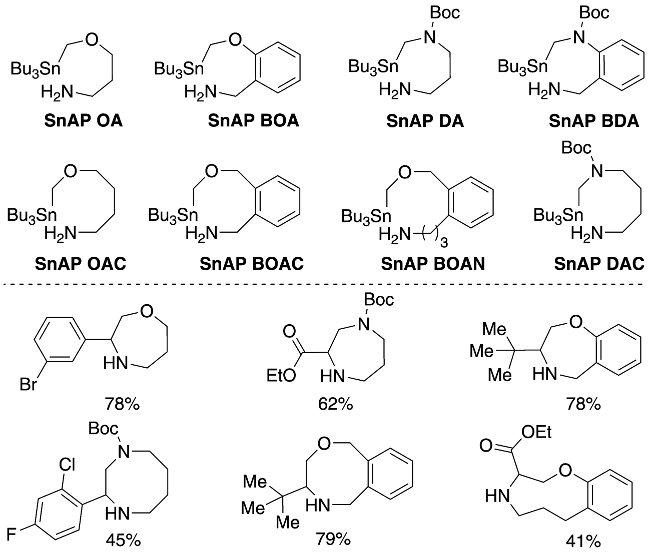


Figure 18. SnAP reagents for the synthesis of medium ring N-heterocycles and selected examples prepared.

CONCLUSION

The recent shift of interest toward saturated N-heterocycles and their poor commercial availability raise the need for synthetic methods that could offer generality and proceed from readily available building blocks. Despite extensive efforts, few methods provide facile access to a variety of substituted saturated N-heterocycles. Most still require a nitrogen protecting group, which are often difficult to remove. Lithiation and transmetalation, followed by metal-catalyzed coupling reactions, are the most effective approaches but are laborious and restricted to the preparation of α-functionalized pyrrolidines and piperidines. For the synthesis of other classes of saturated N-heterocycles with additional heteroatoms or different ring sizes, several approaches have been recently reported, focusing on simplicity and generality to obtain differently substituent patterns of N-heterocycles.

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Notes

The authors declare no competing financial interest.

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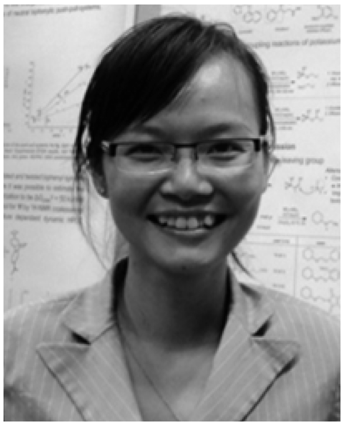

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Prof. Jeffrey W. Bode studied at Trinity University in San Antonio, TX. Following doctoral studies at the California Institute of Technology and ETH−Zürich and postdoctoral research at the Tokyo Institute of Technology, he began his independent academic career at UC−Santa Barbara in 2003. He moved to the University of Pennsylvania as an Associate Professor in 2007 and to ETH−Zürich, Switzerland, as a full Professor in 2010. Since 2013, he is also a Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University.

ACKNOWLEDGMENTS

This research topic was supported by an ETH Research Grant (ETH-12 11-1) and the European Research Council (ERC Starting Grant No. 306793 − CASAA).

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